NON-INTERVENTIONAL STUDY REPORT

TITLE PAGE

Division: Worldwide Development

Information Type: Non-Interventional Study Report

Title:	A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)
Compound Number:	GSK1550188
Effective Date:	02 Sep 2025
Subject:	Observational, registry, belimumab, safety, adverse events, effectiveness
Author(s):	PPD
Indication Studied:	Systemic lupus erythematosus (SLE)

STUDY INFORMATION

Title	A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)
Report version identifier	116543
Date of last version of report	31 January 2023
EU PAS (ENCEPP) register number	EUPAS4966
Active substance	Belimumab (L04AG04)
Medicinal product	BENLYSTA
Product reference	EMEA/H/C/002015
Procedure number	NA
Marketing authorization holder	GlaxoSmithKline (Ireland) Limited,12 River Walk Citywest Business Campus, Dublin, D24 YK11, Ireland
Joint PASS	No
Research question and objectives	The primary objective of this study was to evaluate the incidence of the following adverse events of special interest (AESIs) over 5 years in adults with active autoantibody-positive systemic lupus erythematosus (SLE) who are treated with or without Benlysta: • Malignancies (excluding non-melanoma skin cancers (NMSC)) • Mortality • Opportunistic infections and other infections of interest • NMSC • Selected serious psychiatric events • Serious infections

	Other Objectives: To evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without Benlysta: • Organ damage as assessed by SLICC/ACR Damage Index (SDI) • Concomitant SLE medications including steroids • Hospitalizations
Country(-ies) of study	Argentina, Austria, Belgium, Canada, France, Germany, Israel, Italy, Portugal, Slovakia, Spain, Sweden, and the US
Author	PPD

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder	GlaxoSmithKline (Ireland) Limited, 12 River Walk Citywest Business Campus, Dublin 24, D24 YK11, Ireland
MAH contact person	PPD, PPD, Global Regulatory Affairs Address: GSK HQ, 79 New Oxford Street, London, WC1A 1DG, United Kingdom PPD PPD

STUDY DETAILS

UNIQUE IDENTIFIER	116543(e-track)
TITLE	A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)
STUDY ACCOUNTABLE PERSON	PPD
CONTRIBUTING AUTHORS	
ASSET ID	GSK1550188
GSK ASSET	BENLYSTA
EFFECTIVE DATE	02 Sep 2025
INDICATION	Systemic lupus erythematosus (SLE)

SPONSOR SIGNATORY

Title:	A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)
Compound Number:	GSK1550188

Deepak Assudani
Senior Clinical Development Director

Date (DD Month YYYY)

<<Enter Name>>
Therapy Area Leader/+1 Manager

Date (DD Month YYYY)

Note: Not applicable if an eSignature process is used to get the sponsor approval.

INVESTIGATOR REPORT AGREEMENT PAGE

- I have read this report and confirm that to the best of my knowledge the study was carried out as described in this GSK report
- I acknowledge that I was responsible for overall study conduct. I personally conducted or supervised the described clinical study.
- I ensured that all associates, colleagues, and employees assisting in the conduct of the study were informed about their obligations. Mechanisms were in place to ensure that site staff receive the appropriate information throughout the study.

Investigator Name:

PPD

Investigator Signature	Date (DD Month YYYY)

TABLE OF CONTENTS

PAGE

LIST OF TABLES

LIST OF FIGURES

TRADEMARK INFORMATION

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BENLYSTA

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SAS
SF-12v2

1. ABSTRACT

Title: A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)

Keywords: Observational, registry, belimumab, safety, systemic lupus erythematosus

Rationale and background

Benlysta (belimumab), is a recombinant human IgG1λ monoclonal antibody indicated for systemic lupus erythematosus (SLE).

Identified risks (EU RMP) include infections and serious psychiatric events including depression and suicidality (re-categorized from potential risk to identified risk since this study initiation). Potential risks include progressive multifocal leukoencephalopathy and malignancies.

The study was designed to perform long-term assessment of these risks, in a real-world setting in participants treated for SLE.

Research questions and objectives

Primary objective: To evaluate the incidence of selected adverse events of special interest (AESI) over 5 years in adults with active autoantibody-positive SLE who are treated with or without Benlysta: all cause-mortality, serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, malignancies, and non-melanoma skin cancer (NMSC).

Other objective: To evaluate selected effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without Benlysta: SDI, SLE medications, hospitalizations.

Study design

This was a multi-center, prospective, observational cohort study. All assessments were per routine care. Data was collected at enrollment and at approximate 6-month intervals for 5 years (60 months). Participants were enrolled into 1 of 2 groups, those who, at baseline, were receiving Benlysta (Benlysta exposure group) or were not receiving Benlysta (comparison Non-Benlysta exposure group). All treatment decisions were at the discretion of the participant and their healthcare provider.

Setting

The first participant was enrolled in the study on 21 February 2013 and the last participant last visit was on 28 February 2025. Participants were enrolled at sites in

Argentina, Austria, Belgium, Canada, France, Germany, Israel, Italy, Portugal, Slovakia, Spain, Sweden, and the US.

Subjects and study size, including dropouts

2967 participants (937 Non-Benlysta, 2030 Benlysta) were enrolled (Eligible population). Throughout the study, 49.2% of participants withdrew (48.2% Non-Benlysta vs 49.6% Benlysta).

Variables and data sources

Data was collected from medical records and during clinic visits.

Results

Baseline demographic and disease characteristics were roughly comparable between the exposure groups. While both groups were similar in age and body mass index, a slightly higher proportion of participants in the Benlysta group were female and White. The Benlysta group showed higher baseline rates of allergic reactions, psychiatric disorders, and autoimmune disorders.

Based on the Intent-To-Treat (ITT) (main strategy), AESI incidence rates were higher for Benlysta compared to Non-Benlysta for serious infections and serious psychiatric events. All other AESIs were comparable or lower in the Benlysta group. Based on As-Exposed strategy (14 weeks risk window), incidence rates were comparable or lower in the Benlysta group. Based on the Ever-Exposed strategy, incidence rates for mortality, malignancies, and NMSCs were comparable or lower in the Benlysta group.

In participants in ≥65 years of age, AESI incidence rates (as exposed strategy) were higher in Benlysta compared to Non-Benlysta for serious infections, and opportunistic infections, while all other AESIs were comparable or lower in Benlysta.

Effectiveness outcomes in the ITT group were broadly similar between the groups.

Discussion

The AESIs reported in this registry overall and in the elderly population are consistent with the known safety profile of Benlysta and no new emerging signals were observed.

Marketing authorization holder

GlaxoSmithKline (Ireland) Limited, 12 River Walk Citywest Business Campus, Dublin 24, D24 YK11, Ireland

Names and affiliations of principal investigators

List of Investigators is provided in a stand-alone document and is available upon request.

2. LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ADAM	Analysis Data Model
AE	Adverse Event
AESI	adverse events of special interest
BMI	Body mass index
CI	Confidence interval
COVID-19	Coronavirus Disease 2019
CRD	Controlled repeat dose
CRO	Contract research organization
eCRF	electronic case report forms
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of study
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
GSK	GlaxoSmithKline Research & Development Limited
IB	Investigational Brochure
IEC	Institutional Ethics Committee
IgG1λ	Immunoglobulin G1 lambda
IPTW	Inverse probability of treatment weighting
IRB	Institutional Review Board
ITT	Intent-To-Treat
IV	Intravenous/ Intravenously
MAH	Marketing Authorization Holder

NA	Not applicable
NMSC	Non-melanoma skin cancers
PASS	Post-Authorization Safety Study
PML	Progressive multifocal leukoencephalopathy
PT	Preferred Term
RAP	Reporting and Analysis Plan
RCT	Randomized controlled trial
RMP	Risk Management Plan
SABLE	Safety and effectiveness of belimumab in systemic lupus erythematosus registry
SAC	Scientific Advisory Committee
SAE	Serious Adverse Event
SAS	Statistical Analysis System
SC	Subcutaneous/Subcutaneously
SD	Standard deviation
SDI	SLICC/ACR Damage Index
SF-12	12-item short form
SFI	Systemic Lupus Erythematosus Flare Index
SLE	Systemic lupus erythematosus
SLEDAI 2000	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic lupus international collaborating clinics
SOC	System Organ Class
US	United States

3. INVESTIGATORS

List of Investigators is provided in a stand-alone document and is available upon request.

4. OTHER RESPONSIBLE PARTIES

The person authorized for communication on behalf of the MAH GSK (Ireland) Limited is as below:

Name: PPD PPD, Global Regulatory Affairs

Address: GSK HQ, 79 New Oxford Street, London, WC1A 1DG, United Kingdom

Email: PPD

Tel: PPD

IQVIA was the CRO operationalizing this registry on behalf of GSK. All clinical and scientific decisions were made by GSK and implemented through IQVIA. The study administrative table is provided in a stand-alone document.

A SAC consisting of global clinical experts, along with GSK staff (including clinical, statistics, and epidemiology) was formed in 2012. At a minimum, the SAC was to meet annually to review collected data including periodic reports. The SAC also provided input on study implementation and logistics. List of current SAC members is available upon request.

5. MILESTONES

Milestone	Planned date	Actual Date	Comments
IEC/IRB (First approved)[a]		13 November 2012	
IEC/IRB (Last approved)[a]		14 January 2025	
Start of data collection	February 2013	21 February 2013	
End of data collection	2025	28 February 2025	
Registration in the EU PAS register		16 October 2013	
Interim Report of 1 year EMA submission	28 February 2014	28 February 2014	
Interim Report of 2 years EMA submission	28 February 2015	25 February 2015	
Interim Report of 3 years EMA submission	28 February 2016	17 February 2016	
Interim Report of 4 years EMA submission	28 February 2017	23 February 2017	
Interim Report of 5 years EMA submission	28 February 2018	12 February 2018	
Interim Report of 6 years EMA submission	28 February 2019	20 February 2019	
Amendment to Interim Report of 6 years	NA	17 February 2020	
Interim Report of 7 years EMA submission	28 February 2020	17 February 2020	
Interim Report of 8 years EMA submission	26 February 2021	12 February 2021	
Interim Report of 9 years[b]	NA	NA	
Interim Report of 10 years EMA submission	28 February 2023	31 January 2023	

Milestone	Planned date	Actual Date	Comments
Final study report of study results	28 February 2026	02 Sep 2025	

a. List of all IECs or IRBs is provided as a stand-alone document and is available upon request.

b. Per EMA conclusion for procedure EMEA/H/C/002015/MEA/003.15, the 2022 interim report was not required and the next interim report expected was in 2023. No additional interim reports were needed before the final report in 2025 if there were no new safety concerns in the 2023 interim report.

6. RATIONALE AND BACKGROUND

Benlysta (belimumab) is a recombinant human IgG1λ monoclonal antibody administered by IV infusion or SC injection that is indicated for reducing disease activity in adult participants with active autoantibody-positive SLE who are receiving standard therapy.

Identified risks in the EU RMP include infections and serious psychiatric events including depression and suicidality (re-categorized from a potential risk to an identified risk since this study was initiated). Potential risks associated with SLE and/or its treatments include PML and malignancies.

Benlysta was approved in the European Union in 2011, and an Annex II condition to the marketing authorization was agreed to submit the final 5-year data clinical study report from BEL116543/HGS1006-C1124 (SABLE). This safety registry is a Category 1 study in the EU RMP to evaluate the incidence of all-cause mortality and AESI in participants with SLE.

This study evaluated the incidence of AESIs including malignancies (excluding NMSC), serious infections, opportunistic infections (including PML and other infections of interest), NMSC and selected serious psychiatric events. In addition, all-cause mortality was studied. The study was designed to perform a long-term assessment of these risks, in a real-world practice setting where adult participants were treated for SLE.

At the time of initial Benlysta approval in the EU in July 2011, data on participants ≥65 years of age were limited, and the efficacy and safety of Benlysta in the elderly population could not be established. This was due to the very low number of elderly participants who enrolled in the controlled clinical studies. As a consequence, GSK agreed a post-authorization measure with the EMA to conduct meta-analyses under study ID BEL116559 to assess efficacy and safety in elderly participants in selected belimumab studies. The analyses were conducted sequentially as ongoing and new studies completed until all the studies identified for inclusion were completed, and results have been submitted to EMA in four interim reports.

This is the final report for the elderly analysis EMA post-authorization measure, as BEL116543 is the last included study to complete. Interim reports have been submitted per EU RMP milestone dates. Elderly safety data in this study are not pooled with that from previous studies for this analysis.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of this study was to further evaluate the incidence of malignancies (excluding NMSC), all-cause mortality, serious infections, opportunistic infections (and other infections of interest), NMSC, and selected serious psychiatric events over 5 years in adult participants with active autoantibody-positive SLE being treated with and without Benlysta in real-world practice settings.

Originally, the study was designed to evaluate the following effectiveness measures: organ damage as assessed by SDI, use of concomitant SLE medications including steroids, hospitalizations, quality of life (as assessed by SF-12v2 Health Survey), fatigue (as assessed by the FACIT-Fatigue Scale), SLE disease activity (as assessed by the SLEDAI 2000), and severe flares (as derived by a modified SFI); however, several effectiveness measures were removed with the implementation of Amendment 3 (see details in Section 8).

Primary objective:

To evaluate the incidence of the following AESI over 5 years in adults with active autoantibody-positive SLE who were treated with or without Benlysta:

- Malignancies (excluding NMSC)
- Mortality
- Opportunistic infections and other infections of interest (see Protocol Appendix 1)
- NMSC
- Selected serious psychiatric events (see Protocol Appendix 2)
- Serious infections.

Other objectives:

To evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who were treated with or without Benlysta:

- Organ damage as assessed by SDI (see Protocol Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations.

8. AMENDMENTS AND UPDATES

Amendment or update number	Date	Section of study report	Amendment or update	Reason
1	10 December 2013	Removed questionnaire and evaluation scales to assess quality of life, SF-12v2 and FACIT-Fatigue Scale	Local Addendum for Sweden	At the request of the Swedish Regulatory Authority to classify the protocol as non-interventional PASS as the use of these questionnaire and evaluation scales is not standard clinical practice in follow-up of participants with SLE in Sweden.
2	19 June 2017	Relevant sections were updated accordingly	Global Amendment	To allow inclusion of SC Benlysta users in the BEL116543 registry once the SC formulation was commercially available.
3	12 March 2018	Relevant sections were updated accordingly	Global Amendment	Modifications to 'other endpoints'[a]: Eliminate collections: -SF12v2 Health Survey -FACIT-Fatigue -Severe flares Reduce collections to enrollment visit only: -SLEDAI 2000 -Labs -Tobacco/Alcohol use -Pregnancy -Vaccinations
4	25 November 2020	Relevant sections were updated accordingly	Global Amendment	Sponsor changed from Human Genome Sciences to GSK, LLC. Updated Study Collection Table to include a general medical status check at 24 and 48 months.

Amendment or update number	Date	Section of study report	Amendment or update	Reason
5	25 May 2022	Relevant sections were updated accordingly	Global Amendment	Clarified on the below: - declaration of a participant as lost-to-follow-up - pregnancy registry availability - specific studies that comprise the pooled IV primary safety database. - all the analysis will be described in the statistical analysis plan. - studies used for the safety profile of Benlysta and aligned with the IB. Made changes to align the follow-up period of AESI (serious and non-serious) with the primary study objective without impacting the safety and/or well-being of participants and the interpretation of study results. Aligned the SABLE study protocol wording with GSK safety reporting practices for the SABLE study.

a. As agreed with EMA, protocol changes were made to 'other endpoints' (not primary or secondary endpoints) and are not expected to impact the primary study objective.

9. RESEARCH METHODS

9.1. Study design

This was a multi-center, prospective, observational cohort study to evaluate the incidence of AESIs and effectiveness in participants with active, autoantibody-positive SLE treated with and without Benlysta (participants followed for 5 years). Data were collected at enrollment and at approximately 6-month intervals for 5 years (60 months). All participants were assessed for AESIs including malignancies (excluding NMSC), serious infections, opportunistic infections (and other infections of interest including PML), NMSCs, selected serious psychiatric events, and mortality.

Participants were enrolled into 1 of 2 groups, those who, at baseline, were receiving or initiating Benlysta (Benlysta exposure group) or were not receiving Benlysta (comparison Non-Benlysta exposure group). All treatment decisions were at the discretion of the participant and their healthcare provider and were not mandated by the study design or protocol. All assessments were intended to be performed at the time of clinical encounters, per routine care.

Benlysta and Non-Benlysta participants could be either Treatment Initiators or Current Users. Treatment Initiators were defined as those participants who had initiated immunosuppressants and/or Benlysta in the last 2 months, while the Current Users were those who had received immunosuppressants and/or Benlysta for ≥2 months at the time of entry into the registry.

Participants who became pregnant during their participation in this registry were encouraged to also participate in a separate pregnancy registry (if available at the time).

Participants were free to withdraw from this registry at any time, for any reason. They continued to be followed regardless of changes in medication until study completion. If a participant wished to discontinue participation in the registry, the data collection for the next study evaluation was obtained at the time of the participant’s next routinely scheduled clinical assessment. If data collection had been performed within 2 months before the discontinuation visit, it was not repeated. Participants were considered lost-to-follow-up if no contact was established by the time a participant was beyond 5 years and 3 months from their enrollment date (Day 0).

9.2. Setting

The first participant was enrolled in the study on 21 February 2013. Recruitment was planned to continue until approximately 3000 participants (approximately 2000 Benlysta plus standard of care [Benlysta exposure group] and 1000 standard of care only [comparison Non-Benlysta exposure group]) were enrolled. Enrollment was completed on 16 January 2020 and participants were enrolled at sites in Argentina, Austria, Belgium, Canada, France, Germany, Israel, Italy, Portugal, Slovakia, Spain, Sweden, and the US.

Each participant was followed for 5 years. Data collection was planned to continue through 2025. The last participant last visit was on 28 February 2025.

9.3. Subjects

Participants were enrolled in the registry if they met the following inclusion criteria:

- Males or females aged 18 or older.
- Had a clinical diagnosis of active SLE.
- Current or history of autoantibody-positive SLE.
- Had been treated with SLE therapy including Benlysta and/or immunosuppressants (e.g., azathioprine, methotrexate, cyclophosphamide, mycophenolate, and biologics).
- Had the ability to understand the requirements of the study, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study data collection procedures.

Participants were excluded from participating in the registry if they met any of the following exclusion criteria:

- Treatment with an investigational drug within 1 year of enrollment. Investigational drug applied to any drug not approved for sale in the country it was being used.
- Currently enrolled in a placebo-controlled Benlysta (belimumab) clinical trial or a continuation protocol where belimumab was used as an investigational agent.
- Participants who had a history of Benlysta exposure, but were not currently receiving Benlysta.
- Participants only receiving an anti-malarial for SLE.
- Participants only receiving steroids for SLE.

9.4. Variables

In March 2018, Amendment 3 eliminated the collection of 3 effectiveness endpoints: quality of life (as assessed by SF-12v2 Health Survey), fatigue (as assessed by the FACIT-Fatigue Scale) and severe flares (assessed using a modified SFI). Additionally,

the collection of some data was limited to enrollment visit only: SLE disease activity (as assessed by the SLEDAI 2000), labs, tobacco and alcohol use, pregnancy and vaccination. GSK determined that these amendments were non-substantial and informed the EMA (e-mail correspondence) on 26 April 2018.

The following variables were collected in the study:

- Participant disposition
  - Inclusion/exclusion criteria
  - Date of enrollment
  - Withdrawal from study including date
  - Reason for withdrawal
- Demographic and baseline characteristics:
  - Demographic characteristics (date of birth, sex, ethnicity, race, height, and weight)
  - Tobacco use and alcohol abuse
  - Pregnancy status
  - SLEDAI 2000
  - Laboratory tests
  - Baseline vaccinations status
- Medical history (past and current), vaccinations
- Changes in general medical status
- SLE disease characteristics
  - SDI
  - Date of SLE diagnosis
  - Hospitalization (past and current)
    - Date of admission and discharge, relation to SLE, primary diagnosis
  - Corticosteroid use
    - Past and current use including dates
    - Use in the past 6 months
    - Prednisone equivalent dose
    - Excursions above the daily dose
    - Parenteral/intramuscular
  - SLE Medications (including start and stop date, reasons)
- Serious AESI

- Event, start and stop date and time, outcome, intensity, causality to current SLE therapy, action taken with current SLE therapy, causality to study activities, withdrawal, concomitant medication, diagnostic tests, relevant medical conditions, recurrence of the event after restart of SLE therapy, criteria for seriousness

- AESI

- Event, start and stop date, frequency, outcome, intensity, causality to current SLE therapy, action taken with current SLE therapy, withdrawal, concomitant medication, diagnostic tests, relevant medical conditions, recurrence of the event after restart of SLE therapy

- Possible Suicidality-Related Event

- Date, SLE-related neuropsychiatric events

- Possible Suicidality-Related (past and current) Questionnaire (including date, drug and alcohol use, stress, family history of suicidality and psychiatric disorders).

For potential confounders for malignancies and/or infections are listed in Protocol Appendix 7 and a list of confounding factors included in propensity score analysis is presented in RAP Table 4.

9.5. Data sources and measurement

The schedule of data collection to be performed for the study is presented in the protocol Table 6-1.

Site personnel recorded all data for each study participant through eCRFs.

Data was collected from medical records and during clinic visits.

9.6. Bias

Due to the observational design, there are some sources of bias in this study:

Selection bias occurs when the participants included in the study are not representative of the target population. To address this, only few inclusion and exclusion criteria were selected to reflect the real-world population and to enhance generalizability. Information bias can result from inaccurate recording of data, missing data or erroneous recall historical data. To minimize information bias, the EDC system automatically generated queries resulting from the computed checks to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff were also generated.

Reporting bias might be created if participants receiving commercially available belimumab may be seen more often by their medical care providers as compared to the bi-annual visits of standard of care participants.

Confounding bias may have been present if any factors influenced the treatment a participant received and the outcome of interest. To attempt to address this bias, propensity score analysis methods were introduced into the BEL116543 study final analysis. Key covariates were included in the propensity score models (see RAP Table 4). They were selected based on clinical judgment.

9.7. Study size

This registry targeted enrollment was approximately 3000 participants (approximately 2000 Benlysta plus standard of care [Benlysta exposure group] and 1000 standard of care only [comparison Non-Benlysta exposure group]). Each participant was expected to be followed for 5 years, contributing to an estimated total of approximately 7773 participant-years in the Benlysta exposure group and 3886 participant-years in the Non-Benlysta exposure group, respectively, assuming a 10% annual participant drop-out rate and not accounting for crossover (estimates at the time of protocol development).

The registry was expected to allow the difference in mortality rate in the Benlysta exposure group and Non-Benlysta exposure group to be established with a 95% CI of ±0.32 per 100 participant-years, based on an estimated mortality rate of 0.68 per 100 participant-years in both treatment groups (Table 1). The estimated mortality rate (rates calculated based on data available at the time protocol was written) was based on the mortality rate in the pooled primary safety database in SLE participants derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE CRD studies (i.e., integrated database of LBSL02 [placebo-controlled treatment phase only], HGS1006-C1056/BEL110751, and HGS1006-C1057/BEL110752) for all participants (Benlysta and placebo) adjusted for participant-years. The precision of the rates of the AESI are provided in Table 1.

Table 1 Precision of Differences in Adverse Event Rates Estimated from an expected 7773 Participant-years in the Benlysta Exposure Group and 3886 Participant-years in the Comparison Group, Respectively

AEs	Reference Rate[a] (per 100 participant-years)	95% CI for difference in AE rates[b] (per 100 participant-years)
All Deaths	0.68	±0.32
Serious infection	5.80	±0.93
Opportunistic infection	0.136	±0.14
Malignancy (excl. NMSC)	0.226	±0.19
NMSC	0.226	±0.19
Serious psychiatric events	0.410	±0.25

a. The reference AE rates were based on the AE rates in the pooled primary safety database (derived from the IV SLE CRD studies LBSL02, HGS1006-C1056, HGS1006-C1057) adjusted for participant-years (data available at the time the protocol was written).
b. Assuming that the AE rates in Benlysta and the control groups were the same as the reference rate.

9.8. Data transformation

Study variables that were calculated, derived or transformed are listed in RAP Appendix 5.

The following changes were made at individual participant level:

- One participant was not able to be reconsented after informed consent loss. As the site was closed, deletion of the participant in EDC was not possible and the participant was deleted at ADAM level in the Analysis Dataset Subject Level with proper documentation..
- For 3 participants sites reported corticosteroid dose of 0 instead of unknown due to EDC limitation. A hardcoding was done for these participants at ADAM level in the Steroid dataset for the average dose in the past 6 months, dose units, and average dose category in the past 6 months. These variables were flagged as missing. Consequently, the variables average dose in the past 6 months, corticosteroids change from Baseline and analysis dose automatically remained as missing.
- For 10 participants, sites reported a smoking duration of 0 instead of unknown due to EDC limitation. A hardcoding was done for these participants at ADAM level in the Analysis Dataset Substance Use for the duration of substance use. This variable was flagged as missing. Consequently, duration of substance use in years automatically remained as missing. as missing.

Details are provided in the Data Handling Report.

9.9. Statistical methods

9.9.1. Main summary measures

Categorical variables were summarized as the number of participants and percentages (%) of participants in each category. Percentages did not include the missing category and were calculated over the number of participants with available (non-missing) data.

Continuous variables were summarized using the mean, SD, median, first and third quartiles (Q1, Q3), minimum (min), maximum (max).

9.9.2. Main statistical methods

9.9.2.1. General methods

All analyses were conducted using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA).

Unless otherwise specified, analyses were performed using Evaluable analysis population and presented separately for Current Users and Treatment Initiators study cohorts.

No formal statistical hypotheses testing was conducted since there was no pre-specified hypothesis for any of the study endpoints. The 95% CI was computed for rates to contextualize the extent of random error but was not used for formal statistical hypothesis testing.

Study exposure and sub-group display descriptors

Exposure group comparisons were displayed using the following specified descriptors:

- Benlysta vs Non-Benlysta

Benlysta group is used for participants who are exposed to Benlysta while Non-Benlysta group is used for participants who are not exposed to Benlysta. For summary description of baseline characteristics, the exposure group represents participants' exposure at enrollment (i.e., Initial Exposure).

For summary of safety and effectiveness endpoints, the exposure group was defined using the Initial Exposure, As-Exposed, and/or Ever-Exposed strategies.

As-Exposed was defined based on whether or not a participant is using Benlysta at specific period during the study follow-up time; thus, a participant's exposure group could change over time depending on switching[1] to or off Benlysta.

Ever-Exposed was defined based on whether a participant was exposed to Benlysta at any point in time after enrollment, in this instance a participant's exposure could change only once over time if they were initially Unexposed and then started using Benlysta; once a participant is exposed to Benlysta, they will always be considered As-Exposed.

The Initial Exposure strategy was used to derive weights from the Propensity Scores model for the weighted analyses (see Section 9.9.2.6). This exposure included 2 different analysis approaches:

- Intent-To-Treat (ITT) and
- While On Initial Exposure.

[1] Participants were considered to have switched from Benlysta exposure group if they permanently discontinued Benlysta treatment or missed doses of Benlysta for more than 98 days and did not restart doses of Benlysta on or before Day 99 after the last Benlysta medication end date. Participants were considered to have switched from Non-Benlysta exposure group if they initiated or started receiving Benlysta dose anytime during the study follow-up period. Change of different study-qualifying Non-Benlysta Standard of Care medications did not count as exposure switching.

9.9.2.2. Analysis populations

Table 2 Analysis Population and Study Cohort

Population	Definition / Criteria	Analyses Evaluated
Enrolled	All participants who were enrolled irrespective of whether they met the inclusion/exclusion criteria.	Study Progress
Eligible	Participants in the Enrolled population who met the inclusion/exclusion criteria[a] assigned to either Benlysta or Non-Benlysta group.	Study Population Other Covariates
Evaluable	Subset of the Eligible population with a collection of enrollment data and at least 1 post baseline assessment.	Safety Effectiveness
Sensitivity Analysis		
Sensitivity	Participants in the Enrolled population who were on combination of medications that included both anti-malarials and corticosteroids, or who were in the Eligible population[b]	Study Population
Evaluable Sensitivity	Subset of the Sensitivity population with a collection of enrollment data and at least 1 post-baseline assessment	Safety

a. Based on medications reported in the SLE Medications page and/or baseline corticosteroids page of the eCRF.
b. Compared to the Eligible population, the Sensitivity population was also included participants on combination of medications that include both anti-malarials and corticosteroids, without immunosuppressant at enrollment. These participants were assigned exposure group = Non-Benlysta and used only for a sensitivity analysis.

9.9.2.3. Study population analyses

Study population analyses were based on the Eligible population. These analyses include descriptive summaries of participant's disposition, demographic and baseline characteristics, SLE concomitant medications, historical and baseline medical/disease condition, baseline SLEDAI 2000 (SLEDAI 2000 composite score) and SLE diagnosis. All baseline characteristics summaries are presented by exposure group (Benlysta or Non-Benlysta) for the 2 study cohorts (Current Users and Treatment Initiators).

In addition, the following statistical analyses to describe the rate and risk/probability of study withdrawal were performed:

- Study withdrawal rate
- The rate of study withdrawal using Kaplan-Meier estimator
- Survival probability (the probability of not withdrawing from the study).

9.9.2.4. Safety analyses

A programming process was performed for the creation of AE flags and adjudication variables for assigning each AE to at least a specific AESI category using the current

version of Benlysta Program Safety Analysis Plan term of interest and the GSK Medical Dictionary for Regulatory Activities dictionary in effect at the time of reporting. Any AE terms that could not be automatically categorized were flagged for manual review by GSK medical monitor and GSK safety and risk management physician. Please see RAP Section 9.3 for more details.

All primary endpoint analyses (AESIs) were performed using Evaluable analysis population and comparison was by exposure group (Benlysta vs Non-Benlysta) defined based on exposure assignment strategies: Initial Exposure, As-Exposed (Time Varying), and/or Ever-Exposed (see RAP Section 9.2).

The primary safety endpoint is each category of AESI (listed in Section 7) experienced by participants during study follow-up period.

The summary measures for the safety endpoints are:

- Cumulative count of all AESI combined and count of participants (number and percentage) experiencing at least 1 AESI.
- Cumulative count of each specific AESI category and count of participants (number and percentage) experiencing at least 1 occurrence of each specific AESI category.
- Incidence proportion (expressed as %) for each specific AESI category.
- Incidence rate (see RAP Section 7.1.5.1) for each specific AESI category.
- Event rate (see RAP Section 7.1.5.1) for each specific AESI category (except mortality).

Incidence and event rates were calculated and reported per 100 participant-years. The 95% CI for the rate was calculated assuming an exact Poisson distribution method.

Incidence Rates

Incidence rate was defined as the number of at-risk participants experiencing first event (i.e., number of new cases) during the specified follow-up period divided by total participant-years at-risk of that event for Eligible participants at-risk. The total participant-years-at-risk were calculated for each event type separately.

Event Rates

Event rate was estimated for potentially recurrent events and represents average number of events per unit time of follow-up. It was defined as total number of events experienced by participants during the specified study period divided by total participant-years of follow-up.

9.9.2.5. Effectiveness analyses

The analyses were conducted using Evaluable analysis population and by study exposure defined using the Initial Exposure strategy and/or by strata of clinical covariates listed in RAP Section 5.6.1.

Effectiveness endpoints are listed in Section 7 and in RAP Section 7.2.1.

The following measures were used to summarize endpoints:

- Continuous endpoints such as absolute and change from baseline SDI score, absolute and change from baseline average corticosteroids dose (mg/day).
- Summary statistics including number of observations, mean, SD, median, range (min; max) and interquartile range (Q1; Q3).
- Categorical binary, nominal and/or ordinal endpoints such as SLE medication use (immunosuppressants vs. others), use of corticosteroids (Yes or No), oral corticosteroids dose (mg/day) use (Always <7.5 mg/day, ≥7.5 mg/day for ≤2 weeks or ≥7.5 mg/day for > 2 weeks), presence or absence of each SDI domain item, and SDI worsening (change from baseline ≥1).
- Proportion or frequency (number and percentage) of participants.
- Count of events such as hospitalizations:
- Incidence and events rates with 95% CI.

9.9.2.6. Propensity score analysis

Propensity score analysis was used to control for confounding bias of the BEL116543 study final analysis. Of note, statistical methods used for propensity score analysis applied to primary objectives only and were conducted on the Evaluable population.

First step of analysis: Inverse probability of treatment weighting (IPTW)

Propensity scores were computed as the probability of being exposed to Benlysta at enrollment given an individual's baseline characteristics. Logistic regression was used to derive the PS. Non-stabilized weights (i.e., IPTW) for each individual were calculated as the inverse of the probability of receiving the actual exposure. For more information see RAP Section 7.3.1.

Second step of analysis: Outcome analysis

The primary outcome model was a weighted Poisson regression based on stabilized weights. Weighted incidence rates and event rates were calculated and presented. For further details see RAP Section 7.3.1.5.

9.9.2.7. Sub-group analyses

Current Users and Treatment Initiators

Descriptive summaries and statistical analyses were performed separately for the 2 study cohorts (Current Users and Treatment Initiators).

Study Cohort[a]	Definition / Criteria
Current Users	Participants who have received or started qualifying medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1)
Treatment Initiators	Participants who have initiated or started qualifying medication(s) in the last 2 months (<62 days) prior to enrollment into the study (i.e., Baseline SLE medication initiation <62 days from study Day 1)

a. Study cohort determined for Eligible participants only.

For the purpose of study cohort assignment to either a current user or a treatment initiator, the following rules were used to determine when a participant first received Benlysta and/or Non-Benlysta SLE medications:

- For Benlysta participants: this was the start date of earliest baseline Benlysta medication.
- For Non-Benlysta participants: this was the start date of study-qualifying Non-Benlysta SLE medications or the most recently added immunosuppressant if they were on multiple medications at baseline.

Elderly analyses

- For the elderly population, a sub-group summary was performed as part of the EOS reporting (to fulfil the elderly analysis post-approval commitment). Any analysis for elderly sub-group was restricted to participants aged 65 years and older, grouped as ≥65 years and ≥75 years if feasible.

9.9.3. Missing values

Element	Reporting Detail
Study Withdrawals	
General	• Participant study completion (i.e., as specified in the protocol) was defined as completion of the 5-year follow-up following enrollment into study. • Withdrawn participants were not replaced in the study. Participants who developed AESI remained in the study except for fatality event, withdrawal of consent or withdrawal at physician discretion. • All available data from participants who were withdrawn from the study were listed and all available data were included in summary Tables and Figures.
Handling of Missing Data	
General	Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: • These data were indicated using a "blank" in participant listing displays, unless all data for a specific timepoint were missing in which case the data were excluded from the Table. • Answers of "NA" (i.e., within the section Serious AESI) were not considered to be missing data and were displayed as such.
Data Collection Stopped	For effectiveness endpoints where collection of the underlying data has been stopped as per Protocol amendment 3, data collected for these endpoints prior to their removal from the protocol are available in the previous interim analysis reports.
Handling of Missing and Partial Dates	
General	Partial dates were displayed as captured in participant listing displays.
Adverse Events Concomitant Medications Medical History Hospitalization	The eCRF allows for the possibility of partial dates (i.e., only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the imputation followed the conventions shown in RAP Section 9.6.2.2. In the event the end date was after to the last contact date, the last contact date (RAP Section 9.5.3) was used. Completely missing start or end dates remained missing, with no imputation applied. Consequently, time to onset and duration of such events were missing (where applicable). The recorded partial date is displayed in listings; so, were not overwritten.
Handling of Missing Data for Statistical Analysis	
General	For endpoints not relying on multiple questionnaire items, missing values were not imputed. Data were analyzed only for the time point at which they were collected.

Element	Reporting Detail
SDI Domains	If any item was missing, the total score is missing. However, if the missing item has previously been scored on previous visits, the worst observation was carried forward for that item. If the SDI was scored inconsistently (a decrease score at subsequent follow-up relative to previous visit had occurred) and the data were unable to be queried and/or corrected, the previous score (before the decrease) was carried forward at the item level for the SLICC/Damage Index questions, this corresponds to 'worst observation carried forward'. These carried forward values at items level were then used to calculate the total score which was the value summarized and displayed for reporting.
SLEDAI 2000 Score	For the calculation of SLEDAI 2000 score, all items were taken from the completed SLEDAI 2000 eCRF page; no imputation was performed. Scores for any SLEDAI 2000 items were used as observed. Participants with at least 1 missing, i.e., 'not done' value at baseline assessment were excluded from the analysis of SLEDAI 2000 total score.

Missing Data on Covariates in Propensity Score Model

Among the variables, BMI, Race, Ethnicity, SDI and SLEDAI 2000 score are reported with missing values. The rules below are applied:

The missing data for individual variables were coded into a "missing" category for categorical variables to allow all participants to be used in the analysis; for continuous measures, missing data were set to a fixed value (i.e., median) and an indicator variable was added in the model.

However, in the case of very few missing cases (<10):

- The modal category was assumed for categorical variables.
- The indicator variable was omitted from the model for continuous variable

Specific case of baseline SLEDAI 2000 (SLEDAI 2000 composite score):

- The Assessments of SLEDAI 2000 score consist of 24 individual items (see RAP Section 9.5.5) in which signs and symptoms, laboratory tests, and physician's assessment for each of 9 organ systems are given a weighted score and summed if present (marked 'Yes').
- A 'Clinical SLEDAI 2000 score' was computed considering all items except 'Low Complement' and 'Increased DNA Binding'. The clinical SLEDAI 2000 was computed based on the remaining 22 items, with either 'absent' or 'not done' being regarded as 0.

- A corresponding variable ‘total not-done points’ calculating the sum of not done weights was also included in the model. ‘Total not done points’ = 0 for participants who were assessed for all items. ‘Total not done points’ = 18 for participants with maximum (6) not done items. The variable’s inclusion was to allow the model to differentiate between participants who had scored x points/101 available compared to participants who had scored x points/83 available, or anywhere in between.
    - If the SLEDAI 2000 form was completely missing, then median clinical SLEDAI 2000 (based on participants who answered >0 questions) and median ‘total not done points’ were assumed, and an indicator variable was added in the model.

9.9.4. Sensitivity analyses

Sensitivity analyses were conducted using the Sensitivity (study population analyses) and Evaluable Sensitivity (safety analyses) populations. For details of the planned displays see RAP Appendix 11.

9.9.5. Amendments to the statistical analysis plan

Several changes to planned statistical analyses were made on individual participant level after database lock that were not foreseen in the RAP. These are described in Section 9.8.

Age was not calculated as stated in RAP Section 9.5.3 (‘Any subject with a missing date and month will have this imputed as ‘30th June’’), but as difference in YEAR between the birth date and enrollment date.

9.10. Quality control

Site personnel recorded all data for each study participant through eCRFs using an EDC system provided and approved by the sponsor. Sites were expected to complete the eCRFs in a timely manner and investigators were to promptly review completed eCRFs for each participant. As the person ultimately responsible for the accuracy of all eCRF data, the Investigator signed the Investigator's Statement in each participant's eCRF at study completion.

The EDC system automatically generated queries resulting from the computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff were also generated within the EDC system, where they were tracked. Sites resolved the queries and corrected the entered data when necessary. All data changes were captured in the EDC system audit trail.

Upon completion of the study, or after reaching a pre-specified point in the study, Data Management locked the database and generated the SAS datasets necessary for data analysis and reporting. Upon completion of the study, each site was provided with the eCRFs for each of their participants.

The investigators were to retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They were to retain for the longer of the maximum period required by the country and institution in which the study was conducted, or the period specified by the sponsor at the time the study was completed, terminated, or discontinued. If the investigator left the institution, the records were to be transferred to an appropriate designee who accepted the responsibility for record retention.

10. RESULTS

10.1. Participants

10.1.1. Study population

A full breakdown of study populations is shown in Table 3.

In summary (Enrolled population):

- A total of 3133 participants were enrolled into the study.
- 2967 out of 3133 enrolled participants (937 Non-Benlysta and 2030 Benlysta) were included in the Eligible population, 3041 participants were included in the Sensitivity population, and 2873 participants were included in the Evaluable Sensitivity population.
- Among the Eligible population, >75% of participants were Current Users, with a higher proportion in the Non-Benlysta than in the Benlysta exposure group.

Table 3 Study Populations (Population: Enrolled)

Population	Number (%) of participants		
	Non-Benlysta	Benlysta	Total (N=3133)
Eligible participants[a]	937	2030	2967
Current Users[b]	814/937 (86.9%)	1543/2030 (76.0%)	2357/2967 (79.4%)
Treatment Initiators[c]	123/937 (13.1%)	487/2030 (24.0%)	610/2967 (20.6%)
Evaluable participants[d]	881/937 (94.0%)	1924/2030 (94.8%)	2805/2967 (94.5%)
Current Users[b]	771/814 (94.7%)	1464/1543 (94.9%)	2235/2357 (94.8%)
Treatment Initiators[c]	110/123 (89.4%)	460/487 (94.5%)	570/610 (93.4%)
Sensitivity[e]	1011	2030	3041
Evaluable Sensitivity[f]	949	1924	2873

Source: Table 1.000; Data for each of the 6 month visits were available, but not presented.

a. Excluded 87 participants due to an inclusion/exclusion violation identified after study enrollment, and additional 74 participants who were on combination of medications that include both anti-malarials and corticosteroids (without immunosuppressant) at enrollment and 5 participants due to the lack of baseline treatment information.

b. Current Users were participants assigned to Benlysta or Non-Benlysta Initial Exposure group who had received or started qualifying medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study.

c. Treatment Initiators were participants assigned to Benlysta or Non-Benlysta Initial Exposure group who had initiated or started qualifying medication(s) for <2 months (<62 days) prior to enrollment (Day 1) into the study.
d. Evaluable population: Subset of the Eligible population with a collection of enrollment data and at least 1 post baseline assessment.
e. Sensitivity population: Participants in the Enrolled population who were on combination of medications that included both anti-malarials and corticosteroids (without immunosuppressant) at enrollment, or who were in the Eligible population.
f. Evaluable Sensitivity population: Subset of the Sensitivity population with a collection of enrollment data and at least 1 post-baseline assessment.

10.1.2. Enrollment by country

The majority of participants were enrolled in Europe and the US. Enrollment by country for the Eligible population is presented in Table 4.

Table 4 Enrollment by Country (Population: Eligible)

Country (number of sites)	Number (%) of participants		
	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Argentina	17 (1.8%)	22 (1.1%)	39 (1.3%)
Austria	2 (0.2%)	9 (0.4%)	11 (0.4%)
Belgium	1 (0.1%)	4 (0.2%)	5 (0.2%)
Canada	64 (6.8%)	56 (2.8%)	120 (4.0%)
France	25 (2.7%)	60 (3.0%)	85 (2.9%)
Germany	65 (6.9%)	174 (8.6%)	239 (8.1%)
Israel	45 (4.8%)	72 (3.5%)	117 (3.9%)
Italy	40 (4.3%)	112 (5.5%)	152 (5.1%)
Portugal	5 (0.5%)	11 (0.5%)	16 (0.5%)
Slovakia	5 (0.5%)	33 (1.6%)	38 (1.3%)
Spain	57 (6.1%)	125 (6.2%)	182 (6.1%)
Sweden	0	3 (0.1%)	3 (0.1%)
United States	611 (65.2%)	1349 (66.5%)	1960 (66.1%)

Source: Table 4.000.
Not shown: Table 5.000.

10.1.3. Participant disposition

The study completion status and reasons for withdrawal are shown in Table 5.

In summary (Eligible population):

- 50.4% of participants completed the study (54.1% Non-Benlysta vs 49.9% Benlysta).
- 49.2% withdrew from the study (48.2% Non-Benlysta vs 49.6% Benlysta).
- The most common reason for study withdrawal was Lost to follow-up (25.8%) (25.0% Non-Benlysta vs 26.2% Benlysta).

- Participant disposition was similar between Non-Benlysta and Benlysta exposure groups. This also included withdrawals due to AEs which were similar between the exposure groups over a period of 5 years.

Table 5 Completion Status (Population: Eligible)

	Number (%) of participants[a]		
	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Study Completion Status			
Completed	482 (51.4%)	1013 (49.9%)	1495 (50.4%)
Withdrawn	452 (48.2%)	1007 (49.6%)	1459 (49.2%)
Missing EOS forms	3 (0.3%)	10 (0.5%)	13 (0.4%)
Reason for withdrawal			
AE[b]	28 (3.0%)	56 (2.8%)	84 (2.8%)
AESI	0	4 (0.2%)	4 (0.1%)
Other AE (not of special interest)	0	4 (0.2%)	4 (0.1%)
Death	28 (3.0%)	48 (2.4%)	76 (2.6%)
Lost to follow-up[c]	234 (25.0%)	531 (26.2%)	765 (25.8%)
Withdrew consent	54 (5.8%)	166 (8.2%)	220 (7.4%)
Investigator discretion	79 (8.4%)	175 (8.6%)	254 (8.6%)
Study closed/terminated	57 (6.1%)	79 (3.9%)	136 (4.6%)

Source: Table 2.000.

a. Percentages were calculated from N (number of participants in header column).
b. Number of participants with AE and those who died was based on information from eCRF EOS page and not from AE reporting page.
c. The reason for the withdrawal of 1 participant from the Non-Benlysta group was incorrectly reported as 'Lost to Follow-up'. It should have been reported as an AE and death.

Time to study withdrawal is shown in Table 6. A plot of projected vs. observed withdrawal probabilities is provided in Source Figure 2.000. Withdrawal rates in both exposure groups were close to the projected withdrawal rates (<10% difference).

In summary (Eligible population, 0-60+ Months Time-Period):

- Cumulative number of withdrawals were similar between Benlysta and Non-Benlysta exposure groups over time.
- Overall, the withdrawal survival probability showed downward trend while withdrawal probability showed upward trend in both Non-Benlysta and Benlysta exposure groups.
- The pattern of observed for the Current Users and Treatment Initiators was similar to the overall population (Source Table 50.001 and Table 50.002). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 6 Time to Study Withdrawal (Initial Exposure [ITT] Strategy; Population: Eligible)

	0-12 Month		>12-24 Month		>24-36 Month		>36-48 Month		>48-60 Month[a]	
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Cumulative number of withdrawals[b]	106 (11.3%)	220 (10.8%)	168 (17.9%)	434 (21.4%)	247 (26.4%)	595 (29.3%)	315 (33.6%)	719 (35.4%)	433 (46.2%)	970 (47.8%)
Number at risk at the start of the time period (n)	937	2030	831	1810	769	1596	690	1435	622	1310
Number of withdrawals during the time period[c]	106 (11.3%)	220 (10.8%)	62 (7.5%)	214 (11.8%)	79 (10.3%)	161 (10.1%)	68 (9.9%)	124 (8.6%)	118 (19.0%)	251 (19.2%)
Withdrawal Survival probability (%)[d] (95% CI)	88.69 (86.48,90.55)	89.16 (87.73,90.44)	82.07 (79.46,84.38)	78.62 (76.77,80.34)	73.64 (70.69,76.34)	70.69 (68.66,72.62)	66.38 (63.26,69.31)	64.58 (62.46,66.62)	53.46 (50.19,56.62)	51.90 (49.69,54.07)
Withdrawal probability (%)[d] (95% CI)	11.31 (9.45,13.52)	10.84 (9.56,12.27)	17.93 (15.62,20.54)	21.38 (19.66,23.23)	26.36 (23.66,29.31)	29.31 (27.38,31.34)	33.62 (30.69,36.74)	35.42 (33.38,37.54)	46.54 (43.38,49.81)	48.10 (45.93,50.31)

Source: Table 50.000.

a. Time period ended on day 1827
b. Percentages based on N.
c. Percentages based on n.
d. Withdrawal and withdrawal survival probabilities were calculated using the Kaplan-Meier estimator for the last day of the time period.

10.1.4. Visit attendance and exposure switch

A full breakdown of visit attendance and exposure switch by study periods and exposure groups is provided in Table 7.

In summary (Enrolled population):

- A total of 23.3% of the total Eligible population switched to/off Benlysta at least once during the study period.
- The proportion of participants with exposure switch was generally higher in the Benlysta than the Non-Benlysta exposure group.
- The proportion of participants with exposure switch increased over time in both exposure groups. At the 60 month visit, 17.4% of participants in the Non-Benlysta group and 34.4% in the Benlysta group had switched treatment.
- The pattern of observed for the Current Users and Treatment Initiators was similar to the overall population. However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 7 Visit Attendance and Exposure Switch (Population: Enrolled)

	Current Users		Treatment Initiators		Total		
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Total
Eligible participants	814/937 (86.9%)	1543/2030 (76.0%)	123/937 (13.1%)	487/2030 (24.0%)	937	2030	2967
No exposure group switch	718/814 (88.2%)	1132/1543 (73.4%)	96/123 (78.0%)	330/487 (67.8%)	814/937 (86.9%)	1462/2030 (72.0%)	2276/2967 (76.7%)
Switch exposure group	96/814 (11.8%)	411/1543 (26.6%)	27/123 (22.0%)	157/487 (32.2%)	123/937 (13.1%)	568/2030 (28.0%)	691/2967 (23.3%)
Attended Month 12 Visit[a]	642/814 (78.9%)	1242/1543 (80.5%)	85/123 (69.1%)	389/487 (79.9%)	727/937 (77.6%)	1631/2030 (80.3%)	2358/2967 (79.5%)
Switch exposure group on or before the visit	36/642 (5.6%)	139/1242 (11.2%)	11/85 (12.9%)	65/389 (16.7%)	47/727 (6.5%)	204/1631 (12.5%)	251/2358 (10.6%)
Attended Month 24 Month Visit[a]	574/814 (70.5%)	1064/1543 (69.0%)	75/123 (61.0%)	324/487 (66.5%)	649/937 (69.3%)	1388/2030 (68.4%)	2037/2967 (68.7%)
Switch exposure group on or before the visit	45/574 (7.8%)	216/1064 (20.3%)	15/75 (20.0%)	93/324 (28.7%)	60/649 (9.2%)	309/1388 (22.3%)	369/2037 (18.1%)
Attended Month 36 Visit[a]	517/814 (63.5%)	937/1543 (60.7%)	72/123 (58.5%)	289/487 (59.3%)	589/937 (62.9%)	1226/2030 (60.4%)	1815/2967 (61.2%)
Switch exposure group on or before the visit	49/517 (9.5%)	238/937 (25.4%)	19/72 (26.4%)	105/289 (36.3%)	68/589 (11.5%)	343/1226 (28.0%)	411/1815 (22.6%)

	Current Users		Treatment Initiators		Total		
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Total
Attended Month 48 Visit[a]	475/814 (58.4%)	873/1543 (56.6%)	60/123 (48.8%)	241/487 (49.5%)	535/937 (57.1%)	1114/2030 (54.9%)	1649/2967 (55.6%)
Switch exposure group on or before the visit	65/475 (13.7%)	258/873 (29.6%)	14/60 (23.3%)	95/241 (39.4%)	79/535 (14.8%)	353/1114 (31.7%)	432/1649 (26.2%)
Attended Month 60 Visit[a]	425/814 (52.2%)	794/1543 (51.5%)	57/123 (46.3%)	219/487 (45.0%)	482/937 (51.4%)	1013/2030 (49.9%)	1495/2967 (50.4%)
Switch exposure group on or before the visit	68/425 (16.0%)	257/794 (32.4%)	16/57 (28.1%)	91/219 (41.6%)	84/482 (17.4%)	348/1013 (34.4%)	432/1495 (28.9%)

Source: Table 1.000. Data is available for all 6-mothly visits but not shown here.

Note: Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <months (< 62 days) prior to enrollment (Day 1) into the study.

a. Month xx attendees were participants who attended the month xx visit. Anyone who missed month xx visit but attended at least 1 of the later visits was not counted as month xx visit attendee.

10.1.5. Protocol deviations

A total of 87 participants were identified as having been enrolled despite not fully meeting inclusion/exclusion criteria. Among the Enrolled population, 1.0% of participants did not meet inclusion criteria, while 2.2% of participants met exclusion criteria, details are given in Source Table 3.000.

Throughout the study, in 742 of 2967 (25.0%) participants protocol deviations were reported. Overall, 12.0% of participants had protocol deviations classified as major with the most common being related to the informed consent (4.4%), while 4.6% of participants had critical protocol deviations with the most common being related to safety (3.8%). A full breakdown of all protocol deviations by critical, major and minor are provided in Source Table 52.000.

10.2. Descriptive data

Participant baseline data for the Eligible population are summarized in the following sections. Additional baseline data (not discussed within text) are listed in Table 18 with links to source tables.

10.2.1. Demographics

The baseline demographics data for the Eligible population are summarized in Table 8.

In summary (Eligible population):

- Overall, baseline demographics were roughly comparable between the Benlysta and Non-Benlysta exposure groups. While both groups were similar in age and BMI, a slightly higher proportion of participants in the Benlysta group were female and White as compared to the Non-Benlysta group, while the Non-Benlysta group was more ethnically diverse.
- The pattern observed in the Current Users was similar to the overall population, while, in Treatment Initiators, distribution of baseline demographics between Benlysta and Non-Benlysta exposure groups was more balanced (Source Table 6.010, and Table 6.020). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.
- The pattern observed in the Sensitivity population was similar to the Eligible population (Source Table 6.001).

Table 8 Demographics (Population: Eligible)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Age, Years			
n	937	2030	2967
Mean (SD)	44.1 (14.78)	44.4 (12.93)	44.3 (13.54)
Median	43.0	44.0	44.0
Age group, Years			
n	937	2030	2967
≥ 18-≤ 45	513 (54.7%)	1127 (55.5%)	1640 (55.3%)
>45-<65	328 (35.0%)	763 (37.6%)	1091 (36.8%)
≥65-<75	80 (8.5%)	117 (5.8%)	197 (6.6%)
≥75	16 (1.7%)	23 (1.1%)	39 (1.3%)
Sex, n (%)			
n	937	2030	2967
Female	841 (89.8%)	1899 (93.5%)	2740 (92.3%)
Male	96 (10.2%)	131 (6.5%)	227 (7.7%)
Ethnicity, n (%)			
n	937	2028	2965
Hispanic or Latino	205 (21.9%)	343 (16.9%)	548 (18.5%)
Not Hispanic or Latino	732 (78.1%)	1685 (83.1%)	2417 (81.5%)
Race, n (%)			
n	933	2023	2956
White	645 (69.1%)	1543 (76.3%)	2188 (74.0%)
Asian	64 (6.9%)	63 (3.1%)	127 (4.3%)
Black-African American or African Heritage	190 (20.4%)	342 (16.9%)	532 (18.0%)
Alaska Native or American Indian[a]	21 (2.3%)	42 (2.1%)	63 (2.1%)
Native Hawaiian or Other Pacific Islander	2 (0.2%)	5 (0.2%)	7 (0.2%)
Multiracial	11 (1.2%)	28 (1.4%)	39 (1.3%)
Height			
n	917	2013	2930
Mean (SD)	163.9 (8.28)	164.3 (8.22)	164.1 (8.24)
Median	163.0	165.0	164.0
Weight			
n	930	2028	2958
Mean (SD)	74.87 (20.512)	76.82 (21.894)	76.21 (21.485)
Median	71.85	71.80	71.80
BMI			
n	916	2012	2928
Mean (SD)	27.88 (7.238)	28.52 (8.042)	28.32 (7.804)
Median	26.64	26.67	26.66

Source: Table 6.000.

a. American Indian from North/Central/South America.

10.2.2. Medical history

In both exposure groups, the past medical conditions at baseline were generally similar, with the most common being infections, except for neoplasms which was higher in the Benlysta exposure group than in the Non-Benlysta (30.1% vs. 22.3%) (Source Table 9.011).

Past medical history for Current Users and Treatment Initiators was generally similar to the overall population, with a lower proportion of participants reporting past medical conditions at baseline in the Treatment Initiators (Source Table 9.012 and Table 9.013). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

A summary of medical conditions that were continuing at the time of study entry in the Eligible population is shown in Table 9.

In summary (Eligible population):

- The majority of participants in both exposure groups had current relevant diagnoses or medical conditions other than SLE.
- The most common current medical conditions at baseline were allergic reactions, cardiovascular risk factors, and psychiatric disorders in both exposure groups.
- The proportion of participants with allergic reactions, psychiatric disorders, and autoimmune disorders at baseline was higher in the Benlysta group than in the Non-Benlysta group.
- Current medical history for Current Users and Treatment Initiators were generally similar to the overall population (Source Table 9.022 and Table 9.023). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 9 Summary of Current Medical History at Baseline reported in ≥10% of participants in any exposure group (Population: Eligible)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Participant currently had a relevant diagnosis or medical condition other than SLE (most frequent)	741 (79.1%)	1638 (80.7%)	2379 (80.2%)
Cardiovascular risk factor			
Any	347 (37.0%)	756 (37.2%)	1103 (37.2%)
Hypertension	284 (30.3%)	599 (29.5%)	883 (29.8%)
Hyperlipidemia	143 (15.3%)	250 (12.3%)	393 (13.2%)
Allergic reactions			
Any	355 (37.9%)	848 (41.8%)	1203 (40.5%)
Drug Allergy	314 (33.5%)	746 (36.7%)	1060 (35.7%)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Autoimmune disorders			
Any	166 (17.7%)	549 (27.0%)	715 (24.1%)
Asthma	69 (7.4%)	256 (12.6%)	325 (11.0%)
Sjorgren's Syndrome	105 (11.2%)	327 (16.1%)	432 (14.6%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)			
Any	106 (11.3%)	210 (10.3%)	316 (10.7%)
Family History of Cancer	104 (11.1%)	196 (9.7%)	300 (10.1%)
Psychiatric disorders			
Any	192 (20.5%)	621 (30.6%)	813 (27.4%)
Depression	138 (14.7%)	479 (23.6%)	617 (20.8%)
Anxiety disorder	124 (13.2%)	444 (21.9%)	568 (19.1%)
Other medical conditions	365 (39.0%)	772 (38.0%)	1137 (38.3%)

Source: Table 9.021.

10.2.3. SLE disease characteristics

10.2.3.1. SLE disease duration

The baseline disease duration from diagnosis by study cohorts is summarized in Table 10. The SLE disease duration was similar between Non-Benlysta and Benlysta exposure groups in overall population. The pattern observed for the Current Users was similar to the overall population, while in Treatment Initiators SLE disease duration was higher in the Benlysta than in the Non-Benlysta exposure group and lower compared with the overall population based on the mean duration and category analyses. However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 10 Summary of SLE Disease Duration at Baseline by Study Cohort (Population: Eligible)

	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
SLE duration since diagnosis (Years)						
n	814	1543	123	487	937	2030
Mean (SD)	11.31 (9.069)	11.12 (8.883)	7.88 (9.446)	9.13 (8.911)	10.86 (9.187)	10.64 (8.928)
Median	9.28	8.63	3.55	6.16	8.40	8.10
SLE duration category since diagnosis (Years)						
n	814	1543	123	487	937	2030

	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
0-<1	34 (4.2%)	53 (3.4%)	33 (26.8%)	65 (13.3%)	67 (7.2%)	118 (5.8%)
1-<5	210 (25.8%)	426 (27.6%)	32 (26.0%)	149 (30.6%)	242 (25.8%)	575 (28.3%)
5-<10	197 (24.2%)	377 (24.4%)	24 (19.5%)	97 (19.9%)	221 (23.6%)	474 (23.3%)
10-<15	141 (17.3%)	246 (15.9%)	9 (7.3%)	69 (14.2%)	150 (16.0%)	315 (15.5%)
15-<20	92 (11.3%)	176 (11.4%)	11 (8.9%)	43 (8.8%)	103 (11.0%)	219 (10.8%)
≥20	140 (17.2%)	265 (17.2%)	14 (11.4%)	64 (13.1%)	154 (16.4%)	329 (16.2%)

Source: Table 12.000.
Note: Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (<62 days) prior to enrollment (Day 1) into the study.

10.2.3.2. SDI

The summary of baseline SDI for the Eligible population is provided in Table 11.

In summary (Eligible population):

- At baseline, organ damage as assessed by SDI scores and distribution of participants across SDI score categories were comparable between Benlysta and Non-Benlysta exposure groups.
- Most common SDI score components were musculoskeletal followed by neuropsychiatric and ocular in both exposure groups.

Table 11 Summary of Baseline SDI [Population: Eligible]

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
SDI score			
Participants with SDI data (n)	931	2003	2934
Mean (SD)	1.2 (1.58)	1.2 (1.59)	1.2 (1.59)
Median	1.0	1.0	1.0
SDI score category			
0	418 (44.9%)	909 (45.4%)	1327 (45.2%)
1	239 (25.7%)	481 (24.0%)	720 (24.5%)
2	126 (13.5%)	294 (14.7%)	420 (14.3%)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
≥3	148 (15.9%)	319 (15.9%)	467 (15.9%)
SDI score components (reported in ≥10% of participants in any group)			
Ocular	110 (11.8%)	257 (12.8%)	367 (12.5%)
Any cataract ever	86 (9.2%)	204 (10.2%)	290 (9.9%)
Neuropsychiatric	116 (12.5%)	307 (15.3%)	423 (14.4%)
Renal	106 (11.4%)	103 (5.1%)	209 (7.1%)
Musculoskeletal	151 (16.2%)	343 (17.1%)	494 (16.8%)
Skin	74 (7.9%)	201 (10.0%)	275 (9.4%)

Source: Table 11.000.
Note: The numbers in each subcategory of an SDI component may not add up to the component's main category total because participants may be included in more than 1 subcategory. Percentages were calculated using 'Participants with SDI data (n)' as denominator.

10.2.3.3. SLEDAI 2000

The SLE disease activity as measured by SLEDAI 2000 for the Eligible population are summarized in Table 12. The SLEDAI 2000 data was available only for a subset of participants and hence should be interpreted with caution.

In summary (Eligible population),

- SLEDAI score was similar between the exposure groups.
- In the Current Users SLEDAI score was more balanced between Benlysta and Non-Benlysta exposure groups than in the overall population (Table 12 and Source Table 10.012).
- In the Treatment Initiators mean SLEDAI score was higher in the Non-Benlysta than in the Benlysta exposure group and generally higher than the overall population (Table 12 and Source Table 10.013). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 12 Summary of SLEDAI 2000 at Baseline (Population: Eligible)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
SLEDAI 2000 score[a]			
Participants with data on all SLEDAI components (n)	391 (41.7%)[b]	672 (33.1%)[b]	1063 (35.8%)[b]
Mean (SD)	5.1 (4.73)	5.6 (4.75)	5.4 (4.75)
Median	4.0	4.0	4.0
SLEDAI 2000 score category[a,c]			
0	61 (15.6%)	90 (13.4%)	151 (14.2%)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
1-3	97 (24.8%)	137 (20.4%)	234 (22.0%)
4-7	137 (35.0%)	254 (37.8%)	391 (36.8%)
8-11	55 (14.1%)	110 (16.4%)	165 (15.5%)
≥12	41 (10.5%)	81 (12.1%)	122 (11.5%)
SLEDAI 2000 group[a,c]			
<10	329 (84.1%)	548 (81.5%)	877 (82.5%)
≥10	62 (15.9%)	124 (18.5%)	186 (17.5%)
Participants with data on at least 1 SLEDAI Component	932	2008	2940
SLEDAI components (weight) (reported in ≥10% of participants on any group)[d]			
Arthritis	228 (24.5%)	716 (35.7%)	944 (32.1%)
Urinary casts-Not Done	395 (42.4%)	989 (49.3%)	1384 (47.1%)
Hematuria-Not Done	335 (35.9%)	879 (43.8%)	1214 (41.3%)
Proteinuria-Present	106 (11.4%)	96 (4.8%)	202 (6.9%)
Proteinuria- Not Done	368 (39.5%)	956 (47.6%)	1324 (45.0%)
Pyuria- Not Done	343 (36.8%)	901 (44.9%)	1244 (42.3%)
Rash	137 (14.7%)	482 (24.0%)	619 (21.1%)
Alopecia	101 (10.8%)	336 (16.7%)	437 (14.9%)
Mucosal ulcers	66 (7.1%)	210 (10.5%)	276 (9.4%)
Low complement-Present	260 (27.9%)	452 (22.5%)	712 (24.2%)
Low complement-Not Done	291 (31.2%)	775 (38.6%)	1066 (36.3%)
Increased DNA binding-Present	271 (29.1%)	496 (24.7%)	767 (26.1%)
Increased DNA binding- Not Done	352 (37.8%)	901 (44.9%)	1253 (42.6%)
Thrombocytopenia-Not Done	214 (23.0%)	523 (26.0%)	737 (25.1%)
Leukopenia- Not Done	207 (22.2%)	498 (24.8%)	705 (24.0%)

Source: Table 10.011.

a. Excluded participants with no SLEDAI 2000 assessment at all or at least 1 lab item 'Not Done'.
b. Percentages were calculated by hand.
c. Percentages were calculated using n (number of participants with no SLEDAI components data missing or 'Not Done') as denominator.
d. Percentages were calculated using n2 (number of participants with data on at least 1 SLEDAI component) as denominator.

10.2.3.4. SLE medications

The frequency and duration of prior SLE medications in use at baseline is provided in Table 13 and Table 14. A plot showing baseline medication groupings is provided in Figure 1.

In summary (Eligible population):

- All participants in both exposure groups received SLE medications at baseline.
- Most common concomitant SLE medications at baseline other than Benlysta were anti-malarials, azathioprine, mycophenolate mofetil and methotrexate.
- The proportion of participants with immunosuppressants in use at baseline was lower in the Benlysta than the Non-Benlysta exposure group, while the use of SLE medications other than immunosuppressants was similar.
- The most frequent combination therapies were anti-malarials+corticosterioids+immunosuppressants in both exposure groups, followed by anti-malarials+immunosuppressants in the Non-Benlysta group and anti-malarials+corticosterioids in the Benlysta group.
- The median duration of prior SLE medications was similar between Non-Benlysta and Benlysta exposure groups.
- The pattern observed for Current Users was similar to the overall population, while in the Treatment Initiators, the use of immunosuppressants other than mycophenolate in the Non-Benlysta group was higher than in the overall population and Current Users. In addition, in the Treatment Initiators, median duration of prior SLE medications was lower than both Current Initiators and the overall population, and higher in the Benlysta than in the Non-Benlysta exposure group (Table 13 and Table 14). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Prior SLE medications not in use at baseline (historical) is provided in Source Table 14.000.

Table 13 Frequency of Prior SLE Medications in Use at Baseline reported in ≥10% of participants in any exposure group (Population: Eligible)

SLE Medication (Most frequent)	Current Users		Treatment Initiator		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
Any Immunosuppressants Use[a, b]	814 (100%)	789 (51.1%)	123 (100%)	245 (50.3%)	937 (100%)	1034 (50.9%)
Immunosuppressants Use other than mycophenolate[a, b]	477 (58.6%)	504 (32.7%)	92 (74.8%)	159 (32.6%)	569 (60.7%)	663 (32.7%)
SLE medications Use other than Immunosuppressants[a, b]	630 (77.4%)	1151 (74.6%)	99 (80.5%)	356 (73.1%)	729 (77.8%)	1507 (74.2%)
Benlysta	0	1543 (100%)	0	487 (100%)	0	2030 (100%)
Anti-malarials (e.g. hydroxychloroquine, chloroquine, quinacrine)	625 (76.8%)	1142 (74.0%)	98 (79.7%)	352 (72.3%)	723 (77.2%)	1494 (73.6%)
Azathioprine (6-mercaptopurine)	227 (27.9%)	218 (14.1%)	35 (28.5%)	88 (18.1%)	262 (28.0%)	306 (15.1%)
Mycophenolate Mofetil	360 (44.2%)	311 (20.2%)	45 (36.6%)	90 (18.5%)	405 (43.2%)	401 (19.8%)
Methotrexate	189 (23.2%)	219 (14.2%)	32 (26.0%)	60 (12.3%)	221 (23.6%)	279 (13.7%)

Source: Table 14.200

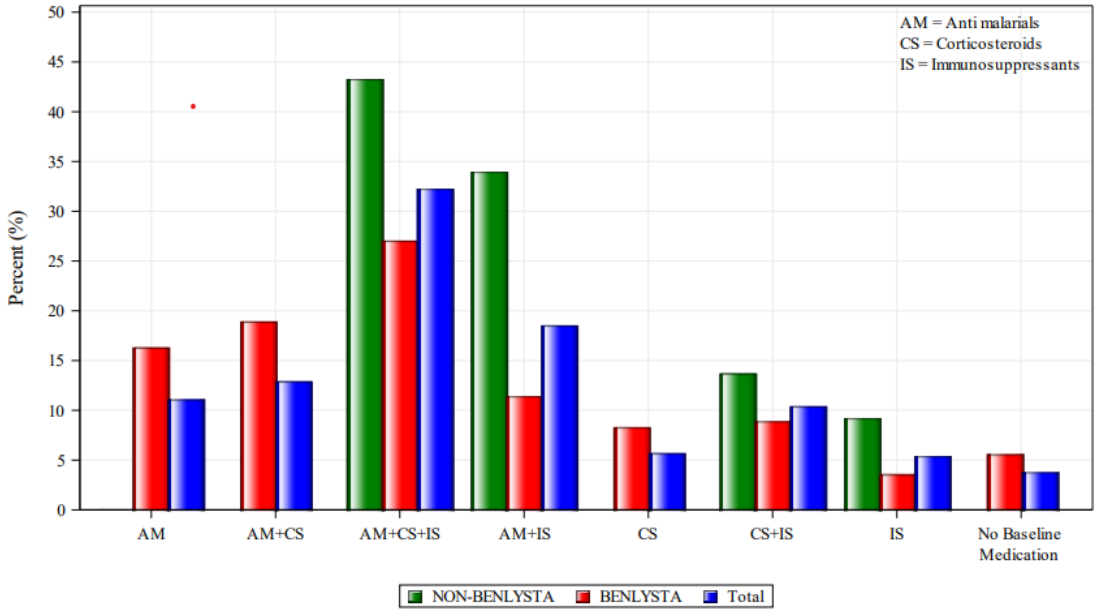
Note: Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (< 62 days) prior to enrollment (Day 1) into the study.

Corticosteroids are not included in this table.

a. Benlysta is not included.

b. Reported SLE medications were used to calculate this category.

Figure 1 Baseline Medication Groupings



Source: Figure 1.000
Note: Per treatment group, bars add up to 100%. IS does not include Benlysta.

Table 14 Duration of Prior SLE Medications in Use at Baseline by Study Cohort (Population: Eligible)

Duration (Years)	Current Users		Treatment Initiator		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
Any Immunosuppressants Use[a, b]						
n	814	789	123	245	937	1034
Mean	7.22 (5.277)	6.93 (4.792)	2.95 (2.975)	5.79 (4.441)	6.66 (5.235)	6.66 (4.734)
Median	6.10	6.17	2.32	5.12	5.69	5.93
Immunosuppressants Use other than mycophenolate[a, b]						
n	477	504	92	159	569	663
Mean	6.91 (5.658)	6.70 (5.017)	2.36 (2.349)	5.39 (4.508)	6.18 (5.525)	6.39 (4.928)
Median	**5.89**	**6.04**	**1.64**	**4.53**	**5.24**	**5.59**
SLE medications Use other than Immunosuppressants[a, b]						
n	630	1151	99	356	729	1507
Mean	10.67 (7.122)	10.58 (6.828)	6.59 (6.094)	8.94 (6.764)	10.12 (7.126)	10.20 (6.846)
Median	8.72	8.83	5.24	6.84	8.24	8.55

Duration (Years)	Current Users		Treatment Initiator		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
Benlysta						
n	0	1543	0	487	0	20230
Mean (SD)	0	4.35 (2.616)	0	2.28 (1.840)	0	3.86 (2.608)
Median	0	4.33	0	1.67	0	3.73
Anti-malarials (e.g. hydroxychloroquine, chloroquine, quinacrine)						
n	625	1142	98	352	723	1494
Mean	10.71 (7.134)	10.62 (6.831)	6.64 (6.107)	8.96 (6.790)	10.16 (7.137)	10.23 (6.856)
Median	8.72	8.87	5.27	6.84	8.28	8.57
Azathioprine (6-mercaptopurine)						
n	227	218	35	88	262	306
Mean	7.70 (6.459)	7.56 (5.521)	2.48 (2.504)	5.81 (4.715)	7.00 (6.332)	7.06 (5.353)
Median	6.20	6.75	1.51	4.41	5.65	6.11
Mycophenolate Mofetil						
n	360	311	45	90	405	401
Mean	7.61 (4.676)	7.04 (4.355)	3.76 (3.287)	6.42 (4.210)	7.18 (4.698)	6.90 (4.326)
Median	6.40	6.49	3.39	5.47	6.02	6.20
Methotrexate						
n	189	219	32	60	221	279
Mean	6.43 (4.897)	6.03 (4.422)	2.59 (2.127)	4.21 (3.430)	5.87 (4.792)	5.63 (4.289)
Median	5.68	5.63	1.80	3.79	5.06	5.11

Source: Table 14.100
Note: Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (< 62 days) prior to enrollment (Day 1) into the study.
Corticosteroids are not included in this table.
a. Benlysta is not included.
b. Reported SLE medications were used to calculate this category.

10.2.3.5. Corticosteroids usage

The corticosteroids usage at baseline for Eligible population is provided in Table 15.

In summary (Eligible population):

- The majority of participants took corticosteroids for SLE, with median duration of 3.33 years in the Non-Benlysta vs 4.58 years in the Benlysta group.

- Approximately 60% of participants were currently (at baseline) on corticosteroids (56.9% in Non-Benlysta vs 63.2% in Benlysta).
- Approximately 70% of participants used corticosteroids in the past 6 months (64.5% in Non-Benlysta vs 71.8% in Benlysta).
- The average median corticosteroid dose in the past 6 months was slightly higher in the Benlysta exposure group than in the Non-Benlysta group (5.0000 mg/day in Non-Benlysta vs 6.0000 mg/day in Benlysta).
- Most frequently participants had corticosteroid dose <7.5 mg/day or ≥7.5 mg/day for >2 weeks.

Table 15 Summary of Corticosteroids Usage at Baseline (Population: Eligible)

Corticosteroids Use	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Participant ever taken corticosteroids for SLE	873 (93.2%)	1863 (91.8%)	2736 (92.2%)
Duration of corticosteroids use (years)			
n	837	1863	2736
Mean (SD)	6.31 (7.151)	7.25 (7.437)	6.95 (7.358)
Median	3.33	4.58	4.08
Participant currently taking corticosteroids for SLE	533 (56.9%)	1283 (63.2%)	1816 (61.2%)
Used Corticosteroids for SLE in the past 6 months	604 (64.5%)	1457 (71.8%)	2061 (69.5%)
Average dose in the past 6 months (mg/day)[a]			
n	604	1457	2061
Mean (SD)	10.9850 (17.48829)	8.9241 (9.20178)	9.5281 (12.25773)
Median	5.0000	6.0000	6.0000
Average Dose category in the past 6 months			
Always <7.5 mg/day	278 (29.7%)	605 (29.8%)	883 (29.8%)
≥7.5 mg/day for ≤2 weeks	53 (5.7%)	169 (8.3%)	222 (7.5%)
≥7.5 mg/day for >2 weeks	273 (29.1%)	683 (33.6%)	956 (32.2%)
≥7.5 mg/day but <20 mg/day	142 (15.2%)	464 (22.9%)	606 (20.4%)
≥20 mg/day but <40 mg/day	69 (7.4%)	151 (7.4%)	220 (7.4%)
≥40 mg/day but <60 mg/day	39 (4.2%)	40 (2.0%)	79 (2.7%)
≥60 mg/day	20 (2.1%)	21 (1.0%)	41 (1.4%)
Parenteral: At least 1 dose ≥40 mg in past 6 months[b]	37 (3.9%)	150 (7.4%)	187 (6.3%)

Corticosteroids Use	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Intramuscular: At least 1 dose ≥40 mg in past 6 months[b]	23 (2.5%)	89 (4.4%)	112 (3.8%)

Source: Table 15.000.

a. Participants with an average dose of 324.2 mg/day were reported to have received pulse steroids.

b. Participants with both Parenteral and Intramuscular routes of administration were counted in both categories.

10.2.4. Hospitalization

A summary of hospitalizations at baseline is shown below in Table 16.

In summary (Eligible population)

- Overall, in the Eligible population, the proportion of participants with any hospitalizations and SLE related hospitalizations were similar in the Non-Benlysta and Benlysta exposure groups.
- Similar trend was observed for Current Users, while in Treatment Initiators the rates were higher in the Non-Benlysta than in the Benlysta exposure group. However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 16 Summary of Hospitalizations at Baseline by Study Cohort (Population: Eligible)

	Current Users		Treatment Initiator		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
Number of participants with any hospitalizations[a]						
at least 1 hospitalization	65 (8.0%)	119 (7.7%)	39 (31.7%)	83 (17.0%)	104 (11.1%)	202 (10.0%)
1	57 (7.0%)	101 (6.5%)	32 (26.0%)	74 (15.2%)	89 (9.5%)	175 (8.6%)
2	6 (0.7%)	15 (1.0%)	4 (3.3%)	6 (1.2%)	10 (1.1%)	21 (1.0%)
≥3	2 (0.2%)	3 (0.2%)	3 (2.4%)	3 (0.6%)	5 (0.5%)	6 (0.3%)
Number of participants with SLE-related hospitalizations[a]						
at least 1 SLE hospitalization	34 (4.2%)	55 (3.6%)	34 (27.6%)	59 (12.1%)	68 (7.3%)	114 (5.6%)
1	31 (3.8%)	48 (3.1%)	31 (25.2%)	54 (11.1%)	62 (6.6%)	102 (5.0%)
2	3 (0.4%)	5 (0.3%)	1 (0.8%)	2 (0.4%)	4 (0.4%)	7 (0.3%)
≥3	0	2 (0.1%)	2 (1.6%)	3 (0.6%)	2 (0.2%)	5 (0.2%)

Source: Table 13.000

Note: Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (< 62 days) prior to enrollment (Day 1) into the study.

a. Admission date was within 6 months prior to study enrollment. Baseline included admission on enrollment date.

10.2.5. Laboratory values

The baseline laboratory values for Eligible population are summarized in Table 17. The laboratory values were generally similar between Non-Benlysta and Benlysta exposure groups. The proportion of participants that were tested positive for proteinuria was higher (>10%) in the Non-Benlysta than the Benlysta exposure group. The pattern observed for the Current Users and Treatment Initiators was generally similar to the overall population (Source Table 19.010 and Table 19.020). However, data on Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 17 Summary of Baseline Laboratory Values (Population: Eligible)

Lab test	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
ANA status			
n	242	462	704
Positive	221 (91.3%)	419 (90.7%)	640 (90.9%)
Negative	21 (8.7%)	43 (9.3%)	64 (9.1%)
Anti-dsDNA			
n	543	1033	1576
Positive	266 (49.0%)	480 (46.5%)	746 (47.3%)
Negative	277 (51.0%)	553 (53.5%)	830 (52.7%)
C3			
n	608	1191	1799
Low	168 (27.6%)	312 (26.2%)	480 (26.7%)
Normal	424 (69.7%)	835 (70.1%)	1259 (70.0%)
High	16 (2.6%)	44 (3.7%)	60 (3.3%)
C4			
n	609	1192	1801
Low	178 (29.2%)	308 (25.8%)	486 (27.0%)
Normal	421 (69.1%)	858 (72.0%)	1279 (71.0%)
High	10 (1.6%)	26 (2.2%)	36 (2.0%)
CH50			
n	75	214	289
Low	8 (10.7%)	24 (11.2%)	32 (11.1%)
Normal	43 (57.3%)	110 (51.4%)	153 (52.9%)
High	24 (32.0%)	80 (37.4%)	104 (36.0%)
Lymphocyte differential % / count			
n	667	1379	2046
Low	176 (26.4%)	391 (28.4%)	567 (27.7%)
Normal	479 (71.8%)	964 (69.9%)	1443 (70.5%)
High	12 (1.8%)	24 (1.7%)	36 (1.8%)
IgA			
n	133	273	406
Low	7 (5.3%)	19 (7.0%)	26 (6.4%)

Lab test	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Normal	107 (80.5%)	220 (80.6%)	327 (80.5%)
High	19 (14.3%)	34 (12.5%)	53 (13.1%)
IgM			
n	132	272	404
Low	21 (15.9%)	69 (25.4%)	90 (22.3%)
Normal	105 (79.5%)	189 (69.5%)	294 (72.8%)
High	6 (4.5%)	14 (5.1%)	20 (5.0%)
IgG			
n	135	278	413
Low	8 (5.9%)	20 (7.2%)	28 (6.8%)
Normal	101 (74.8%)	199 (71.6%)	300 (72.6%)
High	26 (19.3%)	59 (21.2%)	85 (20.6%)
Total White Blood Cell Count			
n	719	1477	2196
<2000/mm^3	8 (1.1%)	24 (1.6%)	32 (1.5%)
2000-2999/mm^3	53 (7.4%)	85 (5.8%)	138 (6.3%)
3000-3999/mm^3	124 (17.2%)	204 (13.8%)	328 (14.9%)
≥4000/mm^3	534 (74.3%)	1164 (78.8%)	1698 (77.3%)
Neutrophil differential Count			
n	631	1298	1929
<1000/mm^3	32 (5.1%)	50 (3.9%)	82 (4.3%)
1000-1999/mm^3	92 (14.6%)	151 (11.6%)	243 (12.6%)
≥2000/mm^3	507 (80.3%)	1097 (84.5%)	1604 (83.2%)
Thrombocytopenia (<100000 platelets /10^9/L)	683	1435	2118
n			
Positive	18 (2.6%)	35 (2.4%)	53 (2.5%)
Negative	665 (97.4%)	1400 (97.6%)	2065 (97.5%)
Urinary Casts (Heme-granular or red blood cell casts)			
n	447	855	1302
Positive	22 (4.9%)	29 (3.4%)	51 (3.9%)
Negative	425 (95.1%)	826 (96.6%)	1251 (96.1%)
Hematuria (>5 red blood cells/high power field)			
n	539	1012	1551
Positive	73 (13.5%)	116 (11.5%)	189 (12.2%)
Negative	466 (86.5%)	896 (88.5%)	1362 (87.8%)
Proteinuria (>0.5 mg/24 hours)			
n	498	899	1397
Positive	109 (21.9%)	103 (11.5%)	212 (15.2%)

Lab test	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Negative	389 (78.1%)	796 (88.5%)	1185 (84.8%)
Pyuria (>5 white blood cells/high power field)			
n	526	981	1507
Positive	78 (14.8%)	167 (17.0%)	245 (16.3%)
Negative	448 (85.2%)	814 (83.0%)	1262 (83.7%)

Source: Table 19.000. C, Complement component, CH50; Total hemolytic compliment activity

10.2.6. Additional baseline data

Source tables showing additional baseline data (not discussed within the text above) are listed in Table 18 with links to source tables.

Table 18 Additional Baseline Tables

Source Table	Table Title
Tobacco Use/Alcohol Abuse	
7.000	Tobacco Use and Alcohol Abuse History at Baseline
7.010	Tobacco Use and Alcohol Abuse History at Baseline - Current Users
7.020	Tobacco Use and Alcohol Abuse History at Baseline - Treatment Initiators
Baseline Pregnancy Status	
8.000	Baseline Pregnancy Status
8.010	Baseline Pregnancy Status - Current Users
8.020	Baseline Pregnancy Status - Treatment Initiators
Vaccination Status	
20.000	Baseline Vaccination Status by Study Cohort

Assessments impacted by Protocol Amendment 3 (see Section 8), only baseline data were presented.

10.3. Outcome data

Study populations used for analyzing outcome data are presented in Table 2.

10.4. Main results

10.4.1. Primary endpoints

As described in Section 9.9.2.1, AESI event summaries and rate calculations were done using 4 exposure strategies:

- Initial Exposure [ITT], see Section 10.4.1.1.
- Initial Exposure [While On Initial Exposure].

- As-Exposed [Time-varying], which considers both Benlysta exposure risk windows (i.e., 14 weeks and 6 months after cessation of treatment), see Section 10.4.1.2.
- Ever-Exposed, see Section 10.4.1.3.

For convenience source tables for the 4 exposure strategies are listed below:

Table 19 Source Tables by Exposure Strategies

Exposure Strategy	Table	Subgroup
Initial Exposure [ITT]	23.000 and 24.110	Evaluable Participants
	23.0001 and 24.1101	Sensitivity Analysis
	23.010 and 24.111	Current Users
	23.020 and 24.112	Treatment Initiators
	23.200 and 23.201	Fatal events by SOC and PT
Initial Exposure [While on Initial Exposure]	23.100 and 24.120	Evaluable Participants
	23.101 and 24.1201	Sensitivity Analysis
	23.110 and 24.121	Current Users
	23.120 and 24.122	Treatment Initiators
As-Exposed [Time-Varying – 14 weeks risk window]	24.210	Evaluable Participants
	24.211	Current Users
	24.212	Treatment Initiators
As-Exposed [Time-Varying – 6 months risk window]	24.310	Evaluable Participants
	24.311	Current Users
	24.312	Treatment Initiators
Ever-Exposed	24.410	Evaluable Participants
	24.411	Current Users
	24.412	Treatment Initiators

In the sections below, numerical differences between incidence rates of the exposure groups >0.1 are described.

A listing of participant deaths and the preferred term for these events is provided in Table 52.

10.4.1.1. Initial Exposure (ITT)

In this strategy AESIs were summarized or analyzed by exposure group (Benlysta or Non-Benlysta) assigned at baseline regardless of any switching that may have occurred. Data summary for this strategy is shown in Table 20. Incidence and event rates are shown in Table 24. For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- AESIs (at least 1) were reported in 135 of 881 (15.3%) participants in the Non-Benlysta group and in 314 of 1924 (16.3%) participants in the Benlysta group.
- 29 (3.3%) participants in the Non-Benlysta group and 48 (2.5%) participants in the Benlysta group died. The most frequent causes of mortality at SOC level were infections and infestations, and cardiac disorders in the Benlysta group and infections and infestations in the Non-Benlysta group. As the proportion of participants with the events were smaller, there were no relevant differences between the groups (Table 20 and Table 21). A listing of participant deaths and the preferred terms for these events are provided in Table 52.
- The proportion of participants with serious infections was slightly higher in the Benlysta (8.7%) than the Non-Benlysta group (7.4%). At SOC and PT level, there were no relevant differences between the groups. The most frequent serious infection was pneumonia in both exposure groups (Table 46; post-hoc analysis).
- A total of 2.4% of participants in the Non-Benlysta group and 2.0% of participants in the Benlysta group had opportunistic infections. At SOC and PT level, there were no relevant differences between the groups. The most frequent opportunistic infections was herpes zoster in both exposure groups (Table 47; post-hoc analysis).
- A total of 2.2% of participants in the Non-Benlysta group and 2.3% of participants in the Benlysta group had other infections of special interest. At SOC and PT level, there were no relevant differences between the groups. The most frequent other infections of special interest was herpes zoster in both exposure groups (Table 48; post-hoc analysis).
- A total of 0.6% of participants in the Non-Benlysta group and 1.4% of participants in the Benlysta group had serious psychiatric events. At SOC and PT level, there were no relevant differences between the groups. The most frequent serious psychiatric events were suicidal ideation (0.4%), suicide attempt (0.4%), and depression (0.3%) in the Benlysta group and suicidal ideation in the Non-Benlysta group (0.3%) (Table 49; post-hoc analysis). However, it has to be noted that in the Benlysta exposure group several of the events occurred after participants had been switched off Benlysta to other SLE medications.
- A total of 2.7% of participants in the Non-Benlysta group and 2.3% of participants in the Benlysta group had malignancies. At SOC and PT level,, there were no relevant differences between the exposure groups. The most frequent malignancies were breast cancer in both exposure groups (0.3% each) and extranodal marginal zone B-cell lymphoma (MALT type) in the Non-Benlysta group (0.3%) (Table 50; post-hoc analysis).
- A total of 0.5% of participants in both exposure groups had NMSCs. There were no relevant differences between the exposure groups at the PT level. At SOC and PT level, there were no relevant differences between the exposure groups at the PT level. The most frequent events were basal cell carcinoma in the Benlysta group (0.3%) and squamous cell carcinoma of skin in both exposure groups (0.2%

in the Benlysta group and 0.3% in the Non-Benlysta group) (Table 51; post-hoc analysis).

- A total of 206 AESIs were reported in 135 participants in the Non-Benlysta group and 463 AESIs were reported in 314 participants in the Benlysta group. The number of AESIs and participants with AESIs were similar for mortality, malignancies, NMSC, and other infections of special interest, while for serious infections, opportunistic infections, and serious psychiatric events participants reported multiple events in both exposure groups (Source Table 23.000). Similar trend was also observed for Current Users and Treatment Initiators (Source Table 23.010 and Table 23.020).
- The overall AESI incidence rates per 100 participant-years follow-up for Evaluable population were (Table 24):
  - Lower for Benlysta compared to Non-Benlysta for mortality,
  - Higher for Benlysta compared to Non-Benlysta serious infections and serious psychiatric events,
  - Comparable between Benlysta and Non-Benlysta for opportunistic infections, other infections of special interest, malignancies, and NMSC.
- The pattern observed for the Current Users was similar to the overall population with the exception of malignancy, where the incidence rates were lower in Benlysta (Table 20 and Source Table 24.111).
- The pattern observed for the Treatment Initiators was similar to the overall population, with the exception of the following AESIs (Table 20 and Source Table 24.112):
  - Opportunistic infections, Serious psychiatric events, and NMSC, where the incidence rates were lower in Benlysta compared to Non-Benlysta,
  - Malignancy, where the incidence rates were higher in Benlysta: 0.59 (0.28,1.09) compared to Non-Benlysta: 0.24 (0.01,1.33),
  - However, this data should be interpreted with caution due to the smaller number of Treatment Initiators and only few events for some AESIs.
- The results observed for the Sensitivity population were similar to the overall population (Table 20 and Source Table 24.1101).

Table 20 Summary of AESIs by Time Period (Initial Exposure [ITT] Strategy; Population: Evaluable; Current Users; Treatment Initiators)

	Number (%) of participants									
	At 12-month time period		At 24-month time period		At 36-month time period		At 48-month time period		At 60+-month time period[a]	
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Evaluable Participants, N	881	1924	881	1924	881	1924	881	1924	881	1924
At least 1 AESI, n (%)	38 (4.3%)	105 (5.5%)	74 (8.4%)	178 (9.3%)	103 (11.7%)	224 (11.6%)	119 (13.5%)	271 (14.1%)	135 (15.3%)	314 (16.3%)
Death[b]	7 (0.8%)	10 (0.5%)	15 (1.7%)	23 (1.2%)	21 (2.4%)	33 (1.7%)	27 (3.1%)	42 (2.2%)	29 (3.3%)	48 (2.5%)
Serious infections[c]	19 (2.2%)	52 (2.7%)	39 (4.4%)	87 (4.5%)	53 (6.0%)	113 (5.9%)	58 (6.6%)	141 (7.3%)	65 (7.4%)	167 (8.7%)
Opportunistic infection	5 (0.6%)	11 (0.6%)	8 (0.9%)	20 (1.0%)	16 (1.8%)	28 (1.5%)	19 (2.2%)	37 (1.9%)	21 (2.4%)	38 (2.0%)
Serious	2 (0.2%)	4 (0.2%)	3 (0.3%)	9 (0.5%)	9 (1.0%)	13 (0.7%)	11 (1.2%)	17 (0.9%)	11 (1.2%)	18 (0.9%)
Non-serious	3 (0.3%)	7 (0.4%)	5 (0.6%)	11 (0.6%)	7 (0.8%)	15 (0.8%)	8 (0.9%)	21 (1.1%)	10 (1.1%)	21 (1.1%)
Other infections of interest	7 (0.8%)	18 (0.9%)	11 (1.2%)	26 (1.4%)	16 (1.8%)	33 (1.7%)	18 (2.0%)	39 (2.0%)	19 (2.2%)	44 (2.3%)
Serious	1 (0.1%)	5 (0.3%)	1 (0.1%)	7 (0.4%)	1 (0.1%)	8 (0.4%)	1 (0.1%)	9 (0.5%)	1 (0.1%)	9 (0.5%)
Non-serious	6 (0.7%)	13 (0.7%)	10 (1.1%)	19 (1.0%)	15 (1.7%)	25 (1.3%)	17 (1.9%)	30 (1.6%)	18 (2.0%)	35 (1.8%)
Serious psychiatric event	1 (0.1%)	8 (0.4%)	2 (0.2%)	15 (0.8%)	3 (0.3%)	21 (1.1%)	4 (0.5%)	23 (1.2%)	5 (0.6%)	26 (1.4%)
Malignancy (excl NMSC)	5 (0.6%)	11 (0.6%)	14 (1.6%)	20 (1.0%)	16 (1.8%)	25 (1.3%)	19 (2.2%)	33 (1.7%)	24 (2.7%)	44 (2.3%)
NMSC	0	3 (0.2%)	1 (0.1%)	6 (0.3%)	1 (0.1%)	8 (0.4%)	2 (0.2%)	9 (0.5%)	4 (0.5%)	10 (0.5%)
Current Users, N	771	1464	771	1464	771	1464	771	1464	771	1464
At least 1 AESI, n (%)	30 (3.9%)	75 (5.1%)	63 (8.2%)	132 (9.0%)	86 (11.2%)	171 (11.7%)	102 (13.2%)	205 (14.0%)	117 (15.2%)	240 (16.4%)
Death[b]	6 (0.8%)	5 (0.3%)	13 (1.7%)	16 (1.1%)	17 (2.2%)	24 (1.6%)	23 (3.0%)	32 (2.2%)	25 (3.2%)	36 (2.5%)

	Number (%) of participants									
	At 12-month time period		At 24-month time period		At 36-month time period		At 48-month time period		At 60+-month time period[a]	
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Serious infections[c]	14 (1.8%)	36 (2.5%)	33 (4.3%)	63 (4.3%)	46 (6.0%)	84 (5.7%)	51 (6.6%)	104 (7.1%)	57 (7.4%)	125 (8.5%)
Opportunistic infection	3 (0.4%)	7 (0.5%)	6 (0.8%)	15 (1.0%)	12 (1.6%)	23 (1.6%)	15 (1.9%)	31 (2.1%)	17 (2.2%)	32 (2.2%)
Serious	0	1 (<0.1%)	1 (0.1%)	6 (0.4%)	6 (0.8%)	10 (0.7%)	8 (1.0%)	14 (1.0%)	8 (1.0%)	15 (1.0%)
Non-serious	3 (0.4%)	6 (0.4%)	5 (0.6%)	9 (0.6%)	6 (0.8%)	13 (0.9%)	7 (0.9%)	18 (1.2%)	9 (1.2%)	18 (1.2%)
Other infections of interest	6(0.8%)	14 (1.0%)	8 (1.0%)	19 (1.3%)	13 (1.7%)	25 (1.7%)	15 (1.9%)	28 (1.9%)	16 (2.1%)	33 (2.3%)
Serious	1 (0.1%)	4 (0.3%)	1 (0.1%)	6 (0.4%)	1 (0.1%)	7 (0.5%)	1 (0.1%)	7 (0.5%)	1 (0.1%)	7 (0.5%)
Non-serious	5 (0.6%)	10 (0.7%)	7 (0.9%)	13 (0.9%)	12 (1.6%)	18 (1.2%)	14 (1.8%)	21 (1.4%)	15 (1.9%)	26 (1.8%)
Serious psychiatric event	1 (0.1%)	7 (0.5%)	2 (0.3%)	13 (0.9%)	2 (0.3%)	19 (1.3%)	3 (0.4%)	21 (1.4%)	4 (0.5%)	24 (1.6%)
Malignancy (excl NMSC)	5 (0.6%)	8 (0.5%)	14 (1.8%)	16 (1.1%)	15 (1.9%)	20 (1.4%)	18 (2.3%)	26 (1.8%)	23 (3.0%)	34 (2.3%)
NMSC	0	2 (0.1%)	1 (0.1%)	5 (0.3%)	1 (0.1%)	6 (0.4%)	2 (0.3%)	7 (0.5%)	3 (0.4%)	8 (0.5%)
Treatment Initiators, N	110	460	110	460	110	460	110	460	110	460
At least 1 AESI, n (%)	8 (7.3%)	30 (6.5%)	11 (10.0%)	46 (10.0%)	17 (15.5%)	53 (11.5%)	17 (15.5%)	66 (14.3%)	18 (16.4%)	74 (16.1%)
Death[b]	1 (0.9%)	5 (1.1%)	2 (1.8%)	7 (1.5%)	4 (3.6%)	9 (2.0%)	4 (3.6%)	10 (2.2%)	4 (3.6%)	12 (2.6%)
Serious infections[c]	5 (4.5%)	16 (3.5%)	6 (5.5%)	24 (5.2%)	7 (6.4%)	29 (6.3%)	7 (6.4%)	37 (8.0%)	8 (7.3%)	42 (9.1%)
Opportunistic infection	2 (1.8%)	4 (0.9%)	2 (1.8%)	5 (1.1%)	4 (3.6%)	5 (1.1%)	4 (3.6%)	6 (1.3%)	4 (3.6%)	6 (1.3%)
Serious	2 (1.8%)	3 (0.7%)	2 (1.8%)	3 (0.7%)	3 (2.7%)	3 (0.7%)	3 (2.7%)	3 (0.7%)	3 (2.7%)	3 (0.7%)
Non-serious	0	1 (0.2%)	0	2 (0.4%)	1 (0.9%)	2 (0.4%)	1 (0.9%)	3 (0.7%)	1 (0.9%)	3 (0.7%)

	Number (%) of participants									
	At 12-month time period		At 24-month time period		At 36-month time period		At 48-month time period		At 60+-month time period[a]	
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Other infections of interest	1 (0.9%)	4 (0.9%)	3 (2.7%)	7 (1.5%)	3 (2.7%)	8 (1.7%)	3 (2.7%)	11 (2.4%)	3 (2.7%)	11 (2.4%)
Serious	0	1 (0.2%)	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.4%)	0	2 (0.4%)
Non-serious	1 (0.9%)	3 (0.7%)	3 (2.7%)	6 (1.3%)	3 (2.7%)	7 (1.5%)	3 (2.7%)	9 (2.0%)	3 (2.7%)	9 (2.0%)
Serious psychiatric event	0	1 (0.2%)	0	2 (0.4%0	1 (0.9%)	2 (0.4%)	1 (0.9%)	2 (0.4%)	1 (0.9%)	2 (0.4%)
Malignancy (excl NMSC)	0	3 (0.7%)	0	4 (0.9%)	1 (0.9%)	5 (1.1%)	1 (0.9%)	7 (1.5%)	1 (0.9%)	10 (2.2%)
NMSC	0	1 (0.2%)	0	1 (0.2%)	0	2 (0.4%)	0	2 (0.4%)	1 (0.9%)	2 (0.4%)

Source: Table 23.000 (Evaluable), Table 23.010(Current Users), and Table 23.020 (Treatment Initiators).

Note: The overall AESI data summary by Initial Exposure (ITT strategy), were shown. ITT strategy analyzed all events experienced using Initial Exposure (exposure group assigned at enrollment) irrespective of switching to or off Benlysta. Participants could be included in more than 1 AESI category or sub-category if they had multiple event types during the reporting period. Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (< 62 days) prior to enrollment (Day 1) into the study.

a. Any events that occurred after 63 months were not reported.
b. Fatal SAE onset date was used for slotting of the mortality events.
c. Serious infections per GSK adjudication and did not include serious opportunistic infections or serious other infection of interest.

Table 21 Summary of Fatal AESI by SOC and PT reported in >1 participant in any exposure group and Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All Deaths	25 (3.2%)	36 (2.5%)	4 (3.6%)	12 (2.6%)	29 (3.3%)	48 (2.5%)
Cardiac disorders	4 (0.5%)	8 (0.5%)	1 (0.9%)	1 (0.2%)	5 (0.6%)	9 (0.5%)
Cardiac arrest	2 (0.3%)	0	0	0	2 (0.2%)	0

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
Cardiac failure	0	0	1 (0.9%)	0	1 (0.1%)	0
Cardiac failure congestive	1 (0.1%)	3 (0.2%)	0	1 (0.2%)	1 (0.1%)	4 (0.2%)
General disorders and administration site conditions	3 (0.4%)	5 (0.3%)	1 (0.9%)	3 (0.7%)	4 (0.5%)	8 (0.4%)
Death	3 (0.4%)	4 (0.3%)	1 (0.9%)	3 (0.7%)	4 (0.5%)	7 (0.4%)
Infections and infestations	8 (1.0%)	7 (0.5%)	2 (1.8%)	2 (0.4%)	10 (1.1%)	9 (0.5%)
COVID-19	0	2 (0.1%)	1 (0.9%)	0	1 (0.1%)	2 (0.1%)
COVID-19 pneumonia	0	0	1 (0.9%)	0	1 (0.1%)	0
Klebsiella sepsis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Pneumonia	3 (0.4%)	0	0	0	3 (0.3%)	0
Sepsis	4 (0.5%)	1 (<0.1%)	0	0	4 (0.5%)	1 (<0.1%)
Injury, poisoning and procedural complications	0	1 (<0.1%)	0	1 (0.2%)	0	2 (0.1%)
Subdural haematoma	0	0	0	1 (0.2%)	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4%)	4 (0.3%)	0	1 (0.2%)	3 (0.3%)	5 (0.3%)
Colon cancer stage IV	0	0	0	1 (0.2%)	0	1 (<0.1%)
Nervous system disorders	1 (0.1%)	2 (0.1%)	0	2 (0.4%)	1 (0.1%)	4 (0.2%)
Cerebral haemorrhage	1 (0.1%)	1 (<0.1%)	0	1 (0.2%)	1 (0.1%)	2 (0.1%)
Encephalopathy	0	0	0	1 (0.2%)	0	1 (<0.1%)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
Renal and urinary disorders	0	1 (<0.1%)	0	1 (0.2%)	0	2 (0.1%)
Chronic kidney disease	0	0	0	1 (0.2%)	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	5 (0.6%)	5 (0.3%)	0	1 (0.2%)	5 (0.6%)	6 (0.3%)
Acute respiratory failure	3 (0.4%)	0	0	0	3 (0.3%)	0
Interstitial lung disease	0	1 (<0.1%)	0	1 (0.2%)	0	2 (0.1%)

Source: Table 23.200.

Note: SOC and PT were coded using MedDRA version 27.1. ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. Percentages were based on total number of participants (N) in each column. Participants could be included in more than 1 SOC or PT if they had multiple fatal AEs.

10.4.1.2. As-Exposed (Time-varying – 14 weeks risk window)

In this strategy, when switching from Benlysta to Non-Benlysta, a 14 weeks risk window was incorporated which means that Benlysta exposure ends 14 weeks (98 days) after cessation (end date) of Benlysta treatment. The AESI summary and rates (incidence and event) are presented not by the participant's Initial Exposure assignment, but by exposure at the time of event onset (i.e., whether the participant was on/off Benlysta at the time the AESI occurred). Data summary and analysis results for this strategy are shown in Table 22 as cumulative incidence by 12-month time periods. The incidence rates at 0-60+ Months Time-Period are also presented in Table 24 alongside incidence rates at the same time period for other exposure strategies. For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- The overall AESI incidence rates per 100 participant-years follow-up in the Evaluable population were:
  - Lower in Benlysta compared to Non-Benlysta for mortality, serious infections, and opportunistic infections,
  - Comparable between Benlysta and Non-Benlysta for other infections of special interest, serious psychiatric events, malignancies, and NMSCs.
- The pattern observed for the Current Users is similar to the overall population (Table 22 and Source Table 24.211).
- Similarly, the pattern observed for the Treatment Initiators was similar to the overall population, except for following AESIs (Table 22 and Source Table 24.212):
  - Other infections of special interest and NMSCs, which were lower in Benlysta than Non-Benlysta,
  - Malignancy, which was higher in Benlysta than Non-Benlysta,
  - However, this data should be interpreted with caution due to the smaller number of Treatment Initiators and few events for some AESIs.

Table 22 Cumulative AESI events and incidence rates by 12-month periods (As-Exposed [Time-Varying - 14 Weeks risk window] Exposure Strategy; Population: Evaluable)

Time Period	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Total participant-years of follow-up	909.8	1804.8	1897.1	3217.7	2849.5	4414.2	3731.1	5472.2	4507.2	6405.3
Mortality[b]										
Number of deaths, n1	8	9	16	22	25	29	35	34	40	37
Total participant-years at-risk	909.8	1804.8	1897.1	3217.7	2849.5	4414.2	3731.1	5472.2	4507.2	6405.3
Incidence rate[c] (95% CI)	0.88 (0.38,1.73)	0.50 (0.23,0.95)	0.84 (0.48,1.37)	0.68 (0.43,1.04)	0.88 (0.57,1.30)	0.66 (0.44,0.94)	0.94 (0.65,1.30)	0.62 (0.43,0.87)	0.89 (0.63,1.21)	0.58 (0.41,0.80)
Serious infection[d]										
Number of first events, n1	21	51	47	83	72	99	86	122	106	137
Number of all events, n2	24	58	55	97	92	124	115	153	155	173
Total participant-years at-risk	902.6	1784.4	1866.3	3156.4	2776.1	4304.1	3609.8	5301.6	4334.5	6166.4
Incidence rate[c] (95% CI)	2.33 1.44,3.56	2.86 2.13,3.76	2.52 1.85,3.35	2.63 2.09,3.26	2.59 2.03,3.27	2.30 1.87,2.80	2.38 1.91,2.94	2.30 1.91,2.75	2.45 2.00,2.96	2.22 1.87,2.63
Events rate[e] (95% CI)	2.64 1.69,3.92	3.21 2.44,4.15	2.90 2.18,3.77	3.01 2.44,3.68	3.23 2.60,3.96	2.81 2.34,3.35	3.08 2.54,3.70	2.80 2.37,3.28	3.44 2.92,4.02	2.70 2.31,3.13
Opportunistic infection										
Number of first events, n1	6	10	10	18	21	23	29	29	32	29
Number of all events, n2	8	10	12	18	23	24	32	31	39	32

Time Period	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Total participant-years at-risk	907.6	1800.7	1887.8	3201.9	2827.5	4382.0	3691.1	5423.4	4447.1	6339.0
Incidence rate[c] (95% CI)	0.66 (0.24,1.44)	0.56 (0.27,1.02)	0.53 (0.25,0.97)	0.56 (0.33,0.89)	0.74 (0.46,1.14)	0.52 (0.33,0.79)	0.79 (0.53,1.13)	0.53 (0.36,0.77)	0.72 (0.49,1.02)	0.46 (0.31,0.66)
Events rate[e] (95% CI)	0.88 (0.38,1.73)	0.55 (0.27,1.02)	0.63 (0.33,1.10)	0.56 (0.33,0.88)	0.81 (0.51,1.21)	0.54 (0.35,0.81)	0.86 (0.59,1.21)	0.57 (0.38,0.80)	0.87 (0.62,1.18)	0.50 (0.34,0.71)
Other infection of special interest										
Number of first events, n1	8	17	12	25	19	30	24	34	28	36
Number of all events, n2	8	19	12	27	19	32	25	36	29	38
Total participant-years at-risk	905.7	1797.2	1885.6	3197.6	2827.4	4379.3	3694.6	5418.4	4452.2	6333.7
Incidence rate[c] (95% CI)	0.88 (0.38,1.74)	0.95 (0.55,1.51)	0.64 (0.33,1.11)	0.78 (0.51,1.15)	0.67 (0.40,1.05)	0.69 (0.46,0.98)	0.65 (0.42,0.97)	0.63 (0.43,0.88)	0.63 (0.42,0.91)	0.57 (0.40,0.79)
Events rate[e] (95% CI)	0.88 (0.38,1.73)	1.05 (0.63,1.64)	0.63 (0.33,1.10)	0.84 (0.55,1.22)	0.67 (0.40,1.04)	0.72 (0.50,1.02)	0.67 (0.43,0.99)	0.66 (0.46,0.91)	0.64 (0.43,0.92)	0.59 (0.42,0.81)
Serious psychiatric event										
Number of first events, n1	1	8	6	12	8	17	10	18	12	20
Number of all events, n2	1	8	7	12	10	19	14	21	16	23
Total participant-years at-risk	909.6	1802.7	1893.0	3211.2	2839.7	4399.2	3714.3	5447.6	4483.0	6373.0
Incidence rate[c] (95% CI)	0.11 (0.00,0.61)	0.44 (0.19,0.87)	0.32 (0.12,0.69)	0.37 (0.19,0.65)	0.28 (0.12,0.56)	0.39 (0.23,0.62)	0.27 (0.13,0.50)	0.33 (0.20,0.52)	0.27 (0.14,0.47)	0.31 (0.19,0.48)

Time Period	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Events rate[e] (95% CI)	0.11 (0.00,0.61)	0.44 (0.19,0.87)	0.37 (0.15,0.76)	0.37 (0.19,0.65)	0.35 (0.17,0.65)	0.43 (0.26,0.67)	0.38 (0.21,0.63)	0.38 (0.24,0.59)	0.35 (0.20,0.58)	0.36 (0.23,0.54)
Malignancy (excl NMSC)										
Number of first events, n1	6	10	17	17	20	21	25	27	30	38
Number of all events, n2	6	10	17	17	21	21	26	28	31	39
Total participant-years at-risk	908.1	1802.5	1883.8	3211.4	2821.3	4401.3	3689.3	5450.6	4448.7	6371.3
Incidence rate[c] (95% CI)	0.66 0.24,1.44	0.55 0.27,1.02	0.90 0.53,1.44	0.53 0.31,0.85	0.71 0.43,1.09	0.48 0.30,0.73	0.68 0.44,1.00	0.50 0.33,0.72	0.67 0.45,0.96	0.60 0.42,0.82
Events rate[e] (95% CI)	0.66 0.24,1.44	0.55 0.27,1.02	0.90 0.52,1.43	0.53 0.31,0.85	0.74 0.46,1.13	0.48 0.29,0.73	0.70 0.46,1.02	0.51 0.34,0.74	0.69 0.47,0.98	0.61 0.43,0.83
NMSC										
Number of first events, n1	0	3	1	6	2	7	3	8	6	8
Number of all events, n2	0	4	1	7	2	9	3	10	6	11
Total participant-years at-risk	909.8	1803.7	1896.5	3212.7	2848.7	4404.7	3729.3	5456.7	4501.6	6383.4
Incidence rate[c] (95% CI)	-	0.17 (0.03,0.49)	0.05 (0.00,0.29)	0.19 (0.07,0.41)	0.07 (0.01,0.25)	0.16 (0.06,0.33)	0.08 (0.02,0.24)	0.15 (0.06,0.29)	0.13 (0.05,0.29)	0.13 (0.05,0.25)
Events rate[e] (95% CI)	-	0.22 (0.06,0.57)	0.05 (0.00,0.29)	0.22 (0.09,0.45)	0.07 (0.01,0.25)	0.20 (0.09,0.39)	0.08 (0.02,0.23)	0.18 (0.09,0.34)	0.13 (0.05,0.29)	0.17 (0.09,0.31)

Source: Table 24.210.

Note: As-exposed (time-varying strategy) analyzed events based on exposure status at the time of events occurrence. When switching from Benlysta to Non-Benlysta a 14 week risk window was incorporated. This assumes that Benlysta exposure ends 14 weeks after cessation (end date) of Benlysta medication.

a. Any events that occurred after 63 months were not reported.
b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.
c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years.
d. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.
e. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

10.4.1.3. Ever-Exposed

The AESI summary and rates (incidence and event) are presented based on whether a participant was ever-exposed to Benlysta at any point during the follow-up period. This exposure strategy was used to analyze the following AESIs only: Mortality, Malignancy and NMSC. Data summary and analysis results for this strategy are shown in Table 23. For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- The overall AESI incidence rates per 100 participant-years follow-up in the Evaluable population were:
  - Lower in Benlysta compared to Non-Benlysta for mortality and malignancies,
  - Comparable between Benlysta and Non-Benlysta for NMSCs.
- The pattern observed for the Current Users was similar to the overall population (Table 23 and Source Table 24.411).
- The pattern observed for the Treatment Initiators subgroup was similar to the overall population, with the exception for the following AESIs (Table 23 and Source Table 24.412):
  - Malignancies, which were higher in Benlysta compared to Non-Benlysta exposure group,
  - NMSCs, which were lower in Benlysta compared to Non-Benlysta exposure group,
  - However, this data should be interpreted with caution due to the smaller number of Treatment Initiators and few events for some AESIs.

Table 23 Cumulative AESI Events and Incidence Rates by 12-Month Periods (Ever-Exposed Strategy; Population: Evaluable)

Time Period (months)	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Total participant-years of follow-up	822.6	1892.0	1532.7	3582.1	2154.0	5109.7	2694.7	6508.7	3151.9	7760.6
Mortality[b]										
Number of deaths, n1	7	10	12	26	18	36	24	45	25	52
Total participant-years at-risk	822.6	1892.0	1532.7	3582.1	2154.0	5109.7	2694.7	6508.7	3151.9	7760.6
Incidence rate[c]	0.85 0.34,1.75	0.53 0.25,0.97	0.78 0.40,1.37	0.73 0.47,1.06	0.84 0.50,1.32	0.70 0.49,0.98	0.89 0.57,1.33	0.69 0.50,0.93	0.79 0.51,1.17	0.67 0.50,0.88
Malignancy (excl NMSC)										
Number of first events, n1	5	11	14	20	16	25	18	34	22	46
Number of all events, n2	5	11	14	20	17	25	19	35	23	47
Total participant-years at-risk	821.0	1888.6	1521.3	3569.4	2130.4	5080.6	2659.7	6461.5	3106.1	7686.2
Incidence rate[c]	0.61 0.20,1.42	0.58 0.29,1.04	0.92 0.50,1.54	0.56 0.34,0.87	0.75 0.43,1.22	0.49 0.32,0.73	0.68 0.40,1.07	0.53 0.36,0.74	0.71 0.44,1.07	0.60 0.44,0.80
Events rate[d]	0.61 0.20,1.42	0.58 0.29,1.04	0.91 0.50,1.53	0.56 0.34,0.86	0.79 0.46,1.26	0.49 0.32,0.72	0.71 0.42,1.10	0.54 0.37,0.75	0.73 0.46,1.09	0.61 0.44,0.81
NMSC										
Number of first events, n1	0	3	1	6	1	8	2	9	3	11
Number of all events, n2	0	4	1	7	1	10	2	11	3	14
Total participant-years at-risk	822.6	1890.2	1532.0	3575.5	2153.4	5096.7	2693.6	6487.3	3148.7	7730.0
Incidence rate[c]	-	0.16 0.03,0.46	0.07 0.00,0.36	0.17 0.06,0.37	0.05 0.00,0.26	0.16 0.07,0.31	0.07 0.01,0.27	0.14 0.06,0.26	0.10 0.02,0.28	0.14 0.07,0.25

Time Period (months)	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Events rate[d]	-	0.21 0.06,0.54	0.07 0.00,0.36	0.20 0.08,0.40	0.05 0.00,0.26	0.20 0.09,0.36	0.07 0.01,0.27	0.17 0.08,0.30	0.10 0.02,0.28	0.18 0.10,0.30

Source: Table 24.410

Note: Ever-Exposed Strategy analyzed events based on whether a participant was ever-exposed to Benlysta at any point during the follow-up period. Follow-up time before first Benlysta exposure was allocated to the comparison group (Non-Benlysta). Once exposed to Benlysta participants were always allocated to Benlysta group irrespective of switching off Benlysta.

a. Any events that occurred after 63 months were not reported.
b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.
c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years
d. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

10.4.1.4. Across strategy comparisons

A table summarizing the overall counts and rates of AESIs in the Evaluable population for the ITT, the As-Exposed [Time-varying – 14 weeks risk window], the As-Exposed [Time-varying – 6 months risk window], and the Ever-Exposed exposure strategies (at the 0 to 60+ month timepoint) are shown for comparison in Table 24. For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- The overall patterns of AESI incidence rates per 100 participant-years follow-up in the Evaluable population were:
  - Mortality was consistently lower in Benlysta than in Non-Benlysta,
  - Serious infections were higher in the Benlysta than in the Non-Benlysta exposure group in the ITT, while the reverse was observed for the As-Exposed strategies,
  - Opportunistic infections were lower in the Benlysta than the Non-Benlysta group in the As-Exposed strategies. The incidence rates were comparable in the ITT, although a numerical trend was seen towards lower incidence rates in the Benlysta exposure group,
  - Other infections of special interest were comparable between the exposure groups,
  - Serious psychiatric events were higher in Benlysta than in Non-Benlysta in the ITT. The incidence rates were comparable in the As-Exposed strategies, although a numerical trend was seen towards higher incidence rates in the Benlysta exposure group,
  - Malignancies were lower in Benlysta than in Non-Benlysta in the Ever-Exposed strategy. The incidence rates were comparable in the ITT and As-Exposed strategies, although a numerical trend was seen towards lower incidence rates in the Benlysta exposure group,
  - NMSCs were comparable between the exposure groups.
- The pattern observed for the Current Users was similar to the overall population (see Table 19 for source tables).
- The pattern observed for Treatment Initiators was similar to the overall population for mortality and serious infections. For the other AESIs, the following patterns were observed for the Treatment Initiators subgroup (see Table 19 for source tables):
  - Opportunistic infections were consistently lower in the Benlysta than the Non-Benlysta group. A similar pattern was seen for the overall population and Current Users although not as clear,

- Other infection of special interest events were lower in Benlysta than in Non-Benlysta in the As-Exposed strategies. The incidence rates were comparable in the ITT strategy, although a numerical trend was seen towards higher incidence rates in the Non-Benlysta exposure group,
- Serious psychiatric events were lower in Benlysta than in Non-Benlysta in the ITT. The incidence rates were comparable in the As-Exposed strategies,
- Malignancies were consistently higher in Benlysta than in Non-Benlysta in the Ever-Exposed strategy,
- NMSCs were consistently lower in Benlysta than in Non-Benlysta,
- However, this data should be interpreted with caution due to the smaller number of Treatment Initiators and few events for some AESIs.

Table 24 Overall AESI event and incidence rates by Exposure Strategies at 0-60+ Time-Period (Population: Evaluable)

Exposure Strategy	Initial Exposure [ITT] Strategy[a]		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window[a]		As-Exposed [Time-Varying] Strategy – 6 months risk window[a]		Ever-Exposed Strategy[a]	
AESI / Exposure Status	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Total participant-years of follow-up	3482.4	7430.2	4507.2	6405.3	4364.0	6548.5	3151.9	7760.6
Mortality[b]								
Number of death cases, n1	29	48	40	37	37	40	25	52
Total participant-years at-risk	3482.4	7430.2	4507.2	6405.3	4364.0	6548.5	3151.9	7760.6
Incidence rate[c] (95% CI)	0.83 (0.56,1.20)	0.65 (0.48,0.86)	0.89 (0.63,1.21)	0.58 (0.41,0.80)	0.85 (0.60,1.17)	0.61 (0.44,0.83)	0.79 (0.51,1.17)	0.67 (0.50,0.88)
Serious infection[d]							NA	NA
Number of first events, n1	65	167	106	137	101	143		
Number of all events, n2	95	233	155	173	143	185		
Total participant-years at-risk	3357.0	7052.5	4334.5	6166.4	4204.6	6293.0		
Incidence rate[c] (95% CI)	1.94 (1.49,2.47)	2.37 (2.02,2.76)	2.45 (2.00,2.96)	2.22 (1.87,2.63)	2.40 (1.96,2.92)	2.27 (1.92,2.68)		
Events rate[e] (95% CI)	2.73 (2.21,3.33)	3.14 (2.75,3.57)	3.44 (2.92,4.02)	2.70 (2.31,3.13)	3.28 (2.76,3.86)	2.83 (2.43,3.26)		
Opportunistic infection							NA	NA
Number of first events, n1	21	38	32	29	31	30		
Number of all events, n2	26	45	39	32	38	33		

Exposure Strategy	Initial Exposure [ITT] Strategy[a]		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window[a]		As-Exposed [Time-Varying] Strategy – 6 months risk window[a]		Ever-Exposed Strategy[a]	
AESI / Exposure Status	**Non-Benlysta (N=881)**	**Benlysta (N=1924)**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Total participant-years at-risk	3434.5	7331.8	4447.1	6339.0	4306.7	6477.8		
Incidence rate[c] (95% CI)	0.61 (0.38,0.93)	0.52 (0.37,0.71)	0.72 (0.49,1.02)	0.46 (0.31,0.66)	0.72 (0.49,1.02)	0.46 (0.31,0.66)		
Events rate[e] (95% CI)	0.75 (0.49,1.09)	0.61 (0.44,0.81)	0.87 (0.62,1.18)	0.50 (0.34,0.71)	0.87 (0.62,1.20)	0.50 (0.35,0.71)		
Other infection of special interest							NA	NA
Number of first events, n1	19	44	28	36	27	37		
Number of all events, n2	20	47	29	38	28	39		
Total participant-years at-risk	3428.3	7320.6	4452.2	6333.7	4309.2	6471.0		
Incidence rate[c] (95% CI)	0.55 (0.33,0.87)	0.60 (0.44,0.81)	0.63 (0.42,0.91)	0.57 (0.40,0.79)	0.63 (0.41,0.91)	0.57 (0.40,0.79)		
Events rate[e] (95% CI)	0.57 (0.35,0.89)	0.63 (0.46,0.84)	0.64 (0.43,0.92)	0.59 (0.42,0.81)	0.64 (0.43,0.93)	0.60 (0.42,0.81)		
Serious psychiatric event							NA	NA
Number of first events, n1	5	26	12	20	11	21		
Number of all events, n2	7	32	16	23	15	24		
Total participant-years at-risk	3475.0	7360.9	4483.0	6373.0	4342.5	6513.2		

Exposure Strategy	Initial Exposure [ITT] Strategy[a]		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window[a]		As-Exposed [Time-Varying] Strategy – 6 months risk window[a]		Ever-Exposed Strategy[a]	
AESI / Exposure Status	**Non-Benlysta (N=881)**	**Benlysta (N=1924)**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Incidence rate[c] (95% CI)	0.14 (0.05,0.34)	0.35 (0.23,0.52)	0.27 (0.14,0.47)	0.31 (0.19,0.48)	0.25 (0.13,0.45)	0.32 (0.20,0.49)		
Events rate[e] (95% CI)	0.20 (0.08,0.41)	0.43 (0.29,0.61)	0.35 (0.20,0.58)	0.36 (0.23,0.54)	0.34 (0.19,0.57)	0.37 (0.23,0.55)		
Malignancy (excl NMSC)					NA	NA		
Number of first events, n1	24	44	30	38			22	46
Number of all events, n2	25	45	31	39			23	47
Total participant-years at-risk	3435.1	7357.0	4448.7	6371.3			3106.1	7686.2
Incidence rate[c] (95% CI)	0.70 (0.45,1.04)	0.60 (0.43,0.80)	0.67 (0.45,0.96)	0.60 (0.42,0.82)			0.71 (0.44,1.07)	0.60 (0.44,0.80)
Events rate[e] (95% CI)	0.72 (0.46,1.06)	0.61 (0.44,0.81)	0.69 (0.47,0.98)	0.61 (0.43,0.83)			0.73 (0.46,1.09)	0.61 (0.44,0.81)
NMSC					NA	NA		
Number of first events, n1	4	10	6	8			3	11
Number of all events, n2	4	13	6	11			3	14
Total participant-years at-risk	3478.0	7400.7	4501.6	6383.4			3148.7	7730.0
Incidence rate[c] (95% CI)	0.12 (0.03,0.29)	0.14 (0.06,0.25)	0.13 (0.05,0.29)	0.13 (0.05,0.25)			0.10 (0.02,0.28)	0.14 (0.07,0.25)
Events rate[e] (95% CI)	0.11 (0.03,0.29)	0.17 (0.09,0.30)	0.13 (0.05,0.29)	0.17 (0.09,0.31)			0.10 (0.02,0.28)	0.18 (0.10,0.30)

Source: Evaluable; Table 24.110 Initial Exposure [ITT] strategy, Table 24.210 As-Exposed [Time-Varying strategy 14 Weeks Risk Window], Table 24.310 As-Exposed [Time Varying strategy 6 Months Risk Window], Table 24.410 Ever-Exposed strategy

Note: ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. While On Initial Exposure Strategy analyzed only events experienced before the first switching on or off Benlysta medication. Time Varying Strategy analyzed events based on exposure status at the time of events occurrence. Ever-Exposed Strategy analyzed events based on whether a participant was ever-exposed to Benlysta at any point during the follow-up period. Follow-up time before first Benlysta exposure was allocated to the comparison group (Non-Benlysta). Once exposed to Benlysta participants were always allocated to Benlysta group irrespective of switching off Benlysta.

a. Any events that occurred after 63 months were not reported.
b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.
c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years.
d. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.
e. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

10.4.2. Other endpoints

As described in the Statistical Methods (see Section 9.9.2.5), the effectiveness endpoints descriptive summaries are presented in the sections below.

10.4.2.1. General medical status

The past and current general medical status was evaluated at 24 and 48 months during the study.

In summary (Eligible, Initial Exposure [ITT] Strategy):

- Past general medical status:
  - Overall, in the Eligible population the past general medical status was comparable in both exposure groups at both 24 and 48 months (Source Table 9.111).
  - The patterns observed for the Current Users and Treatment Initiators subgroups were similar to the overall population (Source Table 9.111, Table 9.112 and Table 9.113). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.
- Current general medical status:
  - Overall, in the Eligible population the current general medical status was comparable in both exposure groups at both 24 and 48 months except autoimmune disorders which were higher in the Benlysta exposure group compared to Non-Benlysta (Source Table 9.121).
  - The pattern observed for the Current Users was similar to the overall population (Source Table 9.121 and Table 9.122).
  - In Treatment Initiators the current general medical status was comparable in both exposure groups at both 24 and 48 months (Source Table 9.121 and Table 9.123). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

10.4.2.2. SDI

A summary of mean (SD) SDI score at each visit and change in SDI scores from baseline is shown in Table 25.

In summary (Evaluable, 0-60+ Months Time-Period):

- Mean (SD) SDI score changes were smaller and similar between the exposure groups over time.
- The majority of participants in both exposure groups had no change in their SDI score.

- Over time, mean changes in SDI score increased from 0.1 in both exposure groups at 6 months to 0.4 in the Non-Benlysta and 0.5 in the Benlysta group at 60 months. The proportion of participants who had no change in their SDI score decreased from approximately >90% at 6 months to approximately 70% at 60 months in both exposure groups, while the proportion of participants with SDI changes increased. At the 60 months visit, approximately 20% of participants had an SDI score change of 1, 7% of 2 and <5% of ³3.

Table 25 Change from Baseline in SDI by Visit (Initial Exposure [ITT] Strategy; Population: Evaluable)

SDI score			SDI score change[a]		
	Non-Benlysta (N=881)	Benlysta (N=1924)		Non-Benlysta (N=881)	Benlysta (N=1924)
Baseline					
n	875	1898		NA	NA
Mean (SD)	1.2 (1.60)	1.2 (1.60)			
Median	1.0	1.0			
6 Months Change From Baseline					
n	764	1673	0	722 (94.5%)	1552 (92.8%)
Mean (SD)	0.1 (0.33)	0.1 (0.42)	1	33 (4.3%)	92 (5.5%)
Median	0	0	2	7 (0.9%)	21 (1.3%)
			≥3	2 (0.3%)	8 (0.5%)
12 Months Change From Baseline					
n	681	1495	0	614 (90.2%)	1310 (87.6%)
Mean (SD)	0.1 (0.41)	0.2 (0.55)	1	56 (8.2%)	136 (9.1%)
Median	0	0	2	9 (1.3%)	35 (2.3%)
			≥3	2 (0.3%)	14 (0.9%)
18 Months Change From Baseline					
n	607	1361	0	507 (83.5%)	1146 (84.2%)
Mean (SD)	0.2 (0.60)	0.2 (0.63)	1	78 (12.9%)	151 (11.1%)
Median	0	0	2	17 (2.8%)	40 (2.9%)
			≥3	5 (0.8%)	24 (1.8%)
24 Months Change From Baseline					
n	610	1257	0	493 (80.8%)	1017 (80.9%)
Mean (SD)	0.2 (0.60)	0.3 (0.70)	1	92 (15.1%)	171 (13.6%)
Median	0	0	2	21 (3.4%)	39 (3.1%)
			≥3	4 (0.7%)	30 (2.4%)
30 Months Change From Baseline					
n	568	1216	0	451 (79.4%)	970 (79.8%)

SDI score			SDI score change[a]		
	Non-Benlysta (N=881)	Benlysta (N=1924)		Non-Benlysta (N=881)	Benlysta (N=1924)
Mean (SD)	0.3 (0.67)	0.3 (0.72)	1	89 (15.7%)	170 (14.0%)
Median	0	0	2	18 (3.2%)	47 (3.9%)
			≥3	10 (1.8%)	29 (2.4%)
36 Months Change From Baseline					
n	542	1133	0	415 (76.6%)	867 (76.5%)
Mean (SD)	0.3 (0.71)	0.4 (0.77)	1	96 (17.7%)	175 (15.4%)
Median	0	0	2	21 (3.9%)	58 (5.1%)
			≥3	10 (1.8%)	33 (2.9%)
42 Months Change From Baseline					
n	530	1076	0	403 (76.0%)	807 (75.0%)
Mean (SD)	0.3 (0.76)	0.4 (0.81)	1	91 (17.2%)	178 (16.5%)
Median	0	0	2	24 (4.5%)	63 (5.9%)
			≥3	12 (2.3%)	28 (2.6%)
48 Months Change From Baseline					
n	505	1025	0	377 (74.7%)	753 (73.5%)
Mean (SD)	0.4 (0.78)	0.4 (0.87)	1	87 (17.2%)	170 (16.6%)
Median	0	0	2	30 (5.9%)	61 (6.0%)
			≥3	11 (2.2%)	41 (4.0%)
54 Months Change From Baseline					
n	469	996	0	336 (71.6%)	716 (71.9%)
Mean (SD)	0.4 (0.83)	0.4 (0.88)	1	90 (19.2%)	177 (17.8%)
Median	0	0	2	32 (6.8%)	67 (6.7%)
			≥3	11 (2.3%)	36 (3.6%)
60 Months Change From Baseline					
n	448	944	0	312 (69.6%	636 (67.4%)
Mean (SD)	0.4 (0.86)	0.5 (0.91)	1	94 (21.0%)	205 (21.7%)
Median	0	0	2	31 (6.9%)	65 (6.9%)
			≥3	11 (2.5%)	38 (4.0%)

Source: Table 11.100
Note: ITT Strategy analyzed all data values at every visit using Initial Exposure irrespective of switching to or off Benlysta.
a. Percentages were calculated using 'Participants with SDI data (n)' at each visit as denominator.

10.4.2.3. SLE medications

A summary of frequency of concomitant SLE medications is shown below in Table 26.

In summary (Eligible, 0-60+ Months Time-Period):

- SLE medication use (any immunosuppressants, immunosuppressants other than mycophenolate, and SLE medications other than immunosuppressants) was generally similar between the exposure groups.
- Over time, percentage of participants with concomitant SLE medications use decreased in both exposure groups.
- The patterns observed for the Current Users and Treatment Initiators were similar to the overall population, except for any immunosuppressant use and use of immunosuppressant other than mycophenolate in the Treatment Initiators, which was higher in the Non-Benlysta than Benlysta during 0 to12 months interval then evens out post 12 months. However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 26 Frequency of Concomitant SLE Medications by Study Cohort (Initial Exposure [ITT] Strategy; Population: Eligible)

SLE Medication Time period	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=814)	Benlysta (N=1543)	Non-Benlysta (N=123)	Benlysta (N=487)	Non-Benlysta (N=937)	Benlysta (N=2030)
Any Immunosuppressants Use[a, b]						
0-12 month	67 (8.2%)	160 (10.4%)	55 (44.7%)	67 (13.8%)	122 (13.0%)	227 (11.2%)
>12-24 month	42 (5.2%)	88 (5.7%)	10 (8.1%)	34 (7.0%)	52 (5.5%)	122 (6.0%)
>24-36 month	39 (4.8%)	74 (4.8%)	7 (5.7%)	24 (4.9%)	46 (4.9%)	98 (4.8%)
>36-48 month	33 (4.1%)	61 (4.0%)	12 (9.8%)	20 (4.1%)	45 (4.8%)	81 (4.0%)
>48-60 month	25 (3.1%)	44 (2.9%)	6 (4.9%)	10 (2.1%)	31 (3.3%)	54 (2.7%)
Immunosuppressants Use other than Mycophenolate[a, b]						
0-12 month	50 (6.1%)	124 (8.0%)	39 (31.7%)	52 (10.7%)	89 (9.5%)	176 (8.7%)
>12-24 month	29 (3.6%)	67 (4.3%)	8 (6.5%)	25 (5.1%)	37 (3.9%)	92 (4.5%)
>24-36 month	30 (3.7%)	56 (3.6%)	5 (4.1%)	21 (4.3%)	35 (3.7%)	77 (3.8%)
>36-48 month	26 (3.2%)	46 (3.0%)	6 (4.9%)	18 (3.7%)	32 (3.4%)	64 (3.2%)
>48-60 month	20 (2.5%)	34 (2.2%)	6 (4.9%)	10 (2.1%)	26 (2.8%)	44 (2.2%)
SLE medications Use other than Immunosuppressants[a, b]						
0-12 month	27 (3.3%)	38 (2.5%)	7 (5.7%)	20 (4.1%)	34 (3.6%)	58 (2.9%)
>12-24 month	12 (1.5%)	24 (1.6%)	1 (0.8%)	8 (1.6%)	13 (1.4%)	32 (1.6%)
>24-36 month	6 (0.7%)	25 (1.6%)	1 (0.8%)	6 (1.2%)	7 (0.7%)	31 (1.5%)
>36-48 month	4 (0.5%)	12 (0.8%)	1 (0.8%)	4 (0.8%)	5 (0.5%)	16 (0.8%)
>48-60 month	3 (0.4%)	17 (1.1%)	1 (0.8%)	4 (0.8%)	4 (0.4%)	21 (1.0%)

Source: Table 14.300.

Note: Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (< 62 days) prior to enrollment (Day 1) into the study.

a. Benlysta is not included.

b. Reported SLE medications were used to calculate this category.

10.4.2.4. Corticosteroid usage

A summary of change from baseline in average corticosteroid dose is shown below in Table 27 and summary of corticosteroid usage by visit is shown in Table 28.

In summary (Eligible, 0-60+ Months Time-Period):

- At baseline, the average median corticosteroid dose was similar between the exposure groups.
- At each post-baseline visit, the average median corticosteroid dose since the last visit was generally higher in the Benlysta exposure group compared to the Non-Benlysta and decreased at each post-baseline visit in both exposure groups.
- The change from baseline in the average median corticosteroid dose was zero in the Non-Benlysta exposure group at each post-baseline visit. In the Benlysta exposure group it was zero until the 30-months visit; thereafter the change from baseline in the average median corticosteroid dose was up to -1.2000 mg/day at 60 months.
- Approximately 30% of corticosteroid users remained on a dose <7.5 mg/day throughout the study, while the proportion of users on a dose ≥7.5 mg/day for >2weeks weeks was approximately 30% at baseline and decreased thereafter in both exposure groups to approximately 10% at 60 months.
- For more details on participants on corticosteroid dosing ≥7.5 mg/day for >2 weeks see Source Table 15.201.

Table 27 Change from Baseline in Average Corticosteroids Dose by Visit (Initial Exposure [ITT] Strategy; Population: Eligible)

	Average dose since last visit (mg/day)		Change from baseline (mg/day)	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)
Baseline[a]				NA
n	881	1924		
Mean	7.0050 (15.15238)	6.3703 (8.82367)		
Median	5.0000	5.0000		
6 Months				
n	788	1738	788	1738
Mean	5.0603 (10.25236)	5.6683 (10.93466)	-1.9855 (15.70738)	-0.7618 (10.51269)
Median	2.5000	4.0000	0	0
12 Months				
n	706	1569	706	1569
Mean	4.1234 (7.89726)	4.5617 (6.78201)	-2.8514 (16.42435)	-1.8574 (9.06083)
Median	2.0000	3.0000	0	0
18 Months				
n	632	1425	632	1425
Mean	4.1997 (12.04487)	4.3221 (6.73182)	-2.8354 (19.12709)	-1.9261 (8.60539)
Median	0	2.5000	0	0
24 Months				
n	627	1313	627	1313
Mean	3.4886 (6.35940)	4.0426 (6.92321)	-2.9967 (10.78960)	-2.3257 (9.90478)
Median	0	2.0000	0	0
30 Months				
n	583	1263	583	1263
Mean	3.6223 (6.63521)	4.0240 (7.89969)	-3.0399 (16.75610)	-2.2272 (8.99114)
Median	0	1.3000	0	0
36 Months				

	Average dose since last visit (mg/day)		Change from baseline (mg/day)	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)
n	555	1181	555	1181
Mean	3.3445 (8.45540)	4.0343 (10.86980)	-3.4104 (18.53165)	-2.4819 (12.51169)
Median	0	1.4000	0	-0.3000
42 Months				
n	549	1118	549	1118
Mean	3.2254 (5.94291)	3.7296 (8.45764)	-3.6241 (17.77965)	-2.6965 (11.19198)
Median	0	1.0000	0	-0.8000
48 Months				
n	520	1067	520	1067
Mean	2.9456 (5.36569)	3.5439 (6.46955)	-3.8634 (17.31010)	-2.7740 (9.57628)
Median	0	0.6000	0	-0.7000
54 Months				
n	491	1029	491	1029
Mean	2.8527 (6.05274)	3.8151 (10.45572)	-4.2209 (18.90304)	-2.6430 (13.00603)
Median	0	0.2000	0	-1.0000
60+ Months				
n	472	991	472	991
Mean	2.4166 (4.30153)	3.4488 (7.65457)	-4.2123 (17.92592)	-2.9847 (11.02870)
Median	0	0	0	-1.2000

Source: Table 15.101

a. Participants with an average dose of 324.2 mg/day was reported to have received pulse steroids.

Table 28 Summary of Corticosteroid Usage by Visit (Initial Exposure [ITT] Strategy; Population: Eligible)

Corticosteroids Use	Non-Benlysta (N=881)	Benlysta (N=1924)
Baseline		
n	881	1924

Corticosteroids Use	Non-Benlysta (N=881)	Benlysta (N=1924)
Participants taken corticosteroids for SLE since last visit	567 (64.4%)	1379 (71.7%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	263 (29.9%)	573 (29.8%)
≥7.5 mg/day for ≤2 weeks	49 (5.6%)	158 (8.2%)
≥7.5 mg/day for >2 weeks	255 (28.9%)	648 (33.7%)
6 Month		
n	806	1782
Participants taken corticosteroids for SLE since last visit	440 (54.6%)	1139 (63.9%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	249 (30.9%)	577 (32.4%)
≥7.5 mg/day for ≤2 weeks	34 (4.2%)	141 (7.9%)
≥7.5 mg/day for >2 weeks	156 (19.4%)	421 (23.6%)
12 Month		
n	727	1631
Participants taken corticosteroids for SLE since last visit	379 (52.1%)	989 (60.6%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	223 (30.7%)	554 (34.0%)
≥7.5 mg/day for ≤2 weeks	32 (4.4%)	106 (6.5%)
≥7.5 mg/day for >2 weeks	124 (17.1%)	328 (20.1%)
18 Month		
n	664	1477
Participants taken corticosteroids for SLE since last visit	312 (47.0%)	858 (58.1%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	176 (26.5%)	471 (31.9%)
≥7.5 mg/day for ≤2 weeks	32 (4.8%)	102 (6.9%)
≥7.5 mg/day for >2 weeks	104 (15.7%)	285 (19.3%)
24 Month		
n	649	1388
Participants taken corticosteroids for SLE since last visit	301 (46.4%)	752 (54.2%)

Corticosteroids Use	Non-Benlysta (N=881)	Benlysta (N=1924)
Average Dose category in the past 6 months		
Always <7.5 mg/day	182 (28.0%)	435 (31.3%)
≥7.5 mg/day for ≤2 weeks	26 (4.0%)	92 (6.6%)
≥7.5 mg/day for >2 weeks	93 (14.3%)	225 (16.2%)
30 Month		
n	592	1286
Participants taken corticosteroids for SLE since last visit	277 (46.8%)	701 (54.5%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	159 (26.9%)	423 (32.9%)
≥7.5 mg/day for ≤2 weeks	17 (2.9%)	62 (4.8%)
≥7.5 mg/day for >2 weeks	101 (17.1%)	215 (16.7%)
36 Month		
n	589	1226
Participants taken corticosteroids for SLE since last visit	245 (41.6%)	647 (52.8%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	148 (25.1%)	387 (31.6%)
≥7.5 mg/day for ≤2 weeks	22 (3.7%)	66 (5.4%)
≥7.5 mg/day for >2 weeks	75 (12.7%)	194 (15.8%)
42 Month		
n	558	1165
Participants taken corticosteroids for SLE since last visit	248 (44.4%)	597 (51.2%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	148 (26.5%)	368 (31.6%)
≥7.5 mg/day for ≤2 weeks	27 (4.8%)	62 (5.3%)
≥7.5 mg/day for >2 weeks	73 (13.1%)	167 (14.3%)
48 Month		
n	535	1114
Participants taken corticosteroids for SLE since last visit	220 (41.1%)	552 (49.6%)
Average Dose category in the past 6 months		

Corticosteroids Use	Non-Benlysta (N=881)	Benlysta (N=1924)
Always <7.5 mg/day	133 (24.9%)	354 (31.8%)
≥7.5 mg/day for ≤2 weeks	25 (4.7%)	46 (4.1%)
≥7.5 mg/day for >2 weeks	62 (11.6%)	152 (13.6%)
54 Month		
n	506	1070
Participants taken corticosteroids for SLE since last visit	210 (41.5%)	516 (48.2%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	145 (28.7%)	318 (29.7%)
≥7.5 mg/day for ≤2 weeks	16 (3.2%)	56 (5.2%)
≥7.5 mg/day for >2 weeks	49 (9.7%)	142 (13.3%)
60 Month		
n	482	1013
Participants taken corticosteroids for SLE since last visit	188 (39.0%)	484 (47.8%)
Average Dose category in the past 6 months		
Always <7.5 mg/day	124 (25.7%)	307 (30.3%)
≥7.5 mg/day for ≤2 weeks	21 (4.4%)	53 (5.2%)
≥7.5 mg/day for >2 weeks	43 (8.9%)	124 (12.2%)

Source: Table 15.201

Note: Percentages were computed using 'Participants who attended the visit (n)' as denominator

10.4.2.5. Treatment switching

A summary of medication switching during study follow-up is shown below in Table 29.

In summary (Eligible, 0-60+ Months Time-Period):

- The proportion of participants with at least 1 switch was higher in Benlysta (28.0%) exposure group than Non-Benlysta exposure group (13.1%).
- Mean and median numbers of switches were similar between the Benlysta and Non-Benlysta exposure groups.
- Most frequently, switches were reported in <1 year of follow-up in both the exposure groups.
- The most common reason for starting Benlysta was additional therapy needed.
- The most common reasons for stopping Benlysta were other reasons (eg insurance/affordability reasons, pregnancy/planned pregnancy, switch to SC treatments) followed by lack of response.
- The patterns observed for the Current Users and Treatment Initiators were generally comparable to the overall population (Source Table 17.000, Table 17.010 and Table 17.020). However, data on the Treatment Initiators should be interpreted with caution due to the smaller number of participants in this subgroup.

Table 29 Summary of Medication Switching During Study Follow-up Period (Initial Exposure [ITT] Strategy; Population: Eligible)

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Participants with on/off Benlysta switch[a]			
at least 1 switch (n)	123 (13.1%)	568 (28.0%)	691 (23.3%)
1	80 (8.5%)	434 (21.4%)	514 (17.3%)
2	28 (3.0%)	91 (4.5%)	119 (4.0%)
3	15 (1.6%)	43 (2.1%)	58 (2.0%)
Number of on/off Benlysta switches[a]			
N	123	568	691
Mean	1.5 (0.86)	1.3 (0.69)	1.4 (0.73)
Median	1.0	1.0	1.0
Duration (yr) of follow-up prior to first exposure switch			
<1	50 (5.3%)	241 (11.9%)	291 (9.8%)
1-<2	24 (2.6%)	147 (7.2%)	171 (5.8%)
2-<3	24 (2.6%)	83 (4.1%)	107 (3.6%)
3-<4	15 (1.6%)	62 (3.1%)	77 (2.6%)
≥4	10 (1.1%)	35 (1.7%)	45 (1.5%)
Duration (yrs) of Medication Use prior to first exposure switch:			
<1	23 (2.5%)	120 (5.9%)	143 (4.8%)
1-<2	23 (2.5%)	138 (6.8%)	161 (5.4%)
2-<3	15 (1.6%)	103 (5.1%)	118 (4.0%)
3-<4	13 (1.4%)	69 (3.4%)	82 (2.8%)
4-<5	10 (1.1%)	73 (3.6%)	83 (2.8%)
≥5	39 (4.2%)	65 (3.2%)	104 (3.5%)
Mean (SD)	4.77 (5.568)	2.66 (1.861)	3.04 (2.996)
Median	3.04	2.23	2.33

	Non-Benlysta (N=937)	Benlysta (N=2030)	Total (N=2967)
Reason for starting Benlysta[b]			
Participants with at least 1 start	123	134	257
Historical therapy	5 (0.5%)	19 (0.9%)	24 (0.8%)
Additional therapy needed	116 (12.4%)	78 (3.8%)	194 (6.5%)
Replacement therapy due to new access	4 (0.4%)	7 (0.3%)	11 (0.4%)
Replacement therapy due to lack of response	1 (0.1%)	2 (<0.1%)	3 (0.1%)
Replacement therapy due to lack of access	0	2 (<0.1%)	2 (<0.1%)
Other	3 (0.3%)	30 (1.5%)	33 (1.1%)
Reason for stopping Benlysta[b]			
Participants with at least 1 stop	43	568	611
No longer needed	0	58 (2.9%)	58 (2.0%)
Adverse event	5 (0.5%)	77 (3.8%)	82 (2.8%)
Tolerability	2 (0.2%)	31 (1.5%)	33 (1.1%)
Participant refusal	2 (0.2%)	54 (2.7%)	56 (1.9%)
Lack of access to drug	12 (1.3%)	32 (1.6%)	44 (1.5%)
Lack of response	16 (1.7%)	156 (7.7%)	172 (5.8%)
Other	11 (1.2%)	182 (9.0%)	193 (6.5%)

Source: Table 17.000.

a. Off Benlysta implies switch from exposed (Benlysta) to not-exposed (Non-Benlysta) exposure group; On Benlysta implies switch from not-exposed (Non-Benlysta) to exposed (Benlysta) exposure group.

b. Participants may be included in more than 1 reason and were uniquely counted once for each start or stop reason.

10.4.2.6. Hospitalization

A summary of all hospitalizations and SLE-related hospitalizations during study follow-up is shown below in Table 30 and, Table 31 respectively.

In summary (Evaluable, Initial Exposure, While On Initial Exposure and As-Exposed - Time Varying Strategy with 14 Weeks Risk Window strategies, 0-60+ Months Time-Period):

- Incidence and event rates for all hospitalizations per 100 participant-years were higher in the Benlysta than Non-Benlysta exposure group over time for the ITT and While On Initial Exposure strategies, while for the As-Exposed strategy the incidence and event rates were initially higher at 12 Months in the Benlysta exposure group however became equal or slightly higher in the Non-Benlysta exposure group over time.
- Over time, events and incidence rates for all hospitalization slightly decreased in both exposure groups for all 3 strategies, except for the As-Exposed strategy in which the Non-Benlysta exposure group showed a smaller increase in event rates.
- Similar to the overall hospitalizations, incidence and event rates for SLE-related hospitalizations per 100 participant-years were numerically higher in the Benlysta than Non-Benlysta exposure group over time for the ITT and While On Initial Exposure strategies, while the reverse was observed for the As-Exposed strategy; however, all CIs were overlapping.
- Over time, all SLE-related hospitalization events and incidence rates decreased in both exposure groups for all 3 strategies.

Table 30 Overall all Hospitalization event and incidence rates by Exposure Strategies at 0-60+ Time-Period (Population: Evaluable)

Exposure Strategy	Initial Exposure [ITT] Strategy		Initial Exposure [While On Initial Exposure] Strategy		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta
12 Month						
Number of at least 1 hospitalization[a], n1	108	272	103	262	123	269
Total participant-years at-risk	797.1	1720.6	771.1	1656.6	852.8	1685.1
Incidence rate[b] (95% CI)	13.55 (11.11,16.36)	15.81 (13.99,17.80)	13.36 (10.90,16.20)	15.82 (13.96,17.85)	14.42 (11.99,17.21)	15.96 (14.11,17.99)
Number of all hospitalization events[c] (n2)	151	401	144	374	169	383
Events rate[d] (95% CI)	17.73 (15.02,20.80)	21.52 (19.47,23.74)	17.51 (14.76,20.61)	21.10 (19.01,23.35)	18.58 (15.88,21.60)	21.22 (19.15,23.46)
24 Month						
Number of at least 1 hospitalization[a], n1	173	433	162	388	243	407
Total participant-years at-risk	1446.1	3038.6	1374.4	2790.3	1690.8	2871.9
Incidence rate[b] (95% CI)	11.96 (10.25,13.89)	14.25 (12.94,15.66)	11.79 (10.04,13.75)	13.91 (12.56,15.36)	14.37 (12.62,16.30)	14.17 (12.83,15.62)
Number of all hospitalization events[c] (n2)	279	746	251	604	383	642
Events rate[d] (95% CI)	17.23 (15.27,19.38)	21.34 (19.84,22.93)	16.38 (14.41,18.53)	19.40 (17.88,21.01)	20.19 (18.22,22.31)	19.95 (18.44,21.56)

Exposure Strategy	Initial Exposure [ITT] Strategy		Initial Exposure [While On Initial Exposure] Strategy		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta
36 Month						
Number of at least 1 hospitalization[a], n1	225	538	211	472	324	497
Total participant-years at-risk	1980.3	4098.7	1858.4	3643.3	2428.2	3803.5
Incidence rate[b] (95% CI)	11.36 (9.93,12.95)	13.13 (12.04,14.28)	11.35 (9.87,12.99)	12.96 (11.81,14.18)	13.34 (11.93,14.88)	13.07 (11.94,14.27)
Number of all hospitalization events[c] (n2)	388	1007	351	775	566	825
Events rate[d] (95% CI)	16.78 (15.15,18.54)	20.34 (19.10,21.63)	16.30 (14.63,18.09)	18.42 (17.14,19.76)	19.86 (18.26,21.57)	18.69 (17.44,20.01)
48 Month						
Number of at least 1 hospitalization[a], n1	266	614	241	525	392	567
Total participant-years at-risk	2422.8	4979.6	2250.8	4314.3	3067.7	4562.3
Incidence rate[b] (95% CI)	10.98 (9.70,12.38)	12.33 (11.37,13.35)	10.71 (9.40,12.15)	12.17 (11.15,13.26)	12.78 (11.54,14.11)	12.43 (11.43,13.49)
Number of all hospitalization events[c] (n2)	499	1269	438	930	750	1012
Events rate[d] (95% CI)	16.99 (15.53,18.55)	20.25 (19.15,21.40)	16.25 (14.77,17.85)	18.11 (16.96,19.31)	20.10 (18.69,21.59)	18.49 (17.37,19.67)

Exposure Strategy	Initial Exposure [ITT] Strategy		Initial Exposure [While On Initial Exposure] Strategy		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta
60+ Month[e]						
Number of at least 1 hospitalization[a], n1	289	674	261	565	448	611
Total participant-years at-risk	2789.7	5702.7	2571.9	4850.3	3603.3	5192.9
Incidence rate[b] (95% CI)	10.36 (9.20,11.63)	11.82 (10.94,12.75)	10.15 (8.95,11.46)	11.65 (10.71,12.65)	12.43 (11.31,13.64)	11.77 (10.85,12.74)
Number of all hospitalization events[c] (n2)	581	1486	500	1042	911	1149
Events rate[d] (95% CI)	16.68 (15.35,18.10)	20.00 (19.00,21.04)	15.86 (14.50,17.32)	17.60 (16.55,18.70)	20.21 (18.92,21.57)	17.94 (16.92,19.01)

Source: Table 13.110 [Initial Exposure (ITT) Strategy], Table 13.210 [While On Initial Exposure Strategy], Table 13.310 [As-Exposed - Time Varying Strategy with 14 Weeks Risk Window]

Note: ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. While On Initial Exposure Strategy analyzed only events experienced before the first switching on or off Benlysta medication. Time Varying Strategy analyzed events based on exposure status at the time of events occurrence.

a. Cumulative count of participant with at least 1 specified hospitalization event irrespective of number of such events occurring in the time period.
b. Incidence rate was calculated as: Number of first events (n1 or n3)/Total participant-years at risk of event expressed per 100 participant-years. Number of first event was the same as participant with at least 1 hospitalization.
c. Cumulative count of multiple occurrences of the specified hospitalization event if participant experienced more than 1 instance of the event.
d. Event rate was calculated as: Number of all events (n2 or n4)/Total participant-years of follow-up expressed per 100 participant-years.
e. Any events that occurred after 63 months were not reported.

Table 31 Overall SLE-related Hospitalization event and incidence rates by Exposure Strategies at 0-60+ Time-Period (Population: Evaluable)

Exposure Strategy	Initial Exposure [ITT] Strategy		Initial Exposure [While On Initial Exposure] Strategy		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta
12 Month						
Number of at least 1 hospitalization[a], n1	44	96	42	91	52	93
Total participant-years at-risk	830.4	1811.1	802.1	1733.6	885.8	1764.8
Incidence rate[b] (95% CI)	5.30 (3.85,7.11)	5.30 (4.29,6.47)	5.24 (3.77,7.08)	5.25 (4.23,6.45)	5.87 (4.38,7.70)	5.27 (4.25,6.46)
Number of all hospitalization events[c] (n2)	53	132	51	120	63	122
Events rate[d] (95% CI)	6.22 (4.66,8.14)	7.09 (5.93,8.40)	6.20 (4.62,8.15)	6.77 (5.61,8.09)	6.92 (5.32,8.86)	6.76 (5.61,8.07)
24 Month						
Number of at least 1 hospitalization[a], n1	64	146	57	130	84	138
Total participant-years at-risk	1553.3	3341.4	1472.1	3014.8	1818.7	3109.9
Incidence rate[b] (95% CI)	4.12 (3.17,5.26)	4.37 (3.69,5.14)	3.87 (2.93,5.02)	4.31 (3.60,5.12)	4.62 (3.68,5.72)	4.44 (3.73,5.24)
Number of all hospitalization events[c] (n2)	85	230	75	182	120	195
Events rate[d] (95% CI)	5.25 (4.19,6.49)	6.58 (5.76,7.49)	4.89 (3.85,6.13)	5.85 (5.03,6.76)	6.33 (5.24,7.56)	6.06 (5.24,6.97)

Exposure Strategy	Initial Exposure [ITT] Strategy		Initial Exposure [While On Initial Exposure] Strategy		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta
36 Month						
Number of at least 1 hospitalization[a], n1	76	177	68	152	107	161
Total participant-years at-risk	2189.6	4669.2	2048.8	4040.5	2701.4	4229.6
Incidence rate[b] (95% CI)	3.47 (2.73,4.34)	3.79 (3.25,4.39)	3.32 (2.58,4.21)	3.76 (3.19,4.41)	3.96 (3.25,4.79)	3.81 (3.24,4.44)
Number of all hospitalization events[c] (n2)	104	294	92	220	162	236
Events rate[d] (95% CI)	4.50 (3.68,5.45)	5.94 (5.28,6.66)	4.27 (3.44,5.24)	5.23 (4.56,5.97)	5.69 (4.84,6.63)	5.35 (4.69,6.07)
48 Month						
Number of at least 1 hospitalization[a], n1	89	199	78	168	127	182
Total participant-years at-risk	2757.8	5839.7	2546.8	4892.8	3507.9	5202.7
Incidence rate[b] (95% CI)	3.23 (2.59,3.97)	3.41 (2.95,3.92)	3.06 (2.42,3.82)	3.43 (2.93,3.99)	3.62 (3.02,4.31)	3.50 (3.01,4.05)
Number of all hospitalization events[c] (n2)	126	356	109	253	206	276
Events rate[d] (95% CI)	4.29 (3.57,5.11)	5.68 (5.11,6.30)	4.04 (3.32,4.88)	4.93 (4.34,5.57)	5.52 (4.79,6.33)	5.04 (4.47,5.68)
60+ Month[e]						
Number of at least 1 hospitalization[a], n1	95	217	83	179	146	197

Exposure Strategy	Initial Exposure [ITT] Strategy		Initial Exposure [While On Initial Exposure] Strategy		As-Exposed [Time-Varying] Strategy - 14 Weeks risk window	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta	Benlysta
Total participant-years at-risk	3251.7	6861.3	2966.5	5611.2	4210.4	6055.4
Incidence rate[b] (95% CI)	2.92 (2.36,3.57)	3.16 (2.76,3.61)	2.80 (2.23,3.47)	3.19 (2.74,3.69)	3.47 (2.93,4.08)	3.25 (2.81,3.74)
Number of all hospitalization events[c] (n2)	135	408	116	274	241	302
Events rate[d] (95% CI)	3.88 (3.25,4.59)	5.49 (4.97,6.05)	3.68 (3.04,4.41)	4.63 (4.10,5.21)	5.35 (4.69,6.07)	4.71 (4.20,5.28)

Source: Table 13.110 [Initial Exposure (ITT) Strategy], Table 13.210 [While On Initial Exposure Strategy], Table 13.310 [As-Exposed - Time Varying Strategy with 14 Weeks Risk Window].

Note: ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. While On Initial Exposure Strategy analyzed only events experienced before the first switching on or off Benlysta medication. Time Varying Strategy analyzed events based on exposure status at the time of events occurrence.

a. Cumulative count of participant with at least 1 specified hospitalization event irrespective of number of such events occurring in the time period.
b. Incidence rate was calculated as: Number of first events (n1 or n3)/Total participant-years at risk of event expressed per 100 participant-years. Number of first event was the same as participant with at least 1 hospitalization.
c. Cumulative count of multiple occurrences of the specified hospitalization event if participant experienced more than 1 instance of the event.
d. Event rate was calculated as: Number of all events (n2 or n4)/Total participant-years of follow-up expressed per 100 participant-years.
e. Any events that occurred after 63 months were not reported.

10.5. Other analyses

10.5.1. Propensity score analysis

10.5.1.1. Model development

All pre-specified variables collected at baseline, considered by medical experts to be potentially important covariates, with respect to both treatment assignment and likelihood of experiencing outcome, are presented in RAP Table 4.

These baseline characteristics were tested for balance between the exposure groups. Results are presented in Source Table 53.011. In summary, year of entry into the study, sex, BMI at baseline (including imputed), ethnicity, race (including imputed), region, SLEDAI score at baseline (including imputed), corticosteroid use in the past 6 months, and a medical history of allergic reactions, autoimmune disorders, family history of cancer, end stage renal failure, depression and/or anxiety disorders, and dialysis were shown to be unbalanced ($p<0.05$). Current Users were similar to the overall Evaluable population, except for region, which was balanced between the groups (Source Table 53.0111). In treatment Initiators, year of entry into the study, ethnicity, and a medical history of interstitial lung disease, end stage renal failure, and dialysis were shown to be unbalanced ($p<0.05$) (Source Table 53.0112).

Standardized mean differences in the overall Evaluable population before and after IPTW adjustment are shown in Table 32. After applying IPTW, the standardized mean differences decreased to means between 0.1 and -0.1, indicating good balance across the measured covariates after weighing. Similar results were also achieved for Current Users and Treatment Initiators (Source Table 53.021 and Table 53.022). The density of the Logit propensity score is shown in Figure 2 for the Benlysta and Non-Benlysta exposure groups.

Table 32 Standardized Mean Differences before and after IPTW Adjustment (Initial Exposure [ITT] strategy; Population: Evaluable)

Covariate	Level	Standardized covariate mean differences for propensity score model			
		Standardized difference		Variance ratio	
		Unweighted	Weighted	Unweighted	Weighted
Year of entry in the study	2015-2016	0.2376	-0.0071	1.1417	0.9969
	2017-2018	0.0727	0.0059	1.1203	1.0090
	2019-2020[a]	-0.4907	-0.0058	0.5387	0.9914
Age at baseline (years)		0.0239	0.0053	0.7645	0.7809
Sex	Male	-	-	-	-
	Female	0.1510	0.0000	0.6265	1.0000
BMI at baseline	Normal (18.5-<25)	-	-	-	-
	Underweight (<18.5)	0.0048	0.0009	1.0254	1.0046
	Overweight (25-<30)	-0.0570	-0.0065	0.9423	0.9933
	Obese (30-<40)	-0.0014	0.0075	0.9983	1.0092
	Extremely obese (≥40)	0.1233	0.0177	1.4776	1.0552
	Missing	-0.1135	-0.0154	0.3983	0.8735
Ethnicity	Not Hispanic or Latino	-	-	-	-
	Hispanic or Latino	-0.1160	-0.0088	0.8374	0.9862
Race[b]	White	-	-	-	-
	Asian	-0.1721	-0.0047	0.4764	0.9786
	Black	-0.0865	0.0034	0.8667	1.0057
	Other	0.0099	0.0082	1.0512	1.0434
Region	United States/Canada	-	-	-	-
	Europe	0.1072	-0.0175	1.1401	0.9804
	Other	-0.0869	0.0043	0.7174	1.0173
Baseline Clinical SLEDAI 2000 score[c]		0.1957	0.0198	1.4612	1.1166
Baseline not done points Clinical SLEDAI 2000 score[c]		0.1635	0.0024	1.0519	0.9992
Baseline Clinical SLEDAI missing indicator	Yes	0.0578	0.0039	1.9130	1.0413
Baseline SDI[c]		0.0107	0.0128	0.9964	1.0062
Baseline SDI missing indicator	Yes	0.0669	0.0199	1.9708	1.2139
SLE duration since diagnosis at baseline (yrs)		-0.0318	-0.0042	0.9356	0.9218

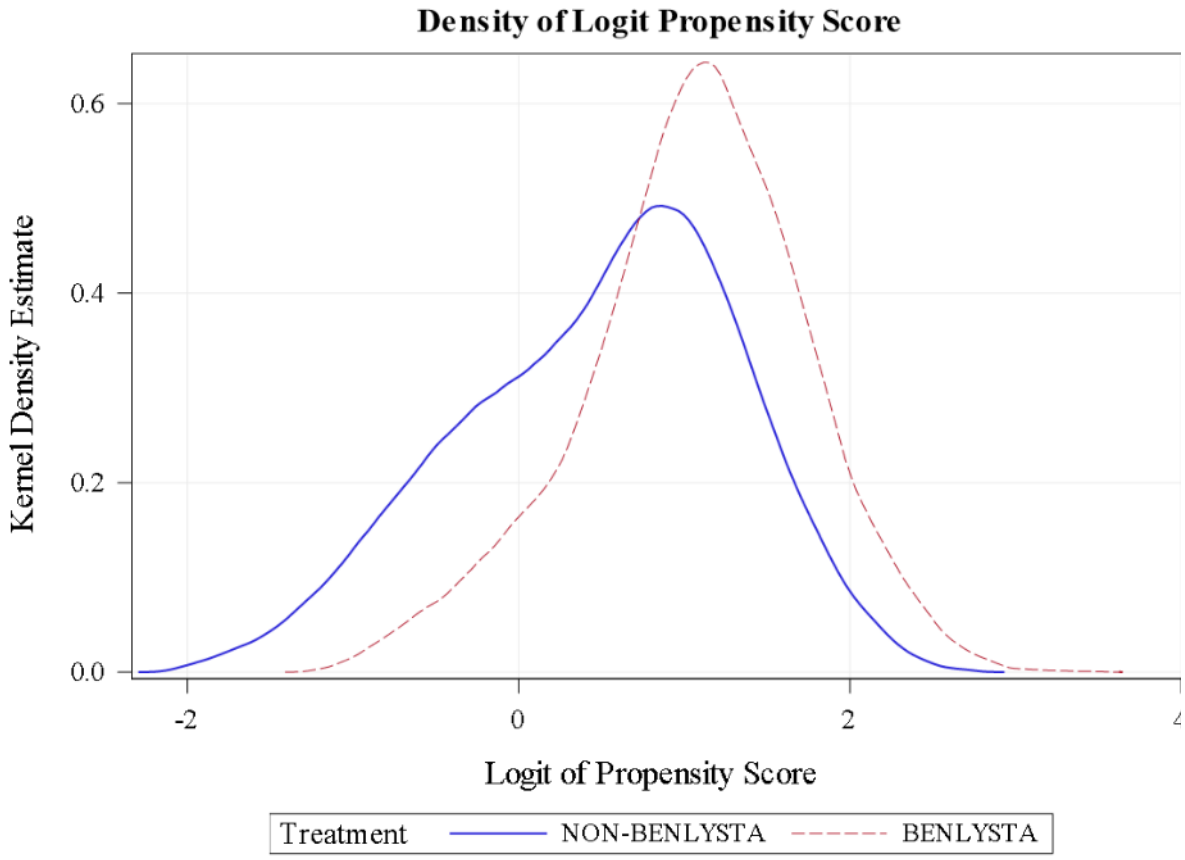
Covariate	Level	Standardized covariate mean differences for propensity score model			
		Standardized difference		Variance ratio	
		Unweighted	Weighted	Unweighted	Weighted
Used corticosteroids for SLE in the past 6 months at baseline	Yes	0.1573	0.0295	0.8851	0.9762
Cardiovascular risk factors	Yes	0.0173	0.0192	1.0008	1.0012
Allergic reactions	Yes	0.1132	0.0156	1.0191	1.0021
Interstitial lung disease	Yes	-0.0292	0.0008	0.8741	1.0037
Chronic Obstructive Pulmonary Disease	Yes	0.0266	-0.0039	1.1724	0.9782
Opportunistic infection	Yes	0.0238	0.0259	1.1185	1.1347
Any other infection	Yes	-0.0138	0.0220	0.9935	1.0114
Autoimmune disorders	Yes	0.2068	0.0236	1.2498	1.0240
Hypogammaglobulinaemia	Yes	0.0190	0.0172	1.1417	1.1285
Cancer	Yes	-0.0452	-0.0088	0.8533	0.9692
NMSC	Yes	0.0586	-0.0150	1.4830	0.9105
Family history of cancer	Yes	0.1569	0.0068	1.1270	1.0048
End stage renal failure	Yes	-0.1662	-0.0072	0.3320	0.9507
Depression and/or anxiety disorder	Yes	0.2267	0.0139	1.1619	1.0080
Suicidal ideation and/or suicidal depression and/or suicidal behavior	Yes	0.0171	0.0138	1.0820	1.0675
Attempted suicide	Yes	-0.0037	0.0004	0.9735	1.0032
Dialysis	Yes	-0.1254	-0.0115	0.3597	0.9119
Splenectomy	Yes	-0.0198	-0.0140	0.8569	0.8978

Source: Table 53.020.

Note: Standardized mean differences of the covariates used for propensity score modeling before and after IPTW adjustment. Other relevant model information, statistics and plots were displayed in the supplementary output Source Figure 53.020. The covariates presented were those retained for the final propensity score model. ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta.

a. Only Non-Benlysta participants enrolled in 2020. Last enrollment 04 February 2020.
b. Missing values assumed modal category.
c. Missing values assumed median value with corresponding indicator covariate set to 1.

Figure 2 Density of logit propensity score plot within each exposure group (Initial Exposure [ITT] strategy; Population: Evaluable)



Source: Figure 53.020
Note: This figure should be read in conjunction with Source Table 53.020. An improvement in the covariate balance after weighting would be indicated by smaller standardized mean differences in the weighted column and variance ratios between 0.5 and 2 in the weighted column. A standardized difference that is less than 0.1 can be considered a negligible difference. A violation of the positivity assumption might result in large inverse probability weights (e.g. > 10).
Performance of propensity score models can be assessed through visual inspection of density plots before and after weighting. The distribution across treatments for continuous covariates after weighting should be more similar than before weighting. ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta.

Before stabilization ,mean (SD) distribution of weight was 3.19 (1.654) in the Non-Benlysta and 1.45 (0.378) in the Benlysta exposure group (Table 33). For Current Users, mean (SD) distribution of weight was 2.90 (1.466) in the Non-Benlysta and 1.52 (0.423) in the Benlysta exposure group (Source Table 53.0311) and in Treatment Initiators mean (SD) distribution of weight was 5.18 (1.867) in the Non-Benlysta and 1.24 (0.110) in the Benlysta exposure group (Source Table 53.0312).

Table 33 Distribution of Weight (Initial Exposure [ITT] strategy; Population: Evaluable)

	Non-Benlysta (N=881)	Benlysta (N=1924)	Total (N=2805)
n	881	1924	2805
Mean (SD)	3.19 (1.654)	1.45 (0.378)	2.00 (1.268)
Quantiles			
100% (Max)	11.85	3.91	11.85
99%	8.59	3.00	7.17
95%	6.55	2.21	4.64
90%	5.33	1.88	3.62
75% (Q3)	3.95	1.53	2.16
50% (Median)	2.85	1.34	1.46
25% (Q1)	1.90	1.22	1.27
10%	1.51	1.15	1.18
5%	1.38	1.12	1.14
1%	1.21	1.08	1.09
0% (Min)	1.17	1.04	1.04

Source: Table 53.031.
Note: ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. N: number of participants in the analysis set; n: number of participants with available data.

Further data on the model development can be found in Source Table 53.012 (Evaluable population), Table 53.0121 (Current Users), and Table 53.0122 (Treatment Initiators), and Source Figure 53.020 (Evaluable population), Figure 53.021 (Current Users), and Figure 53.022 (Treatment Initiators).

After stabilization, mean weights were 1.00 (Non-Benlysta) and 0.99 (Benlysta), and the maximum weight was 3.72 in the Non-Benlysta group (Source Table 53.032). Similar results were also achieved for the Current Users and Treatment Initiators (Source Table 53.0321 and Table 53.0322).

10.5.1.2. AESI incidence rates

Unweighted and Weighted incidence and event rates of AESIs are presented in Table 34 (ITT strategy) and Table 35 (While On Initial Exposure strategy). For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- The overall AESI incidence rates per 100 participant-years follow-up in the Evaluable population were:

- Lower for Benlysta compared with Non-Benlysta for the following AESIs:
  - Mortality for both, the unweighted and weighted rates,
  - Malignancy with differences between the exposure groups being similar in the unweighted analysis (difference 0.1) and differences were more pronounced in the weighted analysis.
- Higher for Benlysta compared with Non-Benlysta for the following AESIs:
  - Serious infections and serious psychiatric event for both, the unweighted and weighted rates,
  - Other infection of special interest with differences between the exposure groups similar in the unweighted analysis (difference 0.05) and differences were more pronounced in the weighted analysis.
- Comparable between Benlysta and Non-Benlysta for opportunistic infections and NMSCs for both, the unweighted and weighted rates.

- The pattern observed for the Current Users was similar to the overall population (Table 34, and Source Table 24.111 and Table 54.011).
- The pattern observed for the Treatment Initiators subgroup showed the following AESI differences (Table 34, and Source Table 24.112 and Table 54.012):
  - Serious infection were higher for Benlysta compared with Non-Benlysta for the unweighted and similar between the exposure groups for the weighted rates,
  - Opportunistic infections, serious psychiatric events, and NMSCs were lower for Benlysta compared with Non-Benlysta for both, the unweighted and weighted rates,
  - Other infections were similar in the Benlysta than in the Non-Benlysta group for both, the unweighted and weighted rates,
  - Malignancies were higher in the Benlysta than in the Non-Benlysta group for both, the unweighted and weighted rates.
- The pattern of results observed for the ITT and the While On Initial Exposure were similar with the following exceptions:
  - Opportunistic infections were lower for Benlysta compared to Non-Benlysta for both, the unweighted and weighted rates in the While On Initial Treatment strategy,
  - Serious psychiatric events were higher for Benlysta compared to Non-Benlysta in the ITT and in the While On Initial Exposure strategy both for the unweighted and weighted rates; the differences however was below the threshold of >0.1 in the While On Initial Exposure weighted analysis.
- The pattern observed for the Current Users subgroup was similar to the overall population, except for other infections, which were higher in the Benlysta than in the

Non-Benlysta group for the weighted rates(Table 35, and Source Table 24.121 and Table 54.021).

- The pattern observed for the Treatment Initiators subgroup for the ITT and the While On Initial Exposure were similar except for the following AESIs (Table 35, and Source Table 24.122 and Table 54.022):
  - Serious infections were higher in the Benlysta than in the Non-Benlysta group for the weighted rates in the While on Initial Exposure strategy and therefore in line with the findings from the overall population and Current Users,
  - Other infections were lower in the Benlysta than in the Non-Benlysta group for both the unweighted and weighted rates,
  - However, this data should be interpreted with caution due to the smaller number of Treatment Initiators and few events for some AESIs.

Table 34 Unweighted and Weighted Rates of AESI (Initial Exposure [ITT] Strategy; Population: Evaluable)

	Unweighted[a]		Weighted[a]	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)
Mortality[b]				
Incidence rate[c] (95% CI)	0.83 (0.56,1.20)	0.65 (0.48,0.86)	0.76 (0.50,1.11)	0.62 (0.46,0.83)
Serious infection[d]				
Incidence rate[c] (95% CI)	1.94 (1.49,2.47)	2.37 (2.02,2.76)	2.00 (1.54, 2.54)	2.39 (2.04, 2.78)
Event rate[e] (95% CI)	2.73 (2.21,3.33)	3.14 (2.75,3.57)	2.88 (2.34, 3.51)	3.18 (2.79, 3.62)
Opportunistic infection				
Incidence rate[c] (95% CI)	0.61 (0.38,0.93)	0.52 (0.37,0.71)	0.62 (0.38, 0.94)	0.54 (0.39, 0.74)
Event rate[e] (95% CI)	0.75 (0.49,1.09)	0.61 (0.44,0.81)	0.71 (0.46, 1.06)	0.66 (0.49, 0.87)
Other infections of special interest				
Incidence rate[c] (95% CI)	0.55 (0.33,0.87)	0.60 (0.44,0.81)	0.49 (0.28, 0.79)	0.64 (0.47, 0.85)
Event rate[e] (95% CI)	0.57 (0.35,0.89)	0.63 (0.46,0.84)	0.49 (0.29, 0.79)	0.66 (0.49, 0.88)
Serious psychiatric event				
Incidence rate[c] (95% CI)	0.14 (0.05,0.34)	0.35 (0.23,0.52)	0.18 (0.07, 0.39)	0.33 (0.22, 0.50)
Event rate[e] (95% CI)	0.20 (0.08,0.41)	0.43 (0.29,0.61)	0.24 (0.10, 0.46)	0.40 (0.27, 0.57)
Malignancy (excl NMSC)				
Incidence rate[c] (95% CI)	0.70 (0.45,1.04)	0.60 (0.43,0.80)	0.77 (0.51, 1.13)	0.57 (0.41, 0.77)
Event rate[e] (95% CI)	0.72 (0.46,1.06)	0.61 (0.44,0.81)	0.78 (0.51, 1.14)	0.57 (0.42, 0.77)
NMSC				
Incidence rate[c] (95% CI)	0.12 (0.03,0.29)	0.14 (0.06,0.25)	0.11 (0.03, 0.29)	0.13 (0.06, 0.24)
Event rate[e] (95% CI)	0.11 (0.03,0.29)	0.17 (0.09,0.30)	0.11 (0.03, 0.29)	0.16 (0.08, 0.28)

Source: Table 24.110 (Unweighted), Table 54.010 (Weighted).

Note: In weighted analysis group, Stabilized IPTW derived from Initial Exposure strategy used to compute weighted incidence and event rates. Weighted number of first events (n1) and weighted number of all events (n2) were rounded to the nearest integer. Incidence rate was calculated as: Weighted number of first events (n1)/Weighted total participant-years at risk of event expressed per 100 participant-years. Event rate was calculated as: Weighted number of all events (n2)/Weighted total participant-years of follow-up expressed per 100 participant-years. 95% CI by exact Poisson distribution method. ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta.

a. Any events that occurred after 63 months were not reported.

b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.
c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years.
d. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.
e. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

Table 35 Unweighted and Weighted Rates of AESI (While On Initial Exposure Strategy; Population: Evaluable)

	Unweighted[a]		Weighted[a]	
	Non-Benlysta (N=881)	Benlysta (N=1924)	Non-Benlysta (N=881)	Benlysta (N=1924)
Mortality[b]				
Incidence rate[c] (95% CI)	0.79 (0.51, 1.17)	0.57 (0.40, 0.80)	0.74 (0.46, 1.11)	0.54 (0.37, 0.76)
Serious infection[d]				
Incidence rate[c] (95% CI)	1.77 (1.33, 2.31)	2.10 (1.74, 2.51)	1.78 (1.33, 2.33)	2.13 (1.76, 2.54)
Event rate[e] (95% CI)	2.51 (1.98, 3.12)	2.55 (2.16, 2.99)	2.61 (2.07, 3.24)	2.59 (2.20, 3.03)
Opportunistic infection				
Incidence rate[c] (95% CI)	0.61 (0.37, 0.95)	0.44 (0.29, 0.65)	0.64 (0.39, 0.99)	0.44 (0.28, 0.64)
Event rate[e] (95% CI)	0.76 (0.49, 1.13)	0.49 (0.33, 0.70)	0.75 (0.47, 1.12)	0.49 (0.33, 0.71)
Other infection of interest				
Incidence rate[c] (95% CI)	0.51 (0.29, 0.84)	0.53 (0.36, 0.75)	0.42 (0.22, 0.72)	0.55 (0.38, 0.78)
Event rate[e] (95% CI)	0.54 (0.31, 0.86)	0.56 (0.38, 0.78)	0.43 (0.23, 0.73)	0.58 (0.40, 0.80)
Serious psychiatric event				
Incidence rate[c] (95% CI)	0.16 (0.05, 0.37)	0.32 (0.19, 0.50)	0.20 (0.07, 0.43)	0.30 (0.18, 0.47)
Event rate[e] (95% CI)	0.22 (0.09, 0.46)	0.35 (0.22, 0.54)	0.27 (0.12, 0.52)	0.32 (0.20, 0.50)
Malignancy (excl NMSC)				
Incidence rate[c] (95% CI)	0.71 (0.44, 1.07)	0.59 (0.41, 0.83)	0.80 (0.51, 1.19)	0.55 (0.37, 0.77)
Event rate[e] (95% CI)	0.73 (0.46, 1.09)	0.59 (0.41, 0.82)	0.81 (0.52, 1.19)	0.54 (0.37, 0.77)
NMSC				
Incidence rate[c] (95% CI)	0.10 (0.02, 0.28)	0.14 (0.06, 0.27)	0.07 (0.01, 0.24)	0.12 (0.05, 0.25)
Event rate[e] (95% CI)	0.10 (0.02, 0.28)	0.19 (0.09, 0.33)	0.07 (0.01, 0.24)	0.17 (0.08, 0.31)

Source: Table 24.120 (Unweighted), Table 54.020 (Weighted).

Note: In the Weighted analysis group: Stabilized IPTW derived from Initial Exposure strategy used to compute weighted incidence and event rates. Weighted number of first events (n1) and weighted number of all events (n2) were rounded to the nearest integer. Incidence rate was calculated as: Weighted number of first events (n1)/Weighted total participant-years at risk of event expressed per 100 participant-years. Event rate was calculated as: Weighted number of all events (n2)/Weighted total participant-years of follow-up expressed per 100 participant-years. 95% CI by exact Poisson distribution method. While On Initial Exposure Strategy analyzed only events experienced before the first switching on or off Benlysta medication.

a. Any events that occurred after 63 months were not reported.

b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.

c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years.
d. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.
e. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

10.5.2. Elderly analyses

10.5.2.1. Participants – Elderly population

The study completion status and reasons for withdrawal are shown in Table 36.

In Summary (Eligible population):

- Of the 2967 participants in the Eligible population, 236 participants were ≥65 years of age (96 Non-Benlysta and 140 Benlysta) and 39 participants were ≥75 years of age (16 Non-Benlysta and 23 Benlysta)
- Participants in ≥65 years of age group:
  - 46.6% of participants completed the study (50.0% Non-Benlysta vs 44.3% Benlysta),
  - 53.4% withdrew from the study
  - (50.0% Non-Benlysta vs 55.7% Benlysta),
  - The most common reason for study withdrawal was Lost to follow-up (19.9%) (17.7% Non-Benlysta vs 21.4% Benlysta).
- Participants in ≥75 years of age group:
  - 23.1% of participants completed the study (31.3% Non-Benlysta vs 17.4% Benlysta),
  - 76.9% withdrew from the study
  - (68.8% Non-Benlysta vs 82.6% Benlysta).
  - The most common reason for study withdrawal:
    - Lost to follow-up (28.2%),
    - (25.0% Non-Benlysta vs 30.4% Benlysta) and
    - Adverse event, that is, Death (25.6%)
    - (18.8% Non-Benlysta vs 30.4% Benlysta).
  - However, this data should be interpreted with caution due to the smaller number of participants in the ≥75 years of age group.
- In both analyses by age group, the proportion of participants who withdrew was higher in the Benlysta exposure group than in the Non-Benlysta exposure group.
- Overall, the proportion of participants who withdrew in the ≥65 years of age group was similar to the overall population.

Table 36 Completion Status – Elderly Population (Population: Eligible)

	Number (%) of participants					
	Participants ≥65 Years of Age			Participants ≥75 Years of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
Study Completion Status						
Completed	48 (50.0%)	62 (44.3%)	110 (46.6%)	5 (31.3%)	4 (17.4%)	9 (23.1%)
Withdrawn	48 (50.0%)	78 (55.7%)	126 (53.4%)	11 (68.8%)	19 (82.6%)	30 (76.9%)
Reason for withdrawal						
Adverse event[a]	7 (7.3%)	15 (10.7%)	22 (9.3%)	3 (18.8%)	7 (30.4%)	10 (25.6%)
AESI	0	0	0	0	0	0
Other adverse event (not of special interest)	0	0	0	0	0	0
Death	7 (7.3%)	15 (10.7%)	22 (9.3%)	3 (18.8%)	7 (30.4%)	10 (25.6%)
Lost to follow-up	17 (17.7%)	30 (21.4%)	47 (19.9%)	4 (25.0%)	7 (30.4%)	11 (28.2%)
Withdrew consent	10 (10.4%)	14 (10.0%)	24 (10.2%)	2 (12.5%)	2 (8.7%)	4 (10.3%)
Investigator discretion	7 (7.3%)	10 (7.1%)	17 (7.2%)	0	2 (8.7%)	2 (5.1%)
Study closed/terminated	7 (7.3%)	9 (6.4%)	16 (6.8%)	2 (12.5%)	1 (4.3%)	3 (7.7%)

Source: Table 2.0001, and Table2.0002.

Percentages were calculated from N (number of participants in header column).

a. Number of participants with AE and those who died was based on information from eCRF end of study page and not from adverse events page.

10.5.2.2. Demographics – Elderly population

The baseline demographics data for the Eligible population are summarized in Table 37.

In summary (Eligible population):

- Participants in ≥65 years of age group:
  - Overall, baseline demographics were similar between Benlysta and Non-Benlysta exposure groups, with a slightly higher proportion of female and White participants in the Benlysta group as compared with the Non-Benlysta group while the Non-Benlysta group was more ethnically diverse.
  - Overall, demographic characteristics were similar in the ≥65 years of age group compared with the overall population except for the mean age, age by categories, and proportion of White participants; all being higher in the ≥65 years of age group compared with the overall population.
- Participants in ≥75 years of age group:
  - Overall, baseline demographics were similar between Benlysta and Non-Benlysta exposure groups, with a slightly higher proportion of females in the Non-Benlysta group than the Benlysta group.
  - However, this data should be interpreted with caution due to the smaller number of participants in the ≥75 years of age group.

Table 37 Demographics – Elderly Population (Population: Eligible)

	Participants ≥65 Years of Age			Participants ≥75 Years of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
Age, Years						
n	96	140	236	16	23	39
Mean (SD)	70.2 (4.14)	70.2 (5.01)	70.2 (4.67)	77.3 (2.41)	79.4 (3.39)	78.5 (3.17)
Median	70.0	69.0	69.0	77.0	79.0	78.0
Sex, n (%)						
n	96	140	236	16	23	39
Female	86 (89.6%)	130 (92.9%)	216 (91.5%)	15 (93.8%)	20 (87.0%)	35 (89.7%)
Male	10 (10.4%)	10 (7.1%)	20 (8.5%)	1 (6.3%)	3 (13.0%)	4 (10.3%)
Ethnicity						
n	96	139	235	16	23	39
Hispanic or Latino	11 (11.5%)	15 (10.8%)	26 (11.1%)	3 (18.8%)	2 (8.7%)	5 (12.8%)
Not Hispanic or Latino	85 (88.5%)	124 (89.2%)	209 (88.9%)	13 (81.3%)	21 (91.3%)	34 (87.2%)
Race, n (%)						
n	96	139	235	16	23	39
White	76 (79.2%)	117 (84.2%)	193 (82.1%)	15 (93.8%)	21 (91.3%)	36 (92.3%)
Asian	5 (5.2%)	4 (2.9%)	9 (3.8%)	1 (6.3%)	0	1 (2.6%)
Black-African American or African Heritage	14 (14.6%)	14 (10.1%)	28 (11.9%)	0	1 (4.3%)	1 (2.6%)
Alaska Native or American Indian[a]	0	3 (2.2%)	3 (1.3%)	0	1 (4.3%)	1 (2.6%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Multiracial	1 (1.0%)	1 (0.7%)	2 (0.9%)	0	0	0
Height						
n	95	139	234	16	22	38
Mean (SD)	161.2 (8.38)	162.6 (8.93)	162.0 (8.72)	157.6 (7.59)	160.4 (9.65)	159.2 (8.84)

	Participants ≥65 Years of Age			Participants ≥75 Years of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
Median	161.0	162.0	162.0	157.5	160.0	160.0
Weight						
n	95	140	235	16	23	39
Mean (SD)	73.97 (15.469)	75.32 (18.944)	74.77 (17.600)	67.52 (10.748)	68.69 (13.084)	68.21 (12.044)
Median	74.80	70.40	72.00	68.85	66.70	67.00
BMI						
n	95	139	234	16	22	38
Mean (SD)	28.55 (6.184)	28.37 (6.514)	28.44 (6.369)	27.35 (4.895)	26.21 (3.964)	26.69 (4.354)
Median	28.67	27.26	27.69	27.95	25.59	25.89

Source: Table 6.0001,Table 6.0002

a. American Indian from North/Central/South America.

10.5.2.3. SLE disease characteristics – Elderly population

10.5.2.3.1. SLE disease duration – Elderly population

The baseline disease duration from diagnosis by study cohorts for participants in both ≥65 years of age and ≥75 years of age is summarized in Table 38.

In summary (Eligible population):

- Participants in ≥65 years of age group:
  - The median SLE duration was similar between the Benlysta and the Non-Benlysta group.
  - Disease duration was higher in the ≥65 years of age group compared with the overall population.
- Participants in ≥75 years of age group:
  - The SLE duration was higher in the Benlysta group than Non-Benlysta.
  - However, this data should be interpreted with caution due to the smaller number of participants in the ≥75 years of age group.

Table 38 Overall Summary of SLE Disease Duration at Baseline by Study Cohort – Elderly Population (Population: Eligible)

	Participants ≥65 Years of Age		Participants ≥75 Years of Age	
	Non-Benlysta (N=96)	Benlysta (N=140)	Non-Benlysta (N=16)	Benlysta (N=23)
SLE duration since diagnosis (Years)				
n	96	140	16	23
Mean (SD)	13.82 (11.796)	14.32 (12.058)	11.65 (12.759)	13.51 (12.310)
Median	10.66	11.08	5.19	7.03
SLE duration category since diagnosis (Years)				
0-<1	8 (8.3%)	7 (5.0%)	1 (6.3%)	1 (4.3%)
1-<5	20 (20.8%)	35 (25.0%)	7 (43.8%)	7 (30.4%)
5-<10	17 (17.7%)	19 (13.6%)	2 (12.5%)	4 (17.4%)
10-<15	12 (12.5%)	24 (17.1%)	0	3 (13.0%)
15-<20	14 (14.6%)	12 (8.6%)	3 (18.8%)	0
≥20	25 (26.0%)	43 (30.7%)	3 (18.8%)	8 (34.8%)

Source: Table 12.0001, Table 12.0002; Not shown: Current Users and Treatment Initiators.

10.5.2.3.2. SDI – Elderly population

The summary of baseline SDI for participants in both ≥65 years of age and ≥75 years of age groups in the Eligible population are summarized in Table 39.

In summary (Eligible population):

- Participants in ≥65 years of age group:
  - At baseline, organ damage as assessed by SDI score was slightly higher in the Benlysta exposure group than the Non-Benlysta group.
  - Most common SDI score components were ocular, followed by musculoskeletal and neuropsychiatric in both exposure groups, and malignancy in the Non-Benlysta group.
  - SDI scores were slightly higher in the ≥65 years of age group compared with the overall population.
- Participants in ≥75 years of age group:
  - At baseline, organ damage as assessed by SDI score was higher in the Benlysta exposure group than the Non-Benlysta with 60% of participants in the Benlysta exposure group having an SDI score ³3.
  - Most common SDI score components were ocular, followed by musculoskeletal, neuropsychiatric, and malignancy.
  - However, this data should be interpreted with caution due to the smaller number of participants in the ≥75 years of age group.

Table 39 Summary of Baseline SDI – Elderly Population (Population: Eligible)

	Participants ≥65 Years Of Age			Participants ≥75 Years Of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
SDI score						
n	94	135	229	16	20	36
Mean (SD)	1.8 (1.90)	2.1 (1.93)	2.0 (1.92)	2.2 (1.76)	3.2 (2.43)	2.7 (2.19)
Median	1.0	2.0	1.0	2.0	3.0	2.0
SDI score category						
0	18 (19.1%)	24 (17.8%)	42 (18.3%)	2 (12.5%)	2 (10.0%)	4 (11.1%)
1	35 (37.2%)	38 (28.1%)	73 (31.9%)	5 (31.3%)	4 (20.0%)	9 (25.0%)
2	21 (22.3%)	33 (24.4%)	54 (23.6%)	4 (25.0%)	2 (10.0%)	6 (16.7%)
≥3	20 (21.3%)	40 (29.6%)	60 (26.2%)	5 (31.3%)	12 (60.0%)	17 (47.2%)
SDI score components (reported in ≥10% of participants on any group)						
Ocular	37 (39.4%)	63 (46.7%)	100 (43.7%)	9 (56.3%)	10 (50.0%)	19 (52.8%)
Any cataract ever	32 (34.0%)	58 (43.0%)	90 (39.3%)	9 (56.3%)	9 (45.0%)	18 (50.0%)
Retinal change or optic atrophy	9 (9.6%)	10 (7.4%)	19 (8.3%)	1 (6.3%)	2 (10.0%)	3 (8.3%)
Neuropsychiatric	13 (13.8%)	28 (20.7%)	41 (17.9%)	4 (25.0%)	6 (30.0%)	10 (27.8%)
Cognitive impairment or major psychosis	5 (5.3%)	13 (9.6%)	18 (7.9%)	1 (6.3%)	3 (15.0%)	4 (11.1%)
Renal	6 (6.4%)	9 (6.7%)	15 (6.6%)	1 (6.3%)	2 (10.0%)	3 (8.3%)
Estimated or measured GFR < 50%	3 (3.2%)	6 (4.4%)	9 (3.9%)	0	2 (10.0%)	2 (5.6%)
Cardiovascular	12 (12.8%)	22 (16.3%)	34 (14.8%)	2 (12.5%)	6 (30.0%)	8 (22.2%)
Angina or coronary artery bypass	7 (7.4%)	4 (3.0%)	11 (4.8%)	2 (12.5%)	1 (5.0%)	3 (8.3%)
Myocardial infarction ever - 1	3 (3.2%)	9 (6.7%)	12 (5.2%)	0	2 (10.0%)	2 (5.6%)

	Participants ≥65 Years Of Age			Participants ≥75 Years Of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
Cardiomyopathy (Ventricular dysfunction)	1 (1.1%)	6 (4.4%)	7 (3.1%)	0	4 (20.0%)	4 (11.1%)
Gastrointestinal	3 (3.2%)	19 (14.1%)	22 (9.6%)	0	4 (20.0%)	4 (11.1%)
Infarction or resection of bowel - 1	2 (2.1%)	13 (9.6%)	15 (6.6%)	0	3 (15.0%)	3 (8.3%)
Stricture or upper gastrointestinal tract surgery ever	1 (1.1%)	4 (3.0%)	5 (2.2%)	0	2 (10.0%)	2 (5.6%)
Musculoskeletal	23 (24.5%)	40 (29.6%)	63 (27.5%)	4 (25.0%)	10 (50.0%)	14 (38.9%)
Muscle atrophy or weakness	13 (13.8%)	16 (11.9%)	29 (12.7%)	2 (12.5%)	6 (30.0%)	8 (22.2%)
Deforming or erosive arthritis	9 (9.6%)	19 (14.1%)	28 (12.2%)	1 (6.3%)	3 (15.0%)	4 (11.1%)
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	11 (11.7%)	18 (13.3%)	29 (12.7%)	3 (18.8%)	5 (25.0%)	8 (22.2%)
Diabetes (regardless of treatment)	8 (8.5%)	14 (10.4%)	22 (9.6%)	1 (6.3%)	3 (15.0%)	4 (11.1%)
Malignancy	13 (13.8%)	11 (8.1%)	24 (10.5%)	4 (25.0%)	6 (30.0%)	10 (27.8%)
Malignancy - 1 site	13 (13.8%)	10 (7.4%)	23 (10.0%)	4 (25.0%)	5 (25.0%)	9 (25.0%)

Source: Table 11.0001, and Table 11.0002. GFR; Glomerular filtration rate.

10.5.2.3.3. Corticosteroids usage – Elderly population

The corticosteroids usage at baseline in both ≥65 years of age and ≥75 years of age groups for the Eligible population is provided in Table 40.

In summary (Eligible population):

- Participants in ≥65 years of age group:
  - The majority of participants who ever took corticosteroids for SLE had a median duration of 2.29 years in Non-Benlysta vs 5.00 years in Benlysta.
  - Approximately 50% of participants were currently (at baseline) on corticosteroids (43.8% Non-Benlysta; 58.6% Benlysta).
  - A total of 51.0% of participants in the Non-Benlysta exposure group and 69.3% of participants in Benlysta exposure group used corticosteroids in the past 6 months.
  - The median corticosteroid dose in the past 6 month was similar between Non-Benlysta and Benlysta exposure groups.
  - The pattern of corticosteroids usage in the ≥65 years of age group was similar to the overall population.
- Participants in ≥75 years of age group:
  - The majority of participants who ever took corticosteroids for SLE, had a median duration of 1.71 years in Non-Benlysta vs 3.92 years in Benlysta.
  - The proportion of participants currently (at baseline) on corticosteroids was considerably lower in the Non-Benlysta (31.3%) than Benlysta (65.2%) exposure group.
  - A total of 37.5% of participants in the Non-Benlysta exposure group and 69.6% of participants in Benlysta exposure group used corticosteroids in the past 6 months.
  - The median corticosteroid dose was higher in the Non-Benlysta exposure group compared to Benlysta.
  - However, this data should be interpreted with caution due to the smaller number of participants in the ≥75 years of age group.

Table 40 Overall Summary of Corticosteroids Usage at Baseline – Elderly Population (Population: Eligible)

Corticosteroids Use	≥65 Years Of Age			≥75 Years Of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
Participant ever taken corticosteroids for SLE	86 (89.6%)	124 (88.6%)	210 (89.0%)	12 (75.0%)	19 (82.6%)	31 (79.5%)
Duration of corticosteroids use (years)						
n	86	124	210	12	19	31
Mean (SD)	5.80 (8.068)	8.09 (8.262)	7.15 (8.241)	4.46 (9.793)	5.80 (6.025)	5.28 (7.576)
Median	2.29	5.00	3.96	1.71	3.92	2.92
Participant currently taking corticosteroids for SLE	42 (43.8%)	82 (58.6%)	124 (52.5%)	5 (31.3%)	15 (65.2%)	20 (51.3%)
Used Corticosteroids for SLE in the past 6 months	49 (51.0%)	97 (69.3%)	146 (61.9%)	6 (37.5%)	16 (69.6%)	22 (56.4%)
Average dose in the past 6 months (mg/day)[a]						
n	49	97	146	6	16	22
Mean	6.9633 (4.82661)	8.3180 (10.44491)	7.8634 (8.96399)	7.0000 (3.94968)	7.0719 (9.25999)	7.0523 (8.05999)
Median	5.0000	5.0000	5.0000	7.5000	5.0000	5.0000
Average Dose category in the past 6 months						
Always <7.5 mg/day	28 (29.2%)	48 (34.3%)	76 (32.2%)	3 (18.8%)	8 (34.8%)	11 (28.2%)
≥7.5 mg/day for ≤2 weeks	3 (3.1%)	14 (10.0%)	17 (7.2%)	0	2 (8.7%)	2 (5.1%)
≥7.5 mg/day for >2 weeks	18 (18.8%)	35 (25.0%)	53 (22.5%)	3 (18.8%)	6 (26.1%)	9 (23.1%)
≥7.5 mg/day but <20 mg/day	14 (14.6%)	24 (17.1%)	38 (16.1%)	2 (12.5%)	4 (17.4%)	6 (15.4%)
≥20 mg/day but <40 mg/day	4 (4.2%)	8 (5.7%)	12 (5.1%)	1 (6.3%)	1 (4.3%)	2 (5.1%)
≥40 mg/day but <60 mg/day	0	1 (0.7%)	1 (0.4%)	0	0	0
≥60 mg/day	0	2 (1.4%)	2 (0.8%)	0	1 (4.3%)	1 (2.6%)

Corticosteroids Use	≥65 Years Of Age			≥75 Years Of Age		
	Non-Benlysta (N=96)	Benlysta (N=140)	Total (N=236)	Non-Benlysta (N=16)	Benlysta (N=23)	Total (N=39)
Parenteral: At least 1 dose ≥40 mg in past 6 months[b]	1 (1.0%)	9 (6.4%)	10 (4.2%)	0	5 (21.7%)	5 (12.8%)
Intramuscular: At least 1 dose ≥40 mg in past 6 months[b]	4 (4.2%)	7 (5.0%)	11 (4.7%)	0	2 (8.7%)	2 (5.1%)

Source: Table 15.0001, Table 15.0002.

Note: Minimum duration of corticosteroids use of <0.1 years corresponds to duration of less than a month.

a. Participants with an average dose of 324.2 mg/day was reported to have received pulse steroids.

b. Participants with both Parenteral and Intramuscular routes of administration were counted in both categories.

10.5.2.4. Adverse events of special interest – Elderly population

10.5.2.4.1. Initial Exposure (ITT) – Elderly Population

The summary of AESIs by time period for participants with ≥65 years of age and ≥75 years of age are shown in Table 41.

In summary (Evaluable population, 0-60+ Months Time-Period):

- Participants in ≥65 years of age group:
- AESIs were reported in 18 (19.6%) participants in the Non-Benlysta group and in 40 (29.9%) participants in the Benlysta group.
- 15 (11.2%) participants in the Benlysta group and 7 (7.6%) participants in the Non-Benlysta group died. The most frequent causes of death at SOC and PT level were cardiac disorders, general disorders and administration site conditions, and infections and infestations in the Benlysta group, and cardiac disorders, infections and infestations, and respiratory, thoracic and mediastinal disorders in the Non-Benlysta group. As the proportion of participants with the events were smaller, data should be interpreted with caution (Table 41 and Table 42).
- 11 (8.2%) participants in the Benlysta group and 2 (2.2%) participants in the Non-Benlysta group had malignancies (Table 41 and Table 43).
- The proportions of participants who died, reported malignancies or serious infections were higher in the Benlysta than the Non-Benlysta exposure groups, while the proportion of participants with opportunistic infections, other infections of special interest, and NMSC was comparable or lower in the Benlysta group compared with the Non-Benlysta group. One of the participants in the Benlysta group and none in the Non-Benlysta group reported serious psychiatric events.
- A total of 32 AESIs were reported in 18 participants in the Non-Benlysta group and 55 AESIs were reported in 40 participants in the Benlysta group. The number of AESIs and participants with AESIs were the same, except for serious infections, for which participants reported multiple events in both exposure groups (Source Table 23.0001).
- Compared with the overall population, the proportion of participants reporting AESIs was higher in the ≥65 years of age group. Differences were also seen in the pattern of AESIs, as in the overall population serious infections were higher in the Benlysta compared with the Non-Benlysta group.
- Participants in ≥75 years of age group:
- AESIs were reported in 3 of 15 (20.0%) participants in the Non-Benlysta group and in 12 of 23 (52.2%) participants in the Benlysta group.

- The proportions of participants who died, reported malignancies, serious infections, NMSC, or serious psychiatric events were higher in the Benlysta than the Non-Benlysta exposure groups. None of the participants reported opportunistic infections or other infections of special interest.
- A total of 5 AESIs were reported in 3 participants in the Non-Benlysta group and 17 AESIs were reported in 12 participants in the Benlysta group. The number of AESIs and participants with AESIs were the same, except for serious infections, for which 1 participant each exposure group reported 2 events (Source Table 23.0002).
- However, this data should be interpreted with caution due to the smaller number of participants in the ≥75 years of age group.

Table 41 Summary of AESIs by Time Period – Elderly Population (Initial Exposure [ITT] strategy; Population: Evaluable)

	Number (%) of participants									
	12-month		24-month		36-month		48-month		≥60-month[a]	
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
≥65 Years Of Age, N	92	134	92	134	92	134	92	134	92	134
At least 1 AESI, n (%)	3 (3.3%)	13 (9.7%)	10 (10.9%)	21 (15.7%)	15 (16.3%)	26 (19.4%)	16 (17.4%)	30 (22.4%)	18 (19.6%)	40 (29.9%)
Death[b]	1 (1.1%)	4 (3.0%)	4 (4.3%)	7 (5.2%)	6 (6.5%)	10 (7.5%)	7 (7.6%)	11 (8.2%)	7 (7.6%)	15 (11.2%)
Serious infections[c]	1 (1.1%)	5 (3.7%)	4 (4.3%)	10 (7.5%)	7 (7.6%)	12 (9.0%)	8 (8.7%)	14 (10.4%)	9 (9.8%)	18 (13.4%)
Opportunistic infection	0	1 (0.7%)	0	1 (0.7%)	1 (1.1%)	1 (0.7%)	1 (1.1%)	2 (1.5%)	1 (1.1%)	2 (1.5%)
Serious	0	0	0	0	1 (1.1%)	0	1 (1.1%)	1 (0.7%)	1 (1.1%)	1 (0.7%)
Non-serious	0	1 (0.7%)	0	1 (0.7%)	0	1 (0.7%)	0	1 (0.7%)	0	1 (0.7%)
Other infections of interest	1 (1.1%)	1 (0.7%)	2 (2.2%)	1 (0.7%)	3 (3.3%)	1 (0.7%)	4 (4.3%)	1 (0.7%)	4 (4.3%)	1 (0.7%)
Serious	0	0	0	0	0	0	0	0	0	0
Non-serious	1 (1.1%)	1 (0.7%)	2 (2.2%)	1 (0.7%)	3 (3.3%)	1 (0.7%)	4 (4.3%)	1 (0.7%)	4 (4.3%)	1 (0.7%)
Serious psychiatric event	0	0	0	0	0	0	0	0	0	1 (0.7%)
Malignancy (excl NMSC)	0	4 (3.0%)	1 (1.1%)	6 (4.5%)	1 (1.1%)	7 (5.2%)	1 (1.1%)	8 (6.0%)	2 (2.2%)	11 (8.2%)
NMSC	0	0	1 (1.1%)	1 (0.7%)	1 (1.1%)	1 (0.7%)	1 (1.1%)	1 (0.7%)	1 (1.1%)	1 (0.7%)

	Number (%) of participants									
	12-month		24-month		36-month		48-month		≥60-month[a]	
	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
≥75 Years Of Age, N	15	23	15	23	15	23	15	23	15	23
At least 1 AESI, n (%)	2 (13.3%)	3 (13.0%)	2 (13.3%)	4 (17.4%)	3 (20.0%)	7 (30.4%)	3 (20.0%)	9 (39.1%)	3 (20.0%)	12 (52.2%)
Death[b]	1 (6.7%)	1 (4.3%)	2 (13.3%)	2 (8.7%)	3 (20.0%)	4 (17.4%)	3 (20.0%)	5 (21.7%)	3 (20.0%)	7 (30.4%)
Serious infections[c]	1 (6.7%)	1 (4.3%)	1 (6.7%)	1 (4.3%)	1 (6.7%)	2 (8.7%)	1 (6.7%)	3 (13.0%)	1 (6.7%)	4 (17.4%)
Opportunistic infection	0	0	0	0	0	0	0	0	0	0
Serious	0	0	0	0	0	0	0	0	0	0
Non-serious	0	0	0	0	0	0	0	0	0	0
Other infections of interest	0	0	0	0	0	0	0	0	0	0
Serious	0	0	0	0	0	0	0	0	0	0
Non-serious	0	0	0	0	0	0	0	0	0	0
Malignancy (excl NMSC)	0	2 (8.7%)	0	2 (8.7%)	0	2 (8.7%)	0	3 (13.0%)	0	3 (13.0%)
Serious psychiatric event	0	0	0	0	0	0	0	0	0	1 (4.3%)
NMSC	0	0	0	1 (4.3%)	0	1 (4.3%)	0	1 (4.3%)	0	1 (4.3%)

Source: Table 23.0001, and Table 23.0002.

Note: ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta.

a. Any events that occurred after 63 months were not reported.

b. Fatal SAE onset date was used for slotting of the mortality events.

c. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.

Table 42 Summary of Fatal AESI by SOC and PT – Elderly Population (Participants ≥65 Years Old) (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Total	
	Non-Benlysta (N=92)	Benlysta (N=134)
All Deaths	7 (7.6%)	15 (11.2%)
Cardiac disorders	2 (2.2%)	4 (3.0%)
Cardiac arrest	2 (2.2%)	0
Cardiac failure congestive	0	2 (1.5%)
Coronary artery disease	0	1 (0.7%)
Ventricular tachycardia	0	1 (0.7%)
General disorders and administration site conditions	0	4 (3.0%)
Death	0	3 (2.2%)
Multiple organ dysfunction syndrome	0	1 (0.7%)
Hepatobiliary disorders	1 (1.1%)	0
Acute hepatic failure	1 (1.1%)	0
Infections and infestations	2 (2.2%)	3 (2.2%)
COVID-19	0	1 (0.7%)
COVID-19 pneumonia	1 (1.1%)	0
Retroperitoneal abscess	0	1 (0.7%)
Septic shock	1 (1.1%)	1 (0.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.7%)
Acute myeloid leukaemia	0	1 (0.7%)
Psychiatric disorders	0	1 (0.7%)
Mental status changes	0	1 (0.7%)
Renal and urinary disorders	0	1 (0.7%)
Renal failure	0	1 (0.7%)
Respiratory, thoracic and mediastinal disorders	2 (2.2%)	1 (0.7%)
Acute respiratory failure	1 (1.1%)	0
Respiratory distress	1 (1.1%)	0
Respiratory failure	0	1 (0.7%)

Source: Table 23.2001; Not shown: Current Users and Treatment Initiators.
Note: SOC and PT were coded using MedDRA version 27.1. ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. Percentages were based on total number of participants (N) in each column. Participants could be included in more than 1 SOC or PT if they had multiple fatal AEs. The SOC and PT for a participant with Verbatim text 'ALTERED MENTAL STATUS' were incorrectly reported as 'Psychiatric disorders' and 'Mental status changes', respectively. The correct classification should be 'Nervous system disorders' and 'Depressed level of consciousness'.

Table 43 Summary of Malignancy (excluding NMSC) by SOC and PT – Elderly Population (Participants ≥65 Years Old) (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Total	
	Non-Benlysta (N=92)	Benlysta (N=134)
All Malignancy (excl. NMSC)	2 (2.2%)	11 (8.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.2%)	11 (8.2%)
Acute myeloid leukaemia	0	1 (0.7%)
Adenocarcinoma pancreas	0	1 (0.7%)
Breast cancer	0	2 (1.5%)
Colon cancer	0	1 (0.7%)
Endometrial adenocarcinoma	0	1 (0.7%)
Gastrointestinal stromal tumour	0	1 (0.7%)
Large granular lymphocytosis	0	1 (0.7%)
Lung neoplasm malignant	1 (1.1%)	0
Malignant melanoma stage I	0	1 (0.7%)
Non-Hodgkin's lymphoma	0	1 (0.7%)
Paget's disease of the vulva	0	1 (0.7%)
Transitional cell carcinoma	1 (1.1%)	0

Source: Table 23.3001; Not shown: Current Users and Treatment Initiators.
Note: SOC and PT were coded using MedDRA version 27.1. ITT Strategy analyzed all data values or events at every time period or visit using Initial Exposure irrespective of switching to or off Benlysta. Percentages were based on total number of participants (N) in each column. Participants could be included in more than 1 SOC or PT if they had multiple fatal AEs.

10.5.2.4.2. As-Exposed (Time-varying – 14 weeks risk window) – Elderly Population

Data summary and analysis results for this strategy are shown in Table 44 as cumulative incidence by 12-month time periods. The incidence rates at 0-60+ Months Time-Period is also presented in Table 45 alongside incidence rates at the same time period for other exposure strategies. For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- The overall AESI incidence rates per 100 participant-years follow-up in the Evaluable population were:
- Lower in Benlysta compared to Non-Benlysta for mortality and other infections of special interest,
- Higher in Benlysta compared to Non-Benlysta for serious infections, and opportunistic infections,

- Comparable between Benlysta and Non-Benlysta for, malignancies and NMSCs,
- Only 1 AESI for serious psychiatric events was reported in the Non-Benlysta group and none in the Benlysta group,
- As the number of events was smaller, data should be interpreted with caution.

Table 44 Cumulative AESI event and incidence rates by 12-month periods – Elderly Population (As-Exposed [Time-Varying - 14 Weeks risk window] Exposure Strategy; Population: Evaluable)

Time Period	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Total participant-years of follow-up	92.8	126.2	181.4	225.6	257.2	311.4	327.5	386.5	389.5	453.7
Mortality[b]										
Number of deaths, n1	1	4	4	7	7	9	9	9	11	11
Total participant-years at-risk	92.8	126.2	181.4	225.6	257.2	311.4	327.5	386.5	389.5	453.7
Incidence rate[c] (95% CI)	1.08 (0.03,6.00)	3.17 (0.86,8.12)	2.20 (0.60,5.65)	3.10 (1.25,6.39)	2.72 (1.09,5.61)	2.89 (1.32,5.49)	2.75 (1.26,5.22)	2.33 (1.06,4.42)	2.82 (1.41,5.05)	2.42 (1.21,4.34)
Serious infection[d]										
Number of first events, n1	0	6	3	11	8	12	9	14	10	19
Number of all events, n2	0	6	3	13	12	14	13	18	18	23
Total participant-years at-risk	92.8	124.5	180.7	219.2	252.4	299.6	318.8	368.8	376.0	427.3
Incidence rate[c] (95% CI)	NA	4.82 (1.77,10.49)	1.66 (0.34, 4.85)	5.02 (2.51,8.98)	3.17 (1.37,6.24)	4.01 (2.07,7.00)	2.82 (1.29,5.36)	3.80 (2.08,6.37)	2.66 (1.28,4.89)	4.45 (2.68,6.94)
Events rate[e] (95% CI)	NA	4.76 (1.75,10.35)	1.65 (0.34, 4.83)	5.76 (3.07,9.86)	4.67 (2.41,8.15)	4.50 (2.46,7.54)	3.97 (2.11,6.79)	4.66 (2.76,7.36)	4.62 (2.74,7.30)	5.07 (3.21,7.61)
Opportunistic infection										
Number of first events, n1	0	1	0	1	1	1	1	2	1	2
Number of all events, n2	0	1	0	1	1	1	1	2	1	2

Time Period	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Total participant-years at-risk	92.8	126.0	181.4	224.4	256.7	309.2	326.0	382.8	386.9	448.3
Incidence rate[c] (95% CI)	NA	0.79 (0.02,4.42)	NA	0.45 (0.01,2.48)	0.39 (0.01,2.17)	0.32 (0.01,1.80)	0.31 (0.01,1.71)	0.52 (0.06,1.89)	0.26 (0.01,1.44)	0.45 (0.05,1.61)
Events rate[e] (95% CI)	NA	0.79 (0.02,4.42)	NA	0.44 (0.01,2.47)	0.39 (0.01,2.17)	0.32 (0.01,1.79)	0.31 (0.01,1.70)	0.52 (0.06,1.87)	0.26 (0.01,1.43)	0.44 (0.05,1.59)
Other infection of special interest										
Number of first events, n1	1	1	1	2	2	2	3	2	3	2
Number of all events, n2	1	1	1	2	2	2	3	2	3	2
Total participant-years at-risk	92.2	125.8	179.8	224.7	254.3	309.5	322.5	383.6	381.3	449.6
Incidence rate[c] (95% CI)	1.08 (0.03,6.04)	0.79 (0.02,4.43)	0.56 (0.01,3.10)	0.89 (0.11,3.22)	0.79 (0.10,2.84)	0.65 (0.08,2.33)	0.93 (0.19,2.72)	0.52 (0.06,1.88)	0.79 (0.16,2.30)	0.44 (0.05,1.61)
Events rate[e] (95% CI)	1.08 (0.03,6.00)	0.79 (0.02,4.42)	0.55 (0.01,3.07)	0.89 (0.11,3.20)	0.78 (0.09,2.81)	0.64 (0.08,2.32)	0.92 (0.19,2.68)	0.52 (0.06,1.87)	0.77 (0.16,2.25)	0.44 (0.05,1.59)
Serious psychiatric event										
Number of first events, n1	0	0	0	0	0	0	0	0	1	0
Number of all events, n2	0	0	0	0	0	0	0	0	1	0
Total participant-years at-risk	92.8	126.2	181.4	225.6	257.2	311.4	327.5	386.5	389.3	453.7
Incidence rate[c] (95% CI)	NA	NA	NA	NA	NA	NA	NA	NA	0.26 (0.01,1.43)	NA

Time Period	0-12 Months		0-24 Months		0-36 Months		0-48 Months		0-60+ Months[a]	
AESI / Exposure Status	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Events rate[e] (95% CI)	NA	NA	NA	NA	NA	NA	NA	NA	0.26 (0.01,1.43)	NA
Malignancy (excl NMSC)										
Number of first events, n1	1	3	3	4	4	4	5	4	6	7
Number of all events, n2	1	3	3	4	4	4	5	4	6	7
Total participant-years at-risk	92.7	125.5	180.1	223.0	253.2	305.8	322.1	378.6	381.7	443.0
Incidence rate[c] (95% CI)	1.08 (0.03,6.01)	2.39 (0.49,6.99)	1.67 (0.34,4.87)	1.79 (0.49,4.59)	1.58 (0.43,4.04)	1.31 (0.36,3.35)	1.55 (0.50,3.62)	1.06 (0.29,2.71)	1.57 (0.58,3.42)	1.58 (0.64,3.26)
Events rate[e] (95% CI)	1.08 (0.03,6.00)	2.38 (0.49,6.95)	1.65 (0.34,4.83)	1.77 (0.48,4.54)	1.56 (0.42,3.98)	1.28 (0.35,3.29)	1.53 (0.50,3.56)	1.03 (0.28,2.65)	1.54 (0.57,3.35)	1.54 (0.62,3.18)
NMSC										
Number of first events, n1	0	0	1	1	1	1	1	1	1	1
Number of all events, n2	0	0	1	1	1	1	1	1	1	1
Total participant-years at-risk	92.8	126.2	180.8	224.8	256.5	309.9	326.9	385.0	388.8	452.3
Incidence rate[c] (95% CI)	NA	NA	0.55 (0.01,3.08)	0.44 (0.01,2.48)	0.39 (0.01,2.17)	0.32 (0.01,1.80)	0.31 (0.01,1.70)	0.26 (0.01,1.45)	0.26 (0.01,1.43)	0.22 (0.01,1.23)
Events rate[e] (95% CI)	NA	NA	0.55 (0.01,3.07)	0.44 (0.01,2.47)	0.39 (0.01,2.17)	0.32 (0.01,1.79)	0.31 (0.01,1.70)	0.26 (0.01,1.44)	0.26 (0.01,1.43)	0.22 (0.01,1.23)

Source: Table 24.21001.

Note: As-exposed (time-varying strategy) analyzed events based on exposure status at the time of events occurrence. When switching from Benlysta to Non-Benlysta a 14 week risk window was incorporated. This assumes that Benlysta exposure ends 14 weeks after cessation (end date) of Benlysta medication.

a. Any events that occurred after 63 months were not reported.
b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.
c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years.
d. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.
e. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

10.5.2.4.3. Across strategy comparison– Elderly Population

A table summarizing the overall counts and rates of AESIs in the Evaluable population for the As-Exposed [Time-varying – 14 weeks risk window], and the As-Exposed [Time-varying – 6 months risk window] exposure strategies (at the 0 to 60+ month timepoint) are shown for comparison in Table 45. For comparison between exposure groups, numerical differences between incidence rates >0.1 are described. CIs were generally overlapping.

In summary (Evaluable, 0-60+ Months Time-Period):

- The overall patterns of AESI incidence rates per 100 participant-years follow-up in the Evaluable population were:
- Mortality and other infections of special interest were lower in Benlysta exposure group than in Non-Benlysta across both strategies,
- Serious infections and opportunistic infections were higher in the Benlysta exposure group than in the Non-Benlysta across both strategies,
- Serious psychiatric events were zero in the Benlysta exposure group across both strategies,
- As the number of events was smaller, data should be interpreted with caution.

Table 45 Overall AESI event and incidence rates by Exposure Strategies at 0-60+ Time-Period – Elderly Population (Population: Evaluable)

Exposure Strategy	As-Exposed [Time-Varying] Strategy - 14 Weeks risk window[a]		As-Exposed [Time-Varying] Strategy – 6 months risk window[a]	
AESI / Exposure Status	Non-Benlysta	Benlysta	Non-Benlysta	Benlysta
Total participant-years of follow-up	389.5	453.7	381.6	461.6
Mortality[b]				
Number of death cases, n1	11	11	11	11
Total participant-years at-risk	389.5	453.7	381.6	461.6
Incidence rate[c] (95% CI)	2.82 (1.41,5.05)	2.42 (1.21,4.34)	2.88 (1.44,5.16)	2.38 (1.19,4.26)
Serious infection[d]				
Number of first events, n1	10	19	10	19
Number of all events, n2	18	23	18	23
Total participant-years at-risk	376.0	427.3	368.3	434.0
Incidence rate[c] (95% CI)	2.66 (1.28,4.89)	4.45 (2.68,6.94)	2.72 (1.30,4.99)	4.38 (2.64,6.84)

Exposure Strategy	As-Exposed [Time-Varying] Strategy - 14 Weeks risk window[a]		As-Exposed [Time-Varying] Strategy – 6 months risk window[a]	
AESI / Exposure Status	**Non-Benlysta**	**Benlysta**	**Non-Benlysta**	**Benlysta**
Events rate[e] (95% CI)	4.62 (2.74,7.30)	5.07 (3.21,7.61)	4.72 (2.80,7.46)	4.98 (3.16,7.48)
Opportunistic infection				
Number of first events, n1	1	2	1	2
Number of all events, n2	1	2	1	2
Total participant-years at-risk	386.9	448.3	379.0	456.1
Incidence rate[c] (95% CI)	0.26 (0.01,1.44)	0.45 (0.05,1.61)	0.26 (0.01,1.47)	0.44 (0.05,1.58)
Events rate[e] (95% CI)	0.26 (0.01,1.43)	0.44 (0.05,1.59)	0.26 (0.01,1.46)	0.43 (0.05,1.57)
Other infection of special interest				
Number of first events, n1	3	2	3	2
Number of all events, n2	3	2	3	2
Total participant-years at-risk	381.3	449.6	373.4	457.5
Incidence rate[c] (95% CI)	0.79 (0.16,2.30)	0.44 (0.05,1.61)	0.80 (0.17,2.35)	0.44 (0.05,1.58)
Events rate[e] (95% CI)	0.77 (0.16,2.25)	0.44 (0.05,1.59)	0.79 (0.16,2.30)	0.43 (0.05,1.57)
Serious psychiatric event				
Number of first events, n1	1	0	1	0
Number of all events, n2	1	0	1	0
Total participant-years at-risk	389.3	453.7	381.5	461.6
Incidence rate[c] (95% CI)	0.26 (0.01,1.43)	NA	0.26 (0.01,1.46)	NA
Events rate[e] (95% CI)	0.26 (0.01,1.43	NA	0.26 (0.01,1.46)	NA
Malignancy (excl NMSC)				
Number of first events, n1	6	7	NA	NA
Number of all events, n2	6	7		
Total participant-years at-risk	381.7	443.0		
Incidence rate[c] (95% CI)	1.57 (0.58,3.42)	1.58 (0.64,3.26)		
Events rate[e] (95% CI)	1.54 (0.57,3.35)	1.54 (0.62,3.18)		
NMSC			NA	NA
Number of first events, n1	1	1		
Number of all events, n2	1	1		
Total participant-years at-risk	388.8	452.3		
Incidence rate[c] (95% CI)	0.26 (0.01,1.43)	0.22 (0.01,1.23)		
Events rate[e] (95% CI)	0.26 (0.01,1.43)	0.22 (0.01,1.23)		

Source: Table 24.21001 As-Exposed [Time-Varying strategy 14 Weeks Risk Window], Table 24.31001 As-Exposed [Time Varying strategy 6 Months Risk Window]
Note: Time Varying Strategy analyzed events based on exposure status at the time of events occurrence.
a. Any events that occurred after 63 months were not reported.
b. Fatal SAE onset date (not date of death) was used when counting mortality events within time periods.
c. Incidence rate was calculated as: Number of first events (n1)/Total participant-years at-risk of event expressed per 100 participant-years.
d. Serious infections per GSK adjudication and does not include Serious opportunistic infections or Serious other infection of interest.
e. Event rate was calculated as: Number of all events (n2)/Total participant-years of follow-up expressed per 100 participant-years.

10.6. Adverse events/adverse reactions

Other adverse events (including serious adverse events) are not collected as AESIs in this registry were to be reported in accordance with the laws and regulations for marketed products in the country where the event occurred.

11. DISCUSSION

11.1. Key results

In this study, 2967 participants (937 Non-Benlysta and 2030 Benlysta) were included in the Eligible population. Throughout the study 49.2% of participants withdrew from the study (48.2% Non-Benlysta vs 49.6% Benlysta).

The proportion of participants with exposure switch was generally higher in the Benlysta than the Non-Benlysta exposure group over time. At the 60-month visit, 17.4% of participants in the Non-Benlysta group and 34.4% in the Benlysta group had switched treatment.

Baseline demographics were roughly comparable between the Benlysta and Non-Benlysta exposure groups, While both groups were similar in age and BMI, a slightly higher proportion of participants in the Benlysta group were female (89.8% Non-Benlysta vs 93.5% Benlysta) and White (69.1% Non-Benlysta vs 76.3% Benlysta) as compared with the Non-Benlysta group, while the Non-Benlysta group was more ethnically diverse. The overall mean age (SD) was 44.3 years of age, 92.3% of participants were female and 74.0% were White. The most common current medical conditions at baseline were allergic reactions, cardiovascular risk factors, and psychiatric disorders in both exposure groups, with higher proportions of participants with allergic reactions (37.9% Non-Benlysta vs 41.8% Benlysta), psychiatric disorders (20.5% Non-Benlysta vs 30.6% Benlysta), and autoimmune disorders (17.7% Non-Benlysta vs 27.0% Benlysta) in the Benlysta group than in the Non-Benlysta group.

At baseline, the SLE disease duration was similar between Non-Benlysta and Benlysta exposure groups (median 8.40 years Non-Benlysta vs 8.10 years Benlysta). Organ damage as

assessed by SDI scores was comparable between Benlysta and Non-Benlysta exposure groups (mean 1.2 in both groups). SLEDAI was low to moderate with a mean SLEDAI score being similar between the exposure groups (5.1 Non-Benlysta vs 5.6 Benlysta).

All participants in both exposure groups received SLE medications at baseline. The proportion of participants with immunosuppressants in use at baseline being lower in the Benlysta than the Non-Benlysta (immunosuppressants: 100% Non-Benlysta vs 50.9% Benlysta; immunosuppressants other than mycophenolate: 60.7% Non-Benlysta vs 32.7% Benlysta). The most frequent combination therapies were anti-malarials+corticosterioids+immunosuppressants in both exposure groups, followed by anti-malarials+immunosuppressants in the Non-Benlysta group and anti-malarials+corticosterioids in the Benlysta group. Current (at baseline) (56.9% Non-Benlysta vs 63.2% Benlysta) and in the past 6 months corticosteroid use (64.5% Non-Benlysta vs 71.8% Benlysta) was higher in the Benlysta than the Non-Benlysta group.

The median duration of prior SLE medications was similar between Non-Benlysta and Benlysta exposure groups (any immunosuppressants: median 5.69 years Non-Benlysta vs 5.93 years Benlysta; SLE medications other than immunosuppressants: median 8.24 years Non-Benlysta vs 8.55 years Benlysta), while the duration of corticosteroid use (median 3.33 years Non-Benlysta vs 4.58 years Benlysta) was higher in the Benlysta than the Non-Benlysta group. The proportion of participants with any hospitalizations at baseline (11.1% Non-Benlysta vs 10.0% Benlysta) and SLE related hospitalizations (7.3% Non-Benlysta vs 5.6% Benlysta) were similar in the Non-Benlysta and Benlysta exposure groups.

Over the course of the study, the proportion of participants with at least 1 treatment switch was higher in Benlysta (28.0%) exposure group than Non-Benlysta exposure group (13.1%). Mean and median numbers of switches were similar between Benlysta and Non-Benlysta than exposure groups (mean: 1.5% Non-Benlysta vs 1.3% Benlysta; median: 1.0 in both groups).

The aim of this study was to evaluate the incidence of AESIs over 5 years in adults with active autoantibody-positive SLE who were treated with or without Benlysta:

- Based on the ITT strategy, AESIs were reported in 15.3% of participants in the Non-Benlysta group and in 16.3% of participants in the Benlysta group.
- A total of 3.3% of participants in the Non-Benlysta group and 2.5% of participants in the Benlysta group died (ITT). The incidence rates (95% CI) for mortality were: Non-Benlysta: 0.83 (0.56,1.20) and Benlysta: 0.65 (0.48,0.86) in the ITT and consistently lower in Benlysta than in Non-Benlysta (ITT, the As-Exposed [Time-varying – 14 weeks risk window], the As-Exposed [Time-varying – 6 months risk window], and the Ever-Exposed exposure strategies). Based on the ITT, there was no peak in the incidence rates at any time period (cumulative rates with 6 to 12 months intervals). The most frequent causes of death at SOC level were infections and infestations in both exposure groups and cardiac disorders in the Benlysta group. As

the proportion of participants with the events were smaller, there were no relevant differences between the groups.

- The proportion of participants with serious infections was slightly higher in the Benlysta (8.7%) than the Non-Benlysta (7.4%) group. The incidence rates (95% CI) of serious infections were: Non-Benlysta: 1.94 (1.49,2.47) and Benlysta: 2.37 (2.02,2.76) in the ITT and were higher in the Benlysta than in the Non-Benlysta exposure group, while the reverse was observed for the As-Exposed strategies. Based on the ITT, there was no peak in the incidence rates at any time period (cumulative rates with 6 to 12 month intervals). At SOC and PT level, there were no relevant differences between the groups. The most frequent serious infection was pneumonia in both exposure groups.
- A total of 2.4% of participants in the Non-Benlysta group and 2.0% of participants in the Benlysta group had opportunistic infections (ITT). The incidence rates (95% CI) of opportunistic infections were: Non-Benlysta: 0.61 (0.38,0.93) and Benlysta: 0.52 (0.37,0.71) in the ITT. Incidence rates were lower in the Benlysta than the Non-Benlysta group in the As-Exposed strategies. The incidence rates were comparable in the ITT, although a numerical trend was seen towards lower incidence rates in the Benlysta exposure group. Based on the ITT, there was no peak in the incidence rates at any time period (cumulative rates with 6 to 12 month intervals). At SOC and PT level, there were no relevant differences between the groups. The most frequent opportunistic infections was herpes zoster in both exposure groups.
- A total of 2.2% of participants in the Non-Benlysta group and 2.3% of participants in the Benlysta group had other infections of special interest (ITT). The incidence rates (95% CI) of other infections of special interest were: Non-Benlysta: 0.55 (0.33,0.87) and Benlysta: 0.60 (0.44,0.81) in the ITT and were comparable between the exposure groups. Based on the ITT, incidence rates were slightly higher in the first 12 months than in the remaining study period (cumulative rates with 6 to 12 month intervals). At SOC and PT level, there were no relevant differences between the groups. The most frequent other infections of special interest was herpes zoster in both exposure groups.
- A total of 0.6% of participants in the Non-Benlysta group and 1.4% of participants in the Benlysta group had serious psychiatric events (ITT). The incidence rates (95% CI) of serious psychiatric events were: Non-Benlysta: 0.14 (0.05,0.34) and Benlysta: 0.35 (0.23,0.52) in the ITT and were higher in Benlysta than in Non-Benlysta in the ITT. The incidence rates were comparable in the As-Exposed strategy strategies, although a numerical trend was seen towards higher incidence rates in the Benlysta exposure group. Based on the ITT, there was no peak in the incidence rates for the Benlysta group at any time period (cumulative rates with 6 to 12 month intervals). In the Non-Benlysta group the incidence rate for the first 12-months was low compared to the other time periods. At SOC and PT level, there were no relevant differences between the groups. The most frequent serious psychiatric events were suicidal ideation (0.4%), suicide attempt (0.4%), and depression (0.3%) in the Benlysta group

and suicidal ideation in the Non-Benlysta group (0.3%). However, it has to be noted that in the Benlysta exposure group several of the events occurred after participants had been switched off Benlysta to other SLE medications.

- A total of 2.7% of participants in the Non-Benlysta group and 2.3% of participants in the Benlysta group had malignancies (ITT). The incidence rates (95% CI) of malignancies were: Non-Benlysta: 0.70 (0.45,1.04) and Benlysta: 0.60 (0.43,0.80) in the ITT. Incidence rates were lower in Benlysta than in Non-Benlysta in the Ever-Exposed strategy. The incidence rates were comparable in the ITT and As-Exposed strategies, although a numerical trend was seen towards lower incidence rates in the Benlysta exposure group. Based on the ITT, there was no peak in the incidence rates at any time period (cumulative rates with 6 to 12 month intervals). At SOC and PT level, there were no relevant differences between the exposure groups. The most frequent malignancies were breast cancer in both exposure groups (0.3% each) and extranodal marginal zone B-cell lymphoma (MALT type) in the Non-Benlysta group (0.3%).
- A total of 0.5% of participants in both exposure groups had NMSC (ITT). The incidence rates (95% CI) of NMSC were: Non-Benlysta: 0.12 (0.03,0.29) and Benlysta: 0.14 (0.06,0.25) in the ITT and were comparable between the exposure groups. Based on the ITT, there was no peak in the incidence rates at any time period (cumulative rates with 6 to 12 month intervals). At SOC and PT level, there were no relevant differences between the exposure groups at the PT level. The most frequent events were basal cell carcinoma in the Benlysta group (0.3%) and squamous cell carcinoma of skin in both exposure groups (0.2% in the Benlysta group and 0.3% in the Non-Benlysta group).
- Confounding bias was addressed by using propensity score analysis methods. Key covariates were included in the propensity score models. They were selected based on clinical judgment In summary, year of entry into the study, sex, BMI at baseline (including imputed), ethnicity, race (including imputed), region, SLEDAI score at baseline (including imputed), corticosteroid use in the past 6 months, and a medical history of allergic reactions, autoimmune disorders, family history of cancer, end stage renal failure, depression and/or anxiety disorders, and dialysis were shown to be unbalanced ($p<0.05$) between the exposure groups. Weighting improved balance of the measured covariates between the exposure groups, reducing confounding by those variables.
- Overall, there was no major difference observed in the rates of AESIs between weighted and unweighted analysis. After weighting, incidence rates were higher in the Benlysta compared with Non-Benlysta group for serious infections, other infections, and serious psychiatric events based on the ITT and the While On Initial Exposure strategy.
- In general, results from the Current User subgroup were in line with the overall population, while there were different patterns in Treatment Initiators. However, the lower number of participants in this subgroup needs to be taken into consideration.

The study also assessed baseline and disease characteristics as well as AESIs in elderly participants. The number of participants ≥75 years of age was smaller (39) and no reliable conclusions can be drawn from this subgroup. Therefore, the following description focuses on participants ≥65 years of age.

- Of the 2967 participants in the Eligible population, 236 participants were ≥65 years of age (96 Non-Benlysta and 140 Benlysta). Withdrawal rates were slightly higher in the Benlysta compared with the Non-Benlysta group (50.0% Non-Benlysta vs 55.7% Benlysta). Baseline demographics were similar between Benlysta and Non-Benlysta exposure groups. The mean age was 70.2 years, 91.5% of participants were female and 82.1% were White. The SLE duration was similar between in the Benlysta exposure group and the Non-Benlysta group (median 10.66 years Non-Benlysta vs 11.08 years Benlysta), while organ damage as assessed by SDI score was slightly higher in the Benlysta exposure group than the Non-Benlysta group (1.8 Non-Benlysta vs 2.1 Benlysta). Duration (median 2.29 years Non-Benlysta vs 5.00 years Benlysta) and proportion of participants using corticosteroids (past 6 months: 51.0% Non-Benlysta vs 69.3% Benlysta) were higher in the Benlysta exposure group than the Non-Benlysta group**.**
- Overall, the proportion participants who withdrew was similar in the ≥65 years of age group compared with the overall population. Demographic characteristics were similar in the ≥65 years of age group compared with the overall population except for the following differences: Participants in the ≥65 years of age group were older compared with the overall population and the proportion of White participants was higher. Overall, the SLE duration and SDI scores were higher in the ≥65 years of age group than in the overall population. The pattern of corticosteroids usage was similar between participants ≥65 years of age group and the overall population, with exception of higher proportion of participants ever taken corticosteroids and its duration of usage in the past in the ≥65 years of age group.
- In participants in ≥65 years of age, AESIs were reported in 18 (19.6%) participants in the Non-Benlysta group and in 40 (29.9%) participants in the Benlysta group. Based on the ITT, the proportions of participants who died (7.6% Non-Benlysta vs 11.2% Benlysta), reported malignancies (2.2% Non-Benlysta vs 8.2% Benlysta) or serious infections (9.8% Non-Benlysta vs 13.4% Benlysta) were higher in the Benlysta than the Non-Benlysta exposure groups, while the proportion of participants with opportunistic infections (1.1% Non-Benlysta vs 1.5% Benlysta), other infections of special interest (4.3% Non-Benlysta vs 0.7% Benlysta), and NMSC (1.1% Non-Benlysta vs 0.7% Benlysta) was comparable or lower in the Benlysta group compared with the Non-Benlysta group. One of the participants in the Benlysta group and none on the Non-Benlysta group reported serious psychiatric events. Compared with the overall population, the proportion of participants reporting AESIs was higher in participants in ≥65 years of age. Differences were also seen in the pattern of AESIs, as in the overall population serious infections were higher in the Benlysta

compared with the Non-Benlysta group. Only 1 AESI for serious psychiatric events was reported in the Non-Benlysta group and none in the Benlysta group.

- Based on the As-Exposed in participants in ≥65 years of age, the overall AESI incidence rates were higher in Benlysta compared to Non-Benlysta for serious infections, and opportunistic infections, while incidence rates for mortality and other infections of special interest, malignancies and NMSCs were lower or comparable in Benlysta compared to Non-Benlysta. Only 1 AESI for serious psychiatric events was reported in the Non-Benlysta group and none in the Benlysta group.

Another objective of the study was to measure effectiveness with respect to organ damage as assessed by SDI, concomitant SLE medications including corticosteroids, and hospitalizations.

- The majority of participants in both exposure groups had no change in their SDI score. Over time, mean changes in SDI score increased from 0.1 in both exposure groups at 6 months to 0.4 in the Non-Benlysta and 0.5 in the Benlysta group at 60 months.
- SLE medication use (any immunosuppressants use, immunosuppressants other than mycophenolate, and SLE medications other than immunosuppressants) was generally similar between exposure groups. Over time, percentage of participants with concomitant SLE medications use decreased in both exposure groups.
- The change from baseline in the average median corticosteroid dose was zero in the Non-Benlysta exposure group at each post-baseline visit. In the Benlysta exposure group it was zero until the 30-months visit; thereafter the median change from baseline in the average median corticosteroid dose was up to -1.2000 mg/day at 60 months.
- Incidence and event rates for all hospitalizations per 100 participant-years were higher in the Benlysta than Non-Benlysta exposure group over time for the ITT and While On Initial Exposure strategies, while for the As-Exposed strategy the incidence and event rates were initially higher at 12 Months in the Benlysta exposure group however became equal or slightly higher in the Non-Benlysta exposure group over time. Similar to the overall hospitalizations, incidence and event rates for SLE-related hospitalizations per 100 participant-years were numerically higher in the Benlysta than Non-Benlysta exposure group over time for the ITT and While On Initial Exposure strategies, while the reverse was observed for the As-Exposed strategy; however, all CIs were overlapping. Over time, all hospitalizations and SLE-related hospitalization events and incidence rates decreased in both exposure groups for all 3 strategies.

11.2. Limitations

This was a registry and, as such, participants are not randomized into study groups. Due to the lack of randomization, there is a significant risk of confounding (i.e., imbalance in

important baseline characteristics between the Benlysta cohort and the comparison cohort where these characteristics are also risk factors for the outcomes). The present study attempted to minimize such confounding by selecting comparison of participants that are as similar as possible to Benlysta cohort and also attempted to account for confounding by further adjustment in the analysis using relevant statistical methods (such as propensity score matching or adjustment for baseline factors) (see Section 9.9.2.6 and Section 10.5.1). However, as with all non-randomized observational studies, residual unmeasured confounding may still exist. In addition, although the study was designed to specifically attempt to enroll a sample of SLE participants who are closely matched in both cohorts, it may be that the final enrolled study sample is not as well matched as desired due to multiple participant factors that can't be controlled for. The Sponsor have monitored enrollment for the proportion of participants who are Treatment Initiators versus Current Users and communicate to the sites the interest to achieve a reasonable balance for both groups.

Participants receiving commercially available belimumab may be seen more often by their medical care providers as compared to the bi-annual visits of standard of care participants. This might have created a reporting bias with increased reporting of events for some outcomes in the Benlysta group.

11.3. Interpretation

Withdrawal rates are expected based on the long study duration and are close to the projected withdrawal rates. These are generally consistent with those observed in RCTs, where discontinuation due to adverse events typically ranges from 7–9% and is similar between belimumab and placebo groups [Singh, 2021]. Baseline demographic and disease characteristics were roughly comparable between the exposure groups. While both groups were similar in age and BMI, a slightly higher proportion of participants in the Benlysta group were female and White as compared to Non-Benlysta group. The Benlysta group also showed higher baseline rates of allergic reactions, psychiatric disorders, and autoimmune disorders. These minor imbalances are common [Navarra, 2011] and should be considered when interpreting non-randomized data, as these may confound outcome comparisons.

Overall, the study population is representative of real-world SLE patients, with a broad age range, diverse racial backgrounds, and varying disease severity and consistent with populations enrolled in pivotal phase III trials [Navarra, 2011; Furie, 2011].

Although a higher proportion of participants in the Benlysta group than the Non-Benlysta group switched treatment, the majority of participants in the Benlysta group were still on Benlysta at the 60-month visit, supporting the validity of the ITT analysis. With regard to the Non-Benlysta group, treatments in this group included a heterogeneous mix of treatments and only the switches to and from Benlysta were analyzed, and treatment switches to other Non-Benlysta medications were not considered.

Different exposure strategies were used to analyze the data, taking into account the different nature of the AESIs under investigation as well as long duration of the study with expected treatment switches and discontinuations.

The main exposure strategy applied was the ITT. Based on this, AESI incidence rates were higher for Benlysta compared to Non-Benlysta for serious infections and serious psychiatric events. All other AESIs were comparable between the exposure groups or lower in the Benlysta group.

As-Exposed analyses were implemented to specifically investigate events with overall short development times like infections. Based on the As-Exposed analyses using a 14 weeks or 6 months risk window, no increased incidence rate for infections (serious infections, opportunistic infections, or other infections of special interest) in the Benlysta group was found. In addition, serious psychiatric events also were comparable between the exposure groups.

Ever-Exposure strategy was used to analyze AESIs that have longer development times, that is, mortality, malignancies, and NMSCs. Based on this strategy, incidence rates were comparable between the exposure groups or lower in the Benlysta group. To mitigate potential confounding bias, the study also attempted to use propensity score analysis to balance baseline characteristics and improve the reliability of comparisons. Medical experts assessed potentially important covariates collected at baseline, with respect to both treatment assignment and likelihood of experiencing outcome. These variables were included in the propensity score model. Several covariates were found that were unbalanced between the exposure groups. Weighting helped to balance measured covariates between the two exposure groups, reducing confounding by those variables. After weighting, estimates of the event rates and incidence rates were adjusted but not substantially different from the unweighted estimates. However, it needs to be considered that only known confounding factors can be adjusted for in the propensity score model. There might be other confounding factors impacting the outcome of the analysis, or confounding variables may have not been adequately specified. In addition, with the exception of the Treatment Initiators group, each treatment group encompasses wide range of treatment experience including duration of treatment prior to study entry and timing of covariate measurement, which is not fully accounted for in this analysis. The sample size of the Treatment Initiators group was too limited for including the full list of covariates in the propensity score model.

Nevertheless, the AESIs reported in this registry are consistent with the known safety profile of belimumab and no new emerging signals were observed. The incidence and event rate estimates of AESIs remained consistent with the known safety profile of belimumab after adjusting for confounding factors.

In summary, the findings are consistent with the established safety profile of Benlysta in SLE, as documented in label, high-quality RCTs and systematic reviews [Furie, 2011; Navarra, 2011; Singh, 2021; Materne, 2023].

At the time of initial Benlysta approval in the EU in July 2011, data on participants ≥65 years of age were limited, and the efficacy and safety of Benlysta in the elderly population could not be established. This was due to the very low number of elderly participants who enrolled in the controlled clinical studies. This study was designed to perform a long-term assessment of these risks, in a real-world practice setting where adult participants were treated for SLE as part of a post-authorization measure with the EMA.

In participants ≥65 years of age, the proportion of participants with AESIs was higher in the Benlysta than the Non-Benlysta group. Regarding the individual AESIs based on the ITT, the proportions of participants who died, reported malignancies or serious infections were higher in the Benlysta than the Non-Benlysta exposure groups. All other AESIs were comparable between the exposure groups or lower in the Benlysta group.

The overall AESI incidence rates based on the As-Exposed exposure strategies were higher incidence rates in Benlysta compared to Non-Benlysta for serious infections, and opportunistic infections. All other AESIs were comparable between the exposure groups or lower in the Benlysta group.

In summary, results in the elderly population were in line with known safety profile and no new signals were detected.

Although baseline characteristics were roughly similar between the exposure groups, differences in SLE disease duration, SDI scores and corticosteroid use indicate a more severe baseline disease in the Benlysta group which might impact the overall higher proportion of AESIs in the Benlysta group.

Compared with the overall population, the proportion of participants reporting AESIs was higher in participants in ≥65 years of age. As would be expected, participants in the ≥65 years of age group were older compared with the overall population and SLE duration and SDI scores were higher. These factors could contribute to the higher rates of AESIs in the elderly subgroup.

Effectiveness outcomes in the ITT group were broadly similar between the groups. However, overall stable disease severity and decreasing proportions of participants with SLE medications including corticosteroids might indicate that participants with more severe disease development might withdraw from the study. Overall, the study was not designed to make conclusive interpretations on comparative effectiveness between the exposure groups.

11.4. Generalizability

While the study design itself supported the enrollment of a population representative of the general population of autoantibody-positive SLE participants, there were limitations

- Certain inclusion/exclusion criteria and site selection procedures may have influenced the composition of the study population. For example, participants who

have a history of Benlysta exposure, but were not currently receiving Benlysta, and participants who were only receiving an anti-malarial or steroids for SLE were excluded from the study, potentially limiting applicability in those subgroups.

- Variations in prescribing behavior, access to different SLE treatments including Benlysta, and local guidelines may affect the extrapolation of findings to other settings.

The study was conducted primarily in the US, Canada, and Europe. Therefore, the study population may only be representative of a broadly Western population and extrapolation to other regions might be limited.

The standard care cohort included a heterogeneous mix of treatments, which may differ from standard care in other regions or time periods. This variability should be considered when interpreting comparative outcomes.

Lastly, baseline characteristics, including demographics, disease characteristics, and past and current treatments, were collected and compared between cohorts. Baseline characteristics were broadly similar between the cohorts, but several parameters were shown to be unbalanced between the exposure groups. Assessment of the primary outcomes using weighted analysis did not show any major differences between the unweighted and weighted analysis supporting applicability of the findings to a general SLE population.

12. OTHER INFORMATION

NA.

13. CONCLUSIONS

Overall, the AESIs reported in this registry are consistent with the known safety profile of Benlysta and no new emerging signals were observed.

The incidence and event rate estimates of AESIs remained consistent with the known safety profile of Benlysta after adjusting for confounding factors.

Results in the elderly population were in line with known safety profile and no new signals were detected.

Effectiveness outcomes in the ITT group were broadly similar between the groups.

14. REFERENCES

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15. TABLES AND FIGURES

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS

No.	Document Reference No	Date	Title
1	TMF-14148167	25 May 2022	Protocol Amendment 05
2	TMF-21884964	27 May 2022	Sample Case Report form (unique pages)
3	TMF-22662103	29 August 2025	List of IECs or IRBs and list of investigators
4	NA (available upon request as individual files)	NA	Investigator CVs
5	TMF-22244897 TMF-22244887	05 April 2018 07 November 2012	Model/Global ICFs
6	TMF-22627738	28 August 2025	Study administrative table
7	TMF-22561000	28 August 2025	Sponsor signature page
8	TMF-22560990	06 August 2025	Investigator signature page
9	TMF-22552425	14 August 2025	Audit certificates
10	TMF-21885902	14 March 2025	Reporting and Analysis Plan
11	TMF-22655164	28 August 2025	Important publications referenced in the report
12	 TMF-22589126 TMF-22589164 TMF-22589191	 15 August 2025 23 May 2025 23 May 2025	Clinical narratives Fatal events Non-fatal events Pregnancy
13	TMF-22359705	12 Jun 2025	Data listings

ANNEX 2 ADDITIONAL INFORMATION

Post-hoc analyses of AESIs by SOC and PT

Additional post-hoc analyses were performed to investigate the AESIs on SOC and PT level.

Table 46 Serious Infections by SOC and PT by Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All serious infections	57 (7.4%)	125 (8.5%)	8 (7.3%)	42 (9.1%)	65 (7.4%)	167 (8.7%)
Blood and lymphatic system disorders	0	0	0	1 (0.2%)	0	1 (<0.1%)
Febrile neutropenia	0	0	0	1 (0.2%)	0	1 (<0.1%)
Gastrointestinal disorders	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Enteritis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Hepatobiliary disorders	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Cholecystitis chronic	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Infections and infestations	54 (7.0%)	122 (8.3%)	8 (7.3%)	39 (8.5%)	62 (7.0%)	161 (8.4%)
Abdominal wall abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Abscess jaw	0	0	0	1 (0.2%)	0	1 (<0.1%)
Abscess limb	0	5 (0.3%)	0	1 (0.2%)	0	6 (0.3%)
Adenovirus infection	0	0	1 (0.9%)	0	1 (0.1%)	0
Appendiceal abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Appendicitis	1 (0.1%)	2 (0.1%)	0	0	1 (0.1%)	2 (0.1%)
Arthritis bacterial	0	0	0	1 (0.2%)	0	1 (<0.1%)
Atypical pneumonia	1 (0.1%)	2 (0.1%)	0	0	1 (0.1%)	2 (0.1%)
Avian influenza	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Babesiosis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Bacteraemia	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Bacterial colitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Bacterial infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Blister infected	1 (0.1%)	0	0	0	1 (0.1%)	0
Breast cellulitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Bronchitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Bursitis infective	0	1 (<0.1%)	1 (0.9%)	0	1 (0.1%)	1 (<0.1%)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
COVID-19	3 (0.4%)	5 (0.3%)	4 (3.6%)	3 (0.7%)	7 (0.8%)	8 (0.4%)
COVID-19 pneumonia	7 (0.9%)	9 (0.6%)	2 (1.8%)	2 (0.4%)	9 (1.0%)	11 (0.6%)
Cellulitis	2 (0.3%)	15 (1.0%)	0	2 (0.4%)	2 (0.2%)	17 (0.9%)
Cellulitis staphylococcal	0	0	0	1 (0.2%)	0	1 (<0.1%)
Clostridium difficile colitis	0	1 (<0.1%)	0	1 (0.2%)	0	2 (0.1%)
Clostridium difficile infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Colonic abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Corneal abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Cystitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Dermo-hypodermitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Diverticulitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Encephalitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Endocarditis	1 (0.1%)	0	0	0	1 (0.1%)	0
Endometritis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Enterobacter infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Enterobacter pneumonia	0	0	0	1 (0.2%)	0	1 (<0.1%)
Enterococcal infection	0	0	0	1 (0.2%)	0	1 (<0.1%)
Escherichia bacteraemia	2 (0.3%)	0	0	0	2 (0.2%)	0
Escherichia infection	0	1 (<0.1%)	0	1 (0.2%)	0	2 (0.1%)
Escherichia pyelonephritis	1 (0.1%)	0	0	0	1 (0.1%)	0
Escherichia sepsis	1 (0.1%)	1 (<0.1%)	0	1 (0.2%)	1 (0.1%)	2 (0.1%)
Escherichia urinary tract infection	3 (0.4%)	3 (0.2%)	0	0	3 (0.3%)	3 (0.2%)
Gastroenteritis	1 (0.1%)	3 (0.2%)	0	0	1 (0.1%)	3 (0.2%)
Gastroenteritis bacterial	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Gastroenteritis salmonella	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Gastroenteritis viral	0	0	0	1 (0.2%)	0	1 (<0.1%)
Herpes simplex meningitis	0	2 (0.1%)	0	0	0	2 (0.1%)
Herpes zoster disseminated	1 (0.1%)	0	0	0	1 (0.1%)	0
Infected dermal cyst	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Infected lymphocele	0	0	0	1 (0.2%)	0	1 (<0.1%)
Infected skin ulcer	1 (0.1%)	0	0	0	1 (0.1%)	0

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
Influenza	3 (0.4%)	4 (0.3%)	0	0	3 (0.3%)	4 (0.2%)
Klebsiella infection	1 (0.1%)	0	0	0	1 (0.1%)	0
Klebsiella sepsis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Large intestine infection	0	2 (0.1%)	0	0	0	2 (0.1%)
Meningitis	1 (0.1%)	1 (<0.1%)	0	0	1 (0.1%)	1 (<0.1%)
Meningitis bacterial	1 (0.1%)	0	0	0	1 (0.1%)	0
Metapneumovirus infection	0	0	1 (0.9%)	0	1 (0.1%)	0
Osteomyelitis	2 (0.3%)	3 (0.2%)	0	0	2 (0.2%)	3 (0.2%)
Otitis externa	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Otitis externa fungal	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pelvic abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pelvic inflammatory disease	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Perihepatitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Periorbital cellulitis	1 (0.1%)	0	0	0	1 (0.1%)	0
Peritonitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Peritonitis bacterial	1 (0.1%)	0	0	0	1 (0.1%)	0
Pilonidal disease	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Plasmodium falciparum infection	1 (0.1%)	0	0	0	1 (0.1%)	0
Pneumonia	13 (1.7%)	32 (2.2%)	1 (0.9%)	5 (1.1%)	14 (1.6%)	37 (1.9%)
Pneumonia aspiration	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pneumonia legionella	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pneumonia viral	0	2 (0.1%)	0	0	0	2 (0.1%)
Postoperative abscess	0	0	0	1 (0.2%)	0	1 (<0.1%)
Postoperative wound infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pseudomonas infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pyelonephritis	2 (0.3%)	4 (0.3%)	0	4 (0.9%)	2 (0.2%)	8 (0.4%)
Pyelonephritis acute	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)	1 (<0.1%)
Respiratory syncytial virus infection	1 (0.1%)	0	0	0	1 (0.1%)	0
Retroperitoneal abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Sepsis	6 (0.8%)	8 (0.5%)	0	3 (0.7%)	6 (0.7%)	11 (0.6%)
Septic shock	1 (0.1%)	0	0	2 (0.4%)	1 (0.1%)	2 (0.1%)
Skin infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
Soft tissue infection	0	0	0	1 (0.2%)	0	1 (<0.1%)
Staphylococcal bacteraemia	0	1 (<0.1%)	0	3 (0.7%)	0	4 (0.2%)
Staphylococcal infection	1 (0.1%)	4 (0.3%)	0	0	1 (0.1%)	4 (0.2%)
Streptococcal sepsis	1 (0.1%)	0	0	0	1 (0.1%)	0
Subcutaneous abscess	0	0	0	1 (0.2%)	0	1 (<0.1%)
Syphilis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Tooth infection	1 (0.1%)	1 (<0.1%)	0	0	1 (0.1%)	1 (<0.1%)
Tubo-ovarian abscess	0	0	0	1 (0.2%)	0	1 (<0.1%)
Upper respiratory tract infection	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)	1 (<0.1%)
Urinary tract infection	4 (0.5%)	8 (0.5%)	1 (0.9%)	3 (0.7%)	5 (0.6%)	11 (0.6%)
Urosepsis	2 (0.3%)	2 (0.1%)	0	2 (0.4%)	2 (0.2%)	4 (0.2%)
Viral infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Viral upper respiratory tract infection	1 (0.1%)	1 (<0.1%)	0	0	1 (0.1%)	1 (<0.1%)
Vulval abscess	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Injury, poisoning and procedural complications	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Traumatic ulcer	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Investigations	1 (0.1%)	0	0	0	1 (0.1%)	0
SARS-CoV-2 test positive	1 (0.1%)	0	0	0	1 (0.1%)	0
Nervous system disorders	0	0	0	1 (0.2%)	0	1 (<0.1%)
Encephalopathy	0	0	0	1 (0.2%)	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	2 (0.3%)	0	0	1 (0.2%)	2 (0.2%)	1 (<0.1%)
Acute respiratory failure	1 (0.1%)	0	0	0	1 (0.1%)	0
Atelectasis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Bronchiectasis	1 (0.1%)	0	0	0	1 (0.1%)	0
Skin and subcutaneous tissue disorders	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Skin ulcer	0	1 (<0.1%)	0	0	0	1 (<0.1%)

Table 47 Opportunistic Infections by SOC and PT by Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All opportunistic infections	17 (2.2%)	32 (2.2%)	4 (3.6%)	6 (1.3%)	21 (2.4%)	38 (2.0%)
Infections and infestations	16 (2.1%)	32 (2.2%)	4 (3.6%)	6 (1.3%)	20 (2.3%)	38 (2.0%)
Aspergillus infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Bacterial infection	1 (0.1%)	0	0	0	1 (0.1%)	0
Candida infection	0	0	0	2 (0.4%)	0	2 (0.1%)
Candida sepsis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Cellulitis	0	2 (0.1%)	0	0	0	2 (0.1%)
Cutaneous nocardiosis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Cytomegalovirus colitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Cytomegalovirus viraemia	0	2 (0.1%)	0	0	0	2 (0.1%)
Disseminated mycobacterium avium complex infection	0	0	0	1 (0.2%)	0	1 (<0.1%)
Endocarditis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Gastroenteritis	1 (0.1%)	0	0	0	1 (0.1%)	0
Herpes simplex	0	0	0	1 (0.2%)	0	1 (<0.1%)
Herpes zoster	6 (0.8%)	8 (0.5%)	1 (0.9%)	1 (0.2%)	7 (0.8%)	9 (0.5%)
Herpes zoster cutaneous disseminated	1 (0.1%)	3 (0.2%)	1 (0.9%)	0	2 (0.2%)	3 (0.2%)
Herpes zoster disseminated	1 (0.1%)	2 (0.1%)	0	0	1 (0.1%)	2 (0.1%)
Herpes zoster meningitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Herpes zoster meningoencephalitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Listeriosis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Meningitis viral	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Metapneumovirus infection	1 (0.1%)	0	0	0	1 (0.1%)	0
Mycobacterium fortuitum infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Mycobacterium kansasii infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Necrotising fasciitis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Nocardia sepsis	0	0	1 (0.9%)	0	1 (0.1%)	0
Oesophageal candidiasis	2 (0.3%)	2 (0.1%)	0	0	2 (0.2%)	2 (0.1%)
Osteomyelitis bacterial	0	0	1 (0.9%)	0	1 (0.1%)	0
Pharyngitis	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pneumonia	2 (0.3%)	2 (0.1%)	1 (0.9%)	0	3 (0.3%)	2 (0.1%)
Pneumonia bacterial	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pneumonia cytomegaloviral	0	0	1 (0.9%)	0	1 (0.1%)	0

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
Sepsis	1 (0.1%)	0	0	0	1 (0.1%)	0
Varicella zoster virus infection	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Skin and subcutaneous tissue disorders	1 (0.1%)	0	0	0	1 (0.1%)	0
Skin ulcer	1 (0.1%)	0	0	0	1 (0.1%)	0

Table 48 Other Infections of Special Interest by SOC and PT by Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All other infections of special interest	16 (2.1%)	33 (2.3%)	3 (2.7%)	11 (2.4%)	19 (2.2%)	44 (2.3%)
Infections and Infestations	16 (2.1%)	33 (2.3%)	3 (2.7%)	11 (2.4%)	19 (2.2%)	44 (2.3%)
Abdominal wall abscess[a]	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Acute hepatitis B	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Gastroenteritis Escherichia coli	1 (0.1%)	0	0	0	1 (0.1%)	0
Genital herpes zoster	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Herpes zoster	15 (1.9%)	29 (2.0%)	2 (1.8%)	10 (2.2%)	17 (1.9%)	39 (2.0%)
Latent tuberculosis	0	1 (<0.1%)	1 (0.9%)	0	1 (0.1%)	1 (<0.1%)
Ophthalmic herpes zoster	0	2 (0.1%)	0	0	0	2 (0.1%)
Varicella zoster virus infection	0	0	0	1 (0.2%)	0	1 (<0.1%)

a. Abscess culture positive for Prevotella Beta-Lactamase positive, Streptococcus Anginosus, and Streptococcus Intermedius.

Table 49 Serious Psychiatric Events by SOC and PT by Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All serious psychiatric events	4 (0.5%)	24 (1.6%)	1 (0.9%)	2 (0.4%)	5 (0.6%)	26 (1.4%)
Injury, poisoning and procedural complications	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)	1 (<0.1%)
Intentional overdose	1 (0.1%)	0	0	0	1 (0.1%)	0
Toxicity to various agents	0	0	0	1 (0.2%)	0	1 (<0.1%)
Psychiatric disorders	3 (0.4%)	24 (1.6%)	1 (0.9%)	1 (0.2%)	4 (0.5%)	25 (1.3%)
Adjustment disorder with mixed anxiety and depressed mood	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Depression	0	6 (0.4%)	0	0	0	6 (0.3%)
Depression suicidal	1 (0.1%)	3 (0.2%)	0	0	1 (0.1%)	3 (0.2%)
Generalised anxiety disorder	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Major depression	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Suicidal behaviour	0	2 (0.1%)	1 (0.9%)	0	1 (0.1%)	2 (0.1%)
Suicidal ideation	2 (0.3%)	7 (0.5%)	1 (0.9%)	1 (0.2%)	3 (0.3%)	8 (0.4%)
Suicide attempt	0	7 (0.5%)	0	0	0	7 (0.4%)

Table 50 Malignancy by SOC and PT by Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All malignancies (excluding NMSC)	23 (3.0%)	34 (2.3%)	1 (0.9%)	10 (2.2%)	24 (2.7%)	44 (2.3%)
Hepatobiliary disorders	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Hepatic lesion	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	23 (3.0%)	33 (2.3%)	1 (0.9%)	10 (2.2%)	24 (2.7%)	43 (2.2%)
Acute myeloid leukaemia	0	1 (<0.1%)	0	1 (0.2%)	0	2 (0.1%)
Adenocarcinoma of colon	1 (0.1%)	1 (<0.1%)	0	1 (0.2%)	1 (0.1%)	2 (0.1%)
Adenocarcinoma pancreas	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Anal cancer stage I	0	1 (<0.1%)	0	0	0	1 (<0.1%)
B-cell lymphoma	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Breast cancer	3 (0.4%)	4 (0.3%)	0	1 (0.2%)	3 (0.3%)	5 (0.3%)
Breast cancer in situ	1 (0.1%)	0	0	0	1 (0.1%)	0
Breast cancer metastatic	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Breast cancer stage I	1 (0.1%)	0	0	0	1 (0.1%)	0
Cholangiocarcinoma	0	0	0	1 (0.2%)	0	1 (<0.1%)
Colon cancer	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Colon cancer stage IV	0	0	0	1 (0.2%)	0	1 (<0.1%)
Diffuse large B-cell lymphoma	0	0	0	1 (0.2%)	0	1 (<0.1%)
Endometrial adenocarcinoma	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Epstein-Barr virus associated lymphoma	1 (0.1%)	0	0	0	1 (0.1%)	0
Extranodal marginal zone B-cell lymphoma (MALT type)	3 (0.4%)	0	0	0	3 (0.3%)	0
Fallopian tube cancer	1 (0.1%)	0	0	0	1 (0.1%)	0
Gastric cancer	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Gastrointestinal stromal tumour	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Glioblastoma multiforme	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Intraductal proliferative breast lesion	0	2 (0.1%)	0	1 (0.2%)	0	3 (0.2%)
Invasive ductal breast carcinoma	1 (0.1%)	2 (0.1%)	0	0	1 (0.1%)	2 (0.1%)
Large granular lymphocytosis	0	0	0	1 (0.2%)	0	1 (<0.1%)
Lung adenocarcinoma	1 (0.1%)	0	0	0	1 (0.1%)	0

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
Lung neoplasm malignant	1 (0.1%)	0	0	1 (0.2%)	1 (0.1%)	1 (<0.1%)
Malignant melanoma	1 (0.1%)	2 (0.1%)	0	1 (0.2%)	1 (0.1%)	3 (0.2%)
Malignant melanoma in situ	1 (0.1%)	0	0	0	1 (0.1%)	0
Malignant melanoma stage I	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Marginal zone lymphoma	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Neoplasm malignant	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Non-Hodgkin's lymphoma	0	2 (0.1%)	0	0	0	2 (0.1%)
Ovarian cancer	1 (0.1%)	1 (<0.1%)	0	0	1 (0.1%)	1 (<0.1%)
Paget's disease of the vulva	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Pancreatic carcinoma metastatic	1 (0.1%)	0	0	0	1 (0.1%)	0
Papillary thyroid cancer	1 (0.1%)	0	0	0	1 (0.1%)	0
Plasma cell myeloma	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Prostate cancer	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Rectal cancer	1 (0.1%)	0	0	0	1 (0.1%)	0
Renal cell carcinoma	1 (0.1%)	1 (<0.1%)	0	0	1 (0.1%)	1 (<0.1%)
Squamous cell carcinoma of the tongue	0	0	1 (0.9%)	0	1 (0.1%)	0
Thyroid cancer	1 (0.1%)	0	0	0	1 (0.1%)	0
Transitional cell carcinoma	1 (0.1%)	2 (0.1%)	0	0	1 (0.1%)	2 (0.1%)
Triple negative breast cancer	1 (0.1%)	0	0	0	1 (0.1%)	0
Tubular breast carcinoma	0	1 (<0.1%)	0	0	0	1 (<0.1%)

Table 51 NMSC by SOC and PT by Study Cohort (Initial Exposure [ITT] strategy; Population: Evaluable)

SOC and PT	Current Users		Treatment Initiators		Total	
	Non-Benlysta (N=771)	Benlysta (N=1464)	Non-Benlysta (N=110)	Benlysta (N=460)	Non-Benlysta (N=881)	Benlysta (N=1924)
All NMSCs	3 (0.4%)	8 (0.5%)	1 (0.9%)	2 (0.4%)	4 (0.5%)	10 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4%)	8 (0.5%)	1 (0.9%)	2 (0.4%)	4 (0.5%)	10 (0.5%)
Atypical fibroxanthoma	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Basal cell carcinoma	0	4 (0.3%)	1 (0.9%)	1 (0.2%)	1 (0.1%)	5 (0.3%)
Bowen's disease	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Skin cancer	0	1 (<0.1%)	0	0	0	1 (<0.1%)
Squamous cell carcinoma of skin	3 (0.4%)	2 (0.1%)	0	1 (0.2%)	3 (0.3%)	3 (0.2%)

Listing of Deaths

Table 52 Listing of Deaths

Participant ID	Age[a] (years)	Sex	Race	Preferred Term	As-Exposed Participant-Years at-Risk of Death on Benlysta (days)[b]	As-Exposed Participant-Years at-Risk of Death on Non-Benlysta (days)[b]
Benlysta Initial Exposure Cohort (n=48)						
Current Users - Benlysta Cohort at Time of Death						
PPD		F	PPD	Coronary artery disease	771	-
		M		COVID-19	1749	-
		F		Death[c]	87	-
		F		Death[c]	511	-
		F		Gastric cancer	1291	-
		M		Accidental overdose	598	-
		F		Cardiac failure congestive	599	-
		F		Breast cancer metastatic	599	-
		F		Cardio-respiratory arrest	477	-
		F		Acute right ventricular failure	837	-
		F		Retroperitoneal abscess	351	-
		F		Deep vein thrombosis	475	-
		F		COVID-19	788	-
		F		Urosepsis	312	-
		F		Septic shock	188	-
		F		Sepsis[e]	904	-
		M		Myocardial infarction	446	-
		F		Cardiac failure congestive	1111	-
		F		Death[c]	1421	-
		F		Renal failure	371	-
		F		Acute myeloid leukemia	62	-
		F		Intestinal infarction	1437	-
		F		Respiratory failure	515	-
		F		Glioblastoma multiforme	1734	-
		F		Brain Injury	1189	-
		F		Aspergillus infection	906	-

Participant ID	Age[a] (years)	Sex	Race	Preferred Term	As-Exposed Participant-Years at-Risk of Death on Benlysta (days)[b]	As-Exposed Participant-Years at-Risk of Death on Non-Benlysta (days)[b]
PPD	PPD	F	PPD	Cerebral haemorrhage	590	-
Current Users – Non-Benlysta Cohort at Time of Death						
PPD		F	PPD	Cardiac failure Congestive	1217	8
		F		Encephalitis	612	646
		F		Interstitial lung disease	246	620
		F		Adenocarcinoma pancreas[e]	261	1543
		F		Chronic obstructive pulmonary disease	200	1277
		M		Respiratory failure	519	80
		F		Respiratory arrest	165	737
		F		Mental status changes	184	291
		F		Multiple organ dysfunction syndrome	947	664
		M		Ventricular tachycardia	131	1129
Treatment Initiators – Benlysta Cohort at Time of Death						
PPD		F	PPD	Death[c]	1166	-
		F		Encephalopathy	128	-
		F		Death[c]	1561	-
		F		Subdural hematoma	439	-
		F		Klebsiella sepsis	33	-
		M		Death[c]	275	-
		F		Cardiac failure congestive	369	-
Treatment Initiators – Non-Benlysta Cohort at Time of Death						
PPD		F	PPD	Colon cancer stage IV	1205	32
		F		Interstitial lung disease	379	1189
		F		Cerebral haemorrhage	476	87
		F		Chronic kidney disease	156	130
		F		Septic shock	623	399
Non-Benlysta Initial Exposure (n=29)						
Current Users – Benlysta Cohort at Time of Death						
PPD	PPD	F	PPD	Pneumonia	11	694
Current Users – Non-Benlysta Cohort at Time of Death						
PPD		F	PPD	Hepatic failure	163	66
		F		Acute respiratory failure	-	857

Participant ID	Age[a] (years)	Sex	Race	Preferred Term	As-Exposed Participant-Years at-Risk of Death on Benlysta (days)[b]	As-Exposed Participant-Years at-Risk of Death on Non-Benlysta (days)[b]
PPD		M	PPD	Sepsis	-	737
		M		Pancreatic carcinoma metastatic	-	990
		F		Malignant melanoma	-	1345
		M		Respiratory Distress	-	900
		F		Death[c]	-	1724
		F		Cardiac arrest	-	348
		F		Pulmonary embolism	-	91
		F		Myocardial infarction	-	214
		F		Cardiac arrest	-	1242
		F		Lung adenocarcinoma	-	1312
		F		Acute respiratory failure[e]	-	366
		F		Performance status decreased	-	1152
		F		Sepsis	129	608
		F		Death[c]	-	1315
		F		Acute hepatic failure	-	547
		F		Sepsis	-	337
		M		Sepsis	-	836
		F		Aortic stenosis	-	329
		F		Septic shock	-	703
		M		Cerebral haemorrhage	-	1249
		M		Cardiac failure congestive	562	1010
		F		Acute respiratory failure	-	1110
		F		Pneumonia	-	1310
		F		Death[c]	-	1395
Treatment Initiators – Benlysta Cohort at Time of Death						
PPD	PPD	F	PPD	COVID-19 pneumonia	400	150
Treatment Initiators – Non-Benlysta Cohort at Time of Death						
PPD		F	PPD	Death[c]	-	799
		F		Cardiac failure	-	349
		F		COVID-19	-	779

Source: Listing 7.000. F; Female, ICF; Informed consent form, M; Male.
Notes: In the case narratives, the Participant ID/number is presented as a 4-digit number (with 2 leading zeros removed). Current Users were participants who have received or started Benlysta or qualifying Non-Benlysta medication(s) for ≥2 months (≥62 days) prior to enrollment (Day 1) into the study. Treatment Initiators were participants who have initiated or started Benlysta or qualifying Non-Benlysta medication(s) for <2 months (< 62 days) prior to enrollment (Day 1) into the study.

a. Only year of birth was collected. Age was calculated assuming 30th June as day and month for all participants.
b. Number of days on specified treatment from enrollment to the day of death.
c. No cause of death identified in Source Listing or Case Narrative.
d. Participant was excluded from analysis as ICF was lost and the participant was not reconsented, hence not present in the Source Listing but a narrative is provided.
e. Cause of death per GSK safety database.
f. This participant was enrolled and subsequently excluded as the participant did not fulfill the criteria for the eligible population (combination of antimalarials and corticosteroids). A narrative is provided but the participant is not included in the Source Listings

CLINICAL PROTOCOL HGS1006-C1124
Protocol Amendment: 05
Date: 25 May 2022

TITLE OF STUDY:

A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)

STUDY SPONSOR:

GlaxoSmithKline, LLC
5 Crescent Drive
Philadelphia, Pennsylvania 19112

Revision Chronology for HGS1006-C1124 (BEL116543)

Document Identifier	Date	Document*
Global	14 August 2012	Original
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Global 2017N316452_01	12 March 2018	Amendment No. 03
Global 2017N316452_02	25 Nov 2020	Amendment No. 04
Global TMF-14148167	25 May 2022	Amendment No. 05

*A Summary of Modifications document which provides a detailed list of changes for the amendment/addendum is available upon request.

Milestones

Milestone	Planned Date
Registration in the EU PAS register	16 October 2013
Start of data collection	February 2013
End of data collection	2025
Interim Report 1	28 February 2014
Interim Report 2	28 February 2015
Interim Report 3	28 February 2016
Interim Report 4	28 February 2017
Interim Report 5	28 February 2018
Interim Report 6	28 February 2019
Interim Report 7	28 February 2020
Interim Report 8	28 February 2021
Interim Report 9	28 February 2022
Interim Report 10	28 February 2023
Interim Report 11	28 February 2024
Interim Report 12	28 February 2025
Final Report	28 February 2026

Investigator Agreement

I will provide copies of the protocol, any subsequent amendments and access to all information furnished by the sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational study agent and the study protocol. I agree to conduct this clinical trial according to the protocol described herein, except when mutually agreed to in writing with the sponsor. I also agree to conduct this study in compliance with guidelines for Good Pharmacoepidemiology Practices (GPP) as defined by the International Society of Pharmacoepidemology (ISPE) all applicable national, state, and local regulations, as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC) and any other institutional requirements.

Principal Investigator:

Signature *Date (dd mmm yy)*

Name (please type or print)

Institution

Address (must include country name)

Study Synopsis

Title of the Study: A 5-Year Observational Prospective Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)

Clinical Development Phase: 4

Objectives:

Primary Objective

To evaluate the incidence of the following adverse events of special interest (AESI) over 5 years in adults with active autoantibody-positive systemic lupus erythematosus (SLE) who are treated with or without BENLYSTA:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

Other Objectives

To evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

Inclusion Criteria:

Patients enrolled in the registry must meet the following inclusion criteria:

1. Males or females age 18 or older.
2. Have a clinical diagnosis of active SLE.
3. Current or history of autoantibody-positive SLE.
4. Must be treated with SLE therapy including BENLYSTA and/or immunosuppressants (eg, azathioprine, methotrexate, cyclophosphamide, mycophenolate, and biologics).
5. Have the ability to understand the requirements of the study, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study data collection procedures.

Exclusion Criteria:

Patients will be excluded from participating in the registry if they meet any of the following exclusion criteria:

1. Treatment with an investigational drug within one year of enrollment. Investigational drug applies to any drug not approved for sale in the country it is being used.
2. Currently enrolled in a placebo-controlled BENLYSTA (belimumab) clinical trial or a continuation protocol where belimumab is used as an investigational agent.
3. Patients who have a history of BENLYSTA exposure, but are not currently receiving BENLYSTA.
4. Patients only receiving an anti-malarial for SLE.
5. Patients only receiving steroids for SLE.

Study Design:

This is a multi-center, prospective, observational cohort study to evaluate the incidence of adverse events of special interest (AESI) and effectiveness in patients with active, autoantibody-positive SLE treated with and without BENLYSTA. BENLYSTA refers to any commercially available formulation of belimumab. BENLYSTA formulation, intravenous (IV) or subcutaneous (SC), will be recorded for each patient in the protocol database. Patients will receive BENLYSTA at the discretion of their physician. All treatment decisions are at the discretion of the patient and their healthcare provider and are not mandated by study design or protocol. All assessments are intended to be performed at the time of clinical encounters, per routine care. Patients will be enrolled into 1 of 2 cohorts, those who, at baseline, are receiving or initiating BENLYSTA (BENLYSTA cohort) or are not receiving BENLYSTA (comparison cohort). BENLYSTA or comparison cohort patients may be either treatment initiators or current users. Treatment initiators are defined as those patients who have initiated immunosuppressants and/or BENLYSTA in the last 2 months, while the current users are those who have received immunosuppressants and/or BENLYSTA for ≥2 months at the time of entry into the registry. The study will enroll approximately 3,000 patients, approximately 2,000 in the BENLYSTA cohort and 1,000 in the comparison cohort. Enrollment is expected to occur primarily in the US, Canada, and Europe. Each patient will be followed for 5 years contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively, assuming a 10% annual patient drop-out rate and not accounting for crossover.

Data will be collected at enrollment and at approximately 6 month intervals for 5 years (60 months). All patients will be assessed for AESI including serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events and mortality. Organ damage as assessed by SLICC/ACR Damage Index (SDI), concomitant SLE medications including steroids, demography (eg, age, gender, race/ethnicity; where allowed by local regulation), smoking history, alcohol use,

hospitalizations, and disease activity of SLE will also be evaluated in all patients at defined visits (see Table 6-1). Adverse events not collected in this study should be reported in accordance with the laws and regulations for marketed products in the country in which the event occurred.

Primary Endpoints:

Incidence of the following adverse events of special interest (AESI):

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

Effectiveness Endpoints:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

Sample Size Consideration:

This registry will enroll approximately 3,000 patients, approximately 2,000 receiving or initiating BENLYSTA plus standard of care (BENLYSTA cohort) and 1,000 standard of care only (comparison cohort). Each patient will be followed for 5 years, contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively), assuming a 10% annual patient drop-out rate and not accounting for crossover.

The registry will allow the difference in mortality rate in the BENLYSTA cohort and comparison cohort to be established with a 95% CI of +/-0.32 per 100-subject years, based on an estimated mortality rate of 0.68 per 100-subject years in both treatment groups (Table 1). The estimated mortality rate was based on the mortality rate in the pooled IV primary safety database in SLE subjects derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE Controlled, Repeat Dose (CRD) studies (ie, integrated database of LBSL02 [placebo-controlled treatment phase only], HGS1006-C1056, and HGS1006-C1057) for all subjects (IV belimumab and placebo) adjusted for subject years. The precision of the rates of the AESI are provided in the table below:

Table 1 Precision of differences in AE rates estimated from a total of 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively

Adverse Events	Reference Rate[1] (per 100-patient years)	95% Confidence Interval for difference in AE rates[2] (per 100-patient years)
All deaths	0.68	±0.32
Serious infection	5.80	±0.93
Opportunistic infection	0.136	±0.14
Malignancy excl. NMSC	0.226	±0.19
NMSC	0.226	±0.19
Selected serious psychiatric events	0.410	±0.25

[1] The reference AE rates were based on the AE rates in the pooled IV primary safety database derived from the IV SLE CRD studies (LBSL02, HGS1006-C1056, HGS1006-C1057) and adjusted for subject years.

[2] Assuming that the AE rates in BENLYSTA and the control groups were the same as the reference rate.

Analysis of Primary Endpoints:

In addition to analyses that consider initial treatment group (BENLYSTA cohort vs comparison cohort), analyses that specifically account for changes in therapy (in either group) by considering a variety of risk windows will be employed. These analyses will attribute events to BENLYSTA treatment if they occur within the designated risk windows for BENLYSTA exposure and to comparison treatment otherwise. These analyses will allow for a registry patient to contribute person-time to both BENLYSTA treatment, and comparison treatment and as a result, will specifically account for treatment switching to BENLYSTA or from BENLYSTA. Switching between BENLYSTA and comparison treatment will be taken into account in a number of ways in the analysis and will be further defined within the statistical analysis plan. No new analyses for changing between BENLYSTA formulation or stratifying by BENLYSTA formulation are planned. Planned analyses are outlined below; all analyses will be detailed in the statistical analysis plan.

- Analysis by initial treatment group of rate per person years of observation time.
- Analysis by initial treatment group of rate per person years of exposure where BENLYSTA exposure ends 14 weeks (approximately 5 half-lives) after cessation of treatment.
- For serious psychiatric events, BENLYSTA exposure is all time on treatment with BENLYSTA ending 14 weeks (approximately 5 half-lives) after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For serious infections, opportunistic infections and other infections of interest, BENLYSTA exposure is all time on treatment with BENLYSTA ending 6 months after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For NMSC and malignancies excluding NMSC, analysis will be performed where all events will be attributed to BENLYSTA if the patient was ever exposed to BENLYSTA treatment prior to the event and attributed to the comparison cohort otherwise (ie, once exposed, always at risk).
- Mortality will be analyzed applying all the above-mentioned risk windows (eg, 14 weeks, 6 months, and ever-exposed).
- Other risk windows (including risk windows for comparison treatment) may also be assessed and defined in the statistical analysis plan.

Additional safety analysis will be performed comparing BENLYSTA treatment initiators with patients from the comparison cohort that start or switch an immunosuppressant and that have comparable background medication and treatment history. Subgroup analysis will be performed that will include but not be limited to analysis of patients with positive anti-dsDNA and low complement at baseline, patients with SLEDAI 2000 score at baseline (<10 vs ≥10), SDI (0 vs ≥1), steroid use (yes vs no; ≤7.5 mg/day vs >7.5 mg/day), immunosuppressant use (yes vs no; mycophenolate vs immunosuppressant other than mycophenolate), region (US/Canada vs Europe vs other), and race (black race vs other). Safety analyses will be adjusted for potential confounding factors (Appendix 7) through propensity score methods or other appropriate statistical methods. No new analyses for changing between BENLYSTA formulation or stratifying by BENLYSTA formulation are planned. Further details of the safety analyses will be described in the statistical analysis plan.

Analysis of Effectiveness Endpoints:

For any effectiveness endpoint analyses performed, methods to reduce the potential impact of confounding may be employed. These methods could include subgroup analysis, modeling adjusting for baseline and/or other confounding variables, or patient matching techniques like propensity score analysis. Furthermore, analyses considering changes in BENLYSTA use over time (eg, on or off treatment, but not changes between BENLYSTA formulations) in order to assess BENLYSTA effectiveness, as well as evaluate how these endpoints vary in response to BENLYSTA treatment will be assessed and further explored as appropriate. These analyses will be described in the statistical analysis plan.

Study Calendar:

See Table 6-1 for data collection time points.

Table of Contents

List of Tables

List of Abbreviations

ACR	American College of Rheumatology
AE	adverse Event
AESI	adverse Events of Special Interest
BAFF	B cell activating factor belonging to the TNF family
BCG	Bacillus Calmette-Guérin
BLyS	B lymphocyte stimulator
CI	Confidence Interval
CMV	cytomegalovirus
CRD	controlled repeat dose
CRF	case report form
eCRF	electronic case report form
EDC	electronic data capture
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
GSK	GlaxoSmithKline
HGS	Human Genome Sciences
HIV	human immunodeficiency virus
HR	hazard ratio
HPV	human papillomavirus
ICH	International Conference on Harmonisation
ICSR	Individual Case Safety Reports
IEC	Independent Ethics Committee
IPSE	International Society of Pharmacoepidemology
IRB	Institutional Review Board
IV	intravenous
NHL	non-Hodgkin's lymphoma
NMSC	non-melanoma skin cancer
PML	Progressive multifocal leukoencephalopathy
PSRHQ	possible suicidality-related history questionnaire
PSRQ	possible suicidality-related questionnaire
SABLE	Safety And effectiveness of Belimumab in Systemic Lupus Erythematosus Registry
SAC	Scientific Advisory Committee
SAE	serious adverse event
SDI	SLICC/ACR Damage Index
SELENA	Safety of Estrogen in Lupus National Assessment trial
SIR	Standardized Incidence Ratio
SLE	systemic lupus erythematosus
SLEDAI 2000	Systemic Lupus Erythematosus Disease Activity Index 2000
SLICC	Systemic Lupus International Collaborating Clinics
TB	tuberculosis
TNF	tumor necrosis factor

US	United States of America
UTI	urinary tract infection
WBC	white blood cell count

1 Background

1.1 Disease Background Relevant to the Registry

SLE is a chronic debilitating autoimmune disease that primarily affects young women of childbearing age, although men, children and teenagers also can develop lupus. SLE is characterized by the presence of autoreactive B cells resulting in elevated levels of autoantibodies, which directly damage the body's cells and tissues or form immune complexes which cause inflammation and tissue damage. A range of organ systems may be involved simultaneously or sequentially. The manifestations of lupus include arthritis, pleuritis, pericarditis, stroke, seizure, nephritis, vasculitis, anemia, thrombocytopenia, alopecia, photosensitivity, and malar rash. Over time, patients with lupus accrue irreversible organ damage which contributes to an increased mortality rate in these patients. Despite advances over the past 40 years in both diagnosis and treatment, patients with SLE have a 2 - 5-fold greater risk of mortality.

SLE most often develops between the ages of 15 – 44 with an insidious onset (Danchenko et al, 2006). In the US, the estimated average of the reported prevalence is approximately 10 cases per 10,000 persons, representing about 300,000 patients, and the incidence has increased 2.5-fold between 1950 and 1979 (Uramoto et al, 1999; Somers et al, 2007; Balluz et al, 2001; Naleway et al, 2005; Ward, 2004; Helmick et al, 2008). In the European Union, an estimated overall average of the reported prevalence is 4 to 5 cases per 10,000 persons (Alamanos et al, 2003; Benucci et al, 2005; Eilertsen et al, 2006; Gourley et al, 1997; Govoni et al, 2006; Gudmundson et al, 1990; Hopkinson et al, 1993; Johnson et al, 1995; Lopez et al, 2003; Nightingale et al, 2007; Nossent, 2001; Piette et al, 2004; Samanta et al, 1992; Stahl-Hallengren et al, 2000; Voss et al, 1998). Recent studies by Bernatsky et al, have emphasized the increased risk of mortality in SLE and have provided data comparing all cause and disease-specific relative mortality across groups characterized by age, sex, SLE duration, calendar-year period, geographic location, and race (Bernatsky et al, 2006). A 2.4-fold greater risk of mortality (95% CI 2.3–2.5) was identified in SLE compared with the general population and there was an increased risk of death due to cardiovascular causes, malignancy, infections, and renal disease.

In an attempt to answer the question as to whether patients with SLE have an increased risk of malignancy in comparison to the general population, several large studies have recently been conducted. In the Swedish cohort of patients with SLE, Bjornadal et al used hospital discharge data to demonstrate an increased relative risk of any malignancy in SLE patients that was 25% higher among SLE patients compared to the general population. Of note, this finding was driven primarily by the higher incidence of non-Hodgkins lymphoma (NHL) in the SLE population which had a relative risk that was 2.86-fold higher (95% CI 1.96, 4.04) than that of the general population. These findings have been subsequently confirmed by the Systemic Lupus International Collaborating Clinics research group (SLICC) in a larger international multi-center cohort study. Using Standardized Incidence Ratio (SIR) estimates, a small increase in all malignancies combined was observed (SIR, 1.15, 95% CI 1.05, 1.27) for SLE compared to that expected for the general population based on data from regional cancer registry linkages

(Bernatsky et al, 2005). Similarly, the increased risk for NHL was also demonstrated (SIR, 3.64, 95% CI 2.63, 4.93) in the SLE population compared to the general population. Unfortunately, no investigations have been able to establish the reason for the close association between SLE and malignancy. Potential considerations in this regard include abnormal immune activity early in the course of the disease, as well as cumulative exposure to immunosuppressive medications. In the SLICC international multi-center cohort study, the adjusted Hazard Ratio (HR) for overall risk of malignancy after administration of any immunosuppressive drug was 0.82 (95% CI 0.50 1.36). However, when specifically considering hematological malignancies (Bernatsky et al, 2009), there was a suggestion of an increased risk after immunosuppressive drug exposures particularly when the medication exposures were lagged by a period of 5 years (adjusted HR 2.29, 95% CI 1.02-5.15).

Infections are responsible for morbidity and mortality in 25-50% of SLE patients; they are the primary cause of death in SLE patients in developing countries (Alarcón et al, 2001; Cervera et al, 1999 and Alarcón, 2006) In a multi-center European study in which 1,000 SLE patients were followed for more than 5 years, infections and disease activity were found to be responsible for more than half of all deaths. Moreover, patients with SLE have higher rates of infections and poorer outcomes compared to the general population (Doria et al, 2008; Petri, 1998). The microorganisms responsible for the overwhelming majority of infections in patients with SLE are bacteria. However, there are many reports of infections occurring in patients with SLE with various outcomes as a consequence of other microorganisms. The increased susceptibility to infections may be multifactorial. Disease activity has been shown to be an independent risk factor for the occurrence of infections (Petri et al, 1992; Zonana-Nacach et al, 2001) presumably because of the abnormal cellular function and complement abnormalities that are more pronounced in the affected patients. The use of corticosteroids and other immunosuppressive medications has also been associated with the increased occurrence of infections in SLE (Gladman et al, 2002; Noel et al, 2001 and Petri et al, 1992). Consequently, the possibility exists that an increased occurrence of infections may occur as a consequence of cytokine suppression, resulting in multiple cellular functional abnormalities (Boumpas et al, 1993).

Neuropsychiatric events are well recognized in the SLE population, with a wide incidence range. In an international inception cohort study (Hanly, 2007), neuropsychiatric events occurred in 28% of subjects near the time of SLE diagnosis, and the incidence of mood disorders attributed to SLE ranged from 4% to 13% depending on the attribution model used. Another study (Bachen et al, 2009) found the prevalence rates of many psychiatric disorders (major depressive disorder, bipolar disorder, panic disorder, etc.) were significantly higher in patients with SLE than the general population. The rate of major depression reported in the literature for patients with SLE ranges from 22.5%-39.1% (Nery et al, 2007; Brey et al, 2002; Ainiala et al, 2001). Severe depression requiring hospitalization was found to be 0.26% (14/5371 SLE patients in a Swedish cohort followed from 1973 to 2004) (Sundquist et al, 2008). Chronic physical illness is also an important risk factor for suicide (Karassa et al, 2003). Patients with SLE are at almost 5 times greater risk for suicide than expected (Harris et al, 1994). Suicide attempts among SLE patients was 5/300 SLE patients who visited a UK Rheumatology Clinic

over a 20-year period (1979-1999) (Karassa et al, 2003) with deaths attributed to suicide ranging from 0.23-0.95% (Mok et al, 2008; Nossent et al, 2001; Karassa et al, 2003).

1.2 BENLYSTA Background Relevant to the Registry

BENLYSTA (belimumab) is a recombinant human IgG1λ monoclonal antibody that binds to soluble human B-lymphocyte stimulator (BLyS; also known as B cell activating factor belonging to the tumor necrosis factor (TNF) family [BAFF] and TNFSF13B) and inhibits its biological activity (Baker, 2003).

The primary safety population, derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE Controlled, Repeat Dose (CRD) studies, included safety data from the double-blind portion of the two phase 3 studies discussed above (HGS1006-C1056 and HGS1006-C1057) as well as the double-blind portion of a Phase 2 study (LBSL02) in 449 subjects with SLE. A summary of adverse events of special interest in this dataset, the same as that to be evaluated in this registry, is provided in Table 1-1. Additional information is provided in the Package Insert/Summary of Product Characteristics.

Table 1-1 Adverse Events of Special Interest (IV SLE CRD) [1]

	Placebo N = 675	1 mg/kg N = 673	10 mg/kg N = 674
All Cause Mortality			
Deaths	3 (0.4%)	5 (0.7%)	6 (0.9%)
Infections and Infestations			
At least 1 Infection AE	455 (67.4%)	484 (71.9%)	477 (70.8%)
At least 1 serious infection AE	37 (5.5%)	48 (7.1%)	36 (5.3%)
Opportunistic infections	-	1 (0.1%)	2 (0.3%)
Malignancies			
Malignancies (all)	3 (0.4%)	4 (0.6%)	3 (0.4%)
Non-melanoma skin cancers (NMSC)	1 (0.1%)	1 (0.1%)	3 (0.4%)
Malignancies excluding NMSC	2 (0.3%)	3 (0.4%)	-
Hematological malignancies	-	-	-
Psychiatric Disorders			
Psychiatric Disorders (SOC)	84 (12.4%)	108 (16.0%)	107 (15.9%)
Serious	3 (0.4%)	4 (0.6%)	8 (1.2%)
Depression/Self-Injury	34 (5.0%)	44 (6.5%)	41 (6.1%)
Serious	2 (0.3%)	3 (0.4%)	4 (0.6%)
Suicide	-	1 (0.1%)	1 (0.1%)

[1] Final integrated safety data from 3 IV SLE CRD trials: LBSL02, HGS1006-C1056 and HGS1006-C1057.

With respect to mortality, 14 deaths occurred during the double-blind periods of these 3 randomized, placebo-controlled SLE trials: 3 (0.4%) in the placebo group, 5 (0.7%) in the

1 mg/kg group and 6 (0.9%) in the 10 mg/kg group. An additional death due to respiratory arrest was reported more than 3 months after the subject's participation in a Phase 3 study (1 mg/kg group). No single cause of death predominated. Etiologies included infection, cardiovascular disease, and suicide. When all IV belimumab SLE studies are considered as of 15 May 2011, including long-term studies, the mortality rate per 100 patient-years was 0.56 and 0.43 in subjects receiving belimumab and placebo, respectively.

In total, 10 malignant neoplasms, 5 solid organ malignancies and 5 non-melanoma skin cancers, were reported in the primary safety population trials. The 5 solid organ malignancies were:

- Stomach carcinoid (placebo, Day 202)
- Breast cancer (placebo, 2 months after last dose)
- Breast cancer (1 mg/kg, Day 102)
- Cervical cancer (1 mg/kg, Stage 0 in situ, 1.2 years)
- Ovarian cancer (1 mg/kg, Day 21)

The ovarian cancer ultimately resulted in the death of the patient. There were 5 non-melanoma skin cancers: 2 basal cell carcinoma and 3 squamous cell carcinoma of the skin (1 in the placebo group, 1 in the 1 mg/kg group, 3 in the 10 mg/kg belimumab group). No solid organ malignancies occurred in the 10 mg/kg group. No hematological malignancies were reported in the primary safety population. The rate of malignancy, excluding non-melanoma skin cancers, across the entire SLE experience as of 15 May 2011 was compared with the malignancy rate in SLE patients reported in the literature (Bernatsky et al, 2005). Excluding non-melanoma skin cancers is appropriate given that it is known that these are underreported in observational studies compared with prospective clinical trials. The malignancy rate per 100 patient-years with belimumab is 0.52 (95% CI: 0.34, 0.77) compared with a background rate in SLE subjects of 0.53 (95% CI: 0.48, 0.59) (Bernatsky et al, 2005). No pattern of malignancies or an increase in any particular type of malignancy was identified in subjects receiving belimumab.

As with other immunomodulating agents, the mechanism of action of belimumab may increase the risk for the development of infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab. Serious infections occurred in 5% to 7% of subjects across the treatment groups in the primary safety population. The top 5 most frequent serious infections (≥ 3 subjects in any treatment group) were pneumonia, UTI, cellulitis, bronchitis, herpes zoster, and pyelonephritis; these events generally occurred at similar rates between the placebo and the belimumab groups. There was no apparent treatment effect or belimumab dose relationship in the incidence of the individual serious infections that occurred most frequently. One placebo and 3 belimumab infectious deaths were related to sepsis, while 1 belimumab 10 mg/kg death was related to infectious diarrhea. Each of these subjects was taking a concomitant steroid and at least 1 other immunosuppressant or antimalarial drug. The 2 opportunistic infections in the 10 mg/kg group included disseminated cytomegalovirus (CMV) infection on Day 62 that resolved after 52 days and Acinetobacter bacteremia on Day 15 that resolved after 28 days. A third potential

opportunistic infection occurred in a subject receiving 1 mg/kg belimumab (preferred term: pneumonia bacterial infection; verbatim: atypical pneumonia, Acinetobacter lwolfii) on Day 1 of study so is unlikely to be causally related to belimumab. The infection was treated with antibiotics, resolved after 11 days, and was considered not related to belimumab; belimumab treatment continued. Overall, in the long-term uncontrolled SLE experience, the incidence of infections, including severe and serious infections, remained stable or declined over time. In terms of potentially opportunistic infections or other infections of interest in the long-term experience as of 09 June 2010, 1 subject had coccidioidomycosis in Year 4 of exposure, and another developed a fatal CMV pneumonia also in Year 4 of exposure. Three cases of mycobacterial infections (1 latent pulmonary tuberculosis TB [serious], 1 extra pulmonary TB [serious], and 1 atypical mycobacterial infection [non-serious]), which had not previously been observed in belimumab-treated SLE subjects have been reported. Another case of non-serious latent pulmonary TB has also been identified. All mycobacterial infections were reported in subjects from countries where TB is endemic. Given that SLE patients are known to be at higher risk for tuberculosis (Erdozain et al, 2006), it is not believed that belimumab treatment increases the risk of tuberculosis.

Progressive multifocal leukoencephalopathy (PML) resulting in neurological deficits, including fatal cases, has been reported in SLE patients receiving immunosuppressant pharmacotherapy, including belimumab. A diagnosis of PML should be considered in any patient presenting with new-onset or deteriorating neurological signs and symptoms. The patient should be referred to a neurologist or other appropriate specialist for evaluation and if PML is confirmed, consideration should be given to stopping immunosuppressant therapy, including belimumab.

Psychiatric events were reported more frequently with belimumab (16%) than with placebo (12%), driven primarily by mild/moderate events of insomnia, depression, and anxiety. Serious psychiatric events also were reported at a slightly higher proportion (0.8% with belimumab compared with 0.4% with placebo), although the numbers of events were small. There were 2 completed suicides in belimumab-treated subjects in the primary safety population. A composite analysis of depression and self-injury/suicide events was performed that showed rates ranging from 5-6% across groups, and serious events were reported in 0.3%, 0.4% and 0.6% of subjects in the placebo, 1 mg/kg and 10 mg/kg groups, respectively. The majority of subjects who reported serious depression or suicidal behavior had a history of depression or other serious psychiatric disorders and most were receiving psychoactive medications; in addition, these events were not judged to be related to belimumab treatment, nor did they (with the exception of the completed suicides) lead to discontinuation of belimumab.

Although not being evaluated as part of this long-term observational registry, infusion and hypersensitivity reactions, including anaphylaxis and death, have been reported in association with belimumab. Delay in the onset of acute hypersensitivity reactions has been observed. Limited data suggest that patients with a history of multiple drug allergies or significant hypersensitivity may be at increased risk. Belimumab should be administered by healthcare providers prepared to manage infusion reactions and anaphylaxis. More information about this risk can be found in the package insert/summary of product characteristics.

Clinical studies of SC belimumab have demonstrated a safety profile consistent with the established safety profile of IV belimumab. The rates of adverse events of special interest, including mortality, (primary endpoints) are not reasonably expected to be affected by route of administration [Stohl, 2017]. Patients treated with either formulation are therefore eligible to participate in this registry.

1.3 Rationale for the Registry

Conservative therapy that is used for non-organ threatening SLE disease may include salicylates, nonsteroidal anti-inflammatory drugs, anti-malarials, and low dose corticosteroids. Therapies for more severe or organ threatening disease may include high dose corticosteroids, methotrexate, leflunomide, azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, rituximab, anti-TNFs, intravenous immune globulin, and plasmapheresis used in combination with or without medications used for milder disease. While there is concern that immunosuppressive medications used in the treatment of SLE are associated with malignancy and with increased occurrence of infection, as well as other potentially serious toxicities (eg, osteoporosis, osteonecrosis, metabolic abnormalities), the use of immunosuppressant medications in SLE may be necessary to reduce the likelihood of disease-related morbidity and death as well as to delay and prevent long term damage resulting from some treatments (Urowitz et al, 2012).

While substantial information exists about the safety of BENLYSTA from clinical trials, it is important to evaluate the safety of BENLYSTA in real world practice settings over a prolonged period of time, particularly with respect to the occurrence of malignancy and serious or opportunistic infections. In order to achieve this, it is necessary to gather data on treatment, safety and effectiveness in the real world setting over an extended period that can be interpreted in the context of other patients not receiving BENLYSTA. It is important to note that differences between patients receiving and not receiving BENLYSA, other than BENLYSTA exposure, may influence the outcomes and hence confound any planned comparisons in this registry. Such factors include baseline disease activity, organ damage, other background treatment, duration of disease, etc. The key challenge in this setting is to attempt to minimize such potential confounding by selecting appropriate comparison patients as well as collating relevant information on potential confounders and making necessary adjustments in the statistical models.

The primary objective of this study is to evaluate the incidence of adverse events of special interest (AESI) over 5 years. AESI collected in this study include: serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events and mortality in patients with SLE being treated with and without BENLYSTA. Additionally, the study may also evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA: organ damage as assessed by SLICC/ACR Damage Index (SDI), concomitant SLE medications including steroids, and hospitalizations.

2 Study Design

This is a multi-center, prospective, observational cohort study to evaluate the incidence of adverse events of special interest (AESI) and effectiveness in patients with active, autoantibody-positive SLE treated with and without BENLYSTA. BENLYSTA refers to any commercially available formulation of belimumab. BENLYSTA formulation, intravenous (IV) or subcutaneous (SC), will be recorded for each patient in the protocol database. Patients will receive BENLYSTA at the discretion of their physician. All treatment decisions are at the discretion of the patient and their healthcare provider and are not mandated by study design or protocol. All assessments are intended to be performed at the time of clinical encounters, per routine care. Patients will be enrolled into 1 of 2 cohorts, those who, at baseline, are receiving or initiating BENLYSTA (BENLYSTA cohort) or are not receiving BENLYSTA (comparison cohort). BENLYSTA and comparison cohort patients may be either treatment initiators or current users. Treatment initiators are defined as those patients who have initiated immunosuppresants and/or BENLYSTA in the last 2 months, while the current users are those who have received immunosuppressants and/or BENLYSTA for ≥ 2 months at the time of entry into the registry. The study will enroll approximately 3,000 patients, approximately 2,000 in the BENLYSTA cohort and 1,000 in the comparison cohort. Enrollment is expected to occur primarily in the US, Canada, and Europe. Each patient will be followed for 5 years contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the comparison cohort, respectively, assuming a 10% annual patient drop-out rate and not accounting for crossover.

Data will be collected at enrollment and at approximately 6 month intervals for 5 years (60 months). All patients will be assessed for AESI including serious infections, opportunistic infections and other infections of interest, malignancies (including NMSC), selected serious psychiatric events and mortality. Organ damage as assessed by SLICC/ACR Damage Index (SDI), concomitant SLE medications including steroids, hospitalizations, demography (eg, age, gender, race/ethnicity, where allowed by local regulation), smoking history, alcohol use, and SLE disease activity (as assessed by the SLEDAI 2000) will also be evaluated in all patients at defined visits (see Table 6-1). Adverse events not collected in this study should be reported in accordance with the laws and regulations for marketed products in the country in which the event occurred.

Patients who become pregnant during their participation in this registry will be encouraged to also participate in a separate pregnancy registry (if available at the time).

3 Objectives

Primary Objective:

To evaluate the incidence of the following adverse events of special interest (AESI) over 5 years in adults with active autoantibody-positive systemic lupus erythematosus (SLE) who are treated with or without BENLYSTA:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

Other Objectives:

To evaluate the following effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

4 Outcome Definitions and Measures

The following outcomes will be collected in the registry:

Safety

- Malignancies (excluding NMSCs): Malignancies are cancers (excluding NMSC) that have the ability to spread to other parts of the body (metastasize) or to invade and destroy tissues and cause death.
- Mortality: Survival status will be collected at each data collection time point after enrollment. If death occurs, the cause of death will be collected.
- Opportunistic infections and other infections of interest: Opportunistic infections are a subset of infections that are caused by organisms that usually do not cause disease in immunocompetent individuals but which may cause illness, or more severe illness, when the immune system is suppressed. Since there are no general guidelines for labeling pathogens as opportunistic without considering the host's immune condition, identification of opportunistic infections in this study is based on a list of pathogens which, when present, may indicate immune suppression in a patient. These pathogens and infections in general are not observed in immunocompetent individuals and will be considered opportunistic. Pathogens and infections considered to be opportunistic include but not limited to those listed in Appendix 1. All potential opportunistic infections (and other infections of interest as noted in Appendix 1), irrespective of seriousness, will be collected.
- Non-melanoma skin cancer: NMSC is a malignant growth of the external surface or epithelial layer of the skin. NMSC most often originates from the external skin surface as a squamous cell carcinoma or a basal cell carcinoma.

- Selected serious psychiatric events: Selected serious psychiatric events suggestive of mood disorders and anxiety, as defined in Appendix 2, will be collected.
- Serious infections: Serious infections, including serious opportunistic infections, are defined as those that result in death, are life-threatening; require inpatient hospitalization or prolongation of existing hospitalization; require treatment with intravenous antimicrobials (eg, antibiotics, antifungals, antivirals); result in persistent or significant disability/incapacity; or are, based upon appropriate medical judgment, important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. All serious infections will be collected. See Section 7.1 for the definition of serious adverse events (SAEs).

Effectiveness

- Organ damage: The SDI (Appendix 5) is designed to capture items of irreversible organ damage present for at least 6 months (Gladman et al, 1996) occurring in patients with SLE regardless of exact cause. It consists of 12 organ system scales each having subscales comprised of up to 6 components.
- Concomitant SLE medications including steroids: The medications used to treat SLE (eg, immunosuppressants, anti-malarials, corticosteroids, biologics, and investigational agents for SLE) will be collected.
- Hospitalization: An inpatient hospitalization is defined as an admission for greater than 24 hours. An admission for administration of medication or for routine or planned clinical procedures should not be considered a hospitalization. Dates of hospital admission and discharge, and whether the hospitalization was SLE-related will be collected, as available.

5 Inclusion and Exclusion Criteria

5.1 Inclusion Criteria

Patients enrolled in the registry must meet the following inclusion criteria:

1. Males or females age 18 or older.
2. Have a clinical diagnosis of active SLE.
3. Current or history of autoantibody-positive SLE.
4. Must be treated with SLE therapy including BENLYSTA and/or immunosuppressants (eg, azathioprine, methotrexate, cyclophosphamide, mycophenolate, and biologics).
5. Have the ability to understand the requirements of the study, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study data collection procedures.

5.2 Exclusion Criteria

Patients will be excluded from participating in the registry if they meet any of the following exclusion criteria:

1. Treatment with an investigational drug within one year of enrollment. Investigational drug applies to any drug not approved for sale in the country it is being used.
2. Currently enrolled in a placebo-controlled BENLYSTA (belimumab) clinical trial or a continuation protocol where belimumab is used as an investigational agent.
3. Patients who have a history of BENLYSTA exposure, but are not currently receiving BENLYSTA.
4. Patients only receiving an anti-malarial for SLE.
5. Patients only receiving steroids for SLE.

6 Data Collection

6.1 Study Enrollment Evaluations

The following data will be collected at enrollment (baseline). Data collection for enrollment may be carried out over more than one clinical evaluation visit.

1. Written informed consent (including consent for the use and disclosure of research-related health information).
2. Demographics (eg, age, gender, race/ethnicity (where allowed by local regulation), smoking history, alcohol use)
3. Medical history (including SLE history). Note: To collect additional important information on potential suicidality-related events, should any of the psychiatric events marked with an asterisk in Appendix 2 be present at enrollment, the investigator should complete the Possible Suicidality-Related History Questionnaire (PSRHQ) eCRF (see Appendix 3).
4. Potential Confounders for Malignancies and/or Infections List (refer to Appendix 7).
5. Obtain historical and current SLE medications (immunosuppressants, antimalarials, corticosteroids and biologics). The name of the each SLE medication and start and stop dates will be recorded. In addition, for corticosteroids, the prescribed dose will be recorded. If the patient is receiving BENLYSTA, the date of first dose, and route of administration (IV or SC) will be recorded as well as name of the other SLE medications the patient was receiving at the time BENLYSTA therapy was initiated.
6. SLEDAI 2000 (see Appendix 6). To complete SLEDAI 2000, data from the following laboratory tests if available: Hematology (WBC, platelets), complement (C3, C4), anti-dsDNA, routine urinalysis, and spot urine for macroscopic/microscopic/proteinuria assessments. Note: Laboratory values should not be attributed on the SLEDAI 2000 unless laboratory values were obtained within 30 days of enrollment otherwise the laboratory values will be noted as not done.
7. SLICC/ACR Damage Index (Appendix 5).
8. Hospitalizations occurring in the previous 6 months.

9. Confirm patient meets study eligibility criteria.

6.2 On Study Evaluations

After enrollment, patients will continue to be followed regardless of changes in medication until study completion. The investigator will manage the patient in accordance with their medical judgment and standard of care. Data will be collected on patients approximately every 6 months as outlined in the study calendar (Table 6-1). Each evaluation may be conducted within 2 months (±2 months) of the scheduled data collection time point, except the last time point (Month 60), where data collection can occur up to +3 months.

The following data will be collected at each 6-month time point:

- SLICC/ACR Damage Index (Appendix 5).
- SLE medications (eg, immunosuppressants, BENLYSTA, antimalarials, corticosteroids, biologics, investigational agents for SLE). The name of each SLE medication and start and stop dates will be recorded. If a patient currently using BENLYSTA changes formulation, the original BENLYSTA record must be updated with a stop date and a new BENLYSTA record needs to be created with a start date for the new formulation. The new BENLYSTA record should also include formulation (IV or SC).
- In addition, the average daily dose of corticosteroids, in prednisone equivalents, will be recorded.
- Hospitalizations. Dates of inpatient hospital admission and discharge, and whether the hospitalization was SLE-related will be collected, as available.
- Adverse events of special interest (see Section 7.2.1). Note: In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 occur, the investigator will be requested to complete the Possible Suicidality-Related History Questionnaire (PSRHQ) eCRF (only the first time a serious suicidality-related event is reported and a Possible Suicidality-Related Questionnaire (PSRQ) eCRF (each time a serious suicidality-related event is reported). The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

6.3 Registry Completion

All patients who do not discontinue, or are not withdrawn, or are not lost to follow-up (see Section 6.4) will remain in the registry for 5 years. Record retention should occur in accordance with Section 11.6.

6.4 Discontinuation and Lost to Follow-Up

Patients will be free to withdraw from this registry at any time, for any reason. It is understood that an excessive rate of withdrawals can render the data un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Patients will continue to be followed regardless of changes in medication until study completion. Patients may be withdrawn from this registry for any of the following reasons:

- Withdrawal of consent
- Lost to follow-up
- At the discretion of the investigator
- Patient enrolls in an interventional trial utilizing an investigational drug or a drug with the same mechanism of action as BENLYSTA
    - *Note: patients who wish to enroll in an interventional trial with a marketed drug being utilized as an investigational agent for the treatment of SLE may be able to continue in SABLE following discussion with the GSK medical monitor.*

If a patient wishes to discontinue participation in the registry, the data collection for the next study evaluation will be obtained at the time of the patient's next routinely scheduled clinical assessment. If data collection has been performed within 2 months before the discontinuation visit, it need not be repeated.

Patients will be considered lost-to-follow-up if no contact can be established by the time a patient is beyond 5 years and 3 months from their enrolment date (Day 0). Investigators or qualified designees should document attempts to re-establish contact with patients throughout the study period. If contact with a patient is re-established before the last follow-up timepoint at 60 months (-2/+3 months), follow-up should resume according to the protocol.

Table 6-1 Study calendar

	Time Points										
Data Collection [7]	**Enrollment**[1] (Day 0)	**6 months** (± 2 months)	**12 months** (± 2 months)	**18 months** (± 2 months)	**24 months** (± 2 months)	**30 months** (± 2 months)	**36 months** (± 2 months)	**42 months** (± 2 months)	**48 months** (± 2 months)	**54 months** (± 2 months)	**60 months** (-2 / +3 months) [6]
Informed Consent	x										
Demographics	x										
Medical History (including SLE history)/ General Medical Status	x				x[3]				x[3]		
Potential Confounders for Malignancies and/or Infections List	x										
Historical SLE Medications	x										
SLEDAI 2000[2]	x										
Verify Eligibility Criteria	x										
SLICC/ACR Damage Index	x	x	x	x	x	X	x	x	x	x	x
Record Current SLE Medications (including corticosteroids)[4]	x	x	x	x	x	X	x	x	x	x	x
Record Hospitalizations	x	x	x	x	x	X	x	x	x	x	x
Record AEs of Special Interest[5]		x	x	x	x	X	x	x	x	x	x

1 Data collection for enrollment may occur over more than one day.

2 Laboratory values should not be attributed on the SLEDAI 2000 unless laboratory values were obtained within 30 days of the assessment.

3 Only General Medical Status (current status of medical condition and/or medical procedure/surgery since last reported) is collected at 24 and 48 months.

4 SLE Medications include immunosuppressants, biologics, antimalarials, corticosteroids, and investigational agents for SLE. If a patient currently using BENLYSTA changes formulation, the original BENLYSTA record must be updated with a stop date and a new BENLYSTA record needs to be created with a start date for the new formulation. The new BENLYSTA record should also include formulation (IV or SC).

5 AEs of special interest for this study include mortality, serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, and malignancies (including NMSC). In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 occur, the investigator will be requested to complete the PSRHQ eCRF (only the first time a serious suicidality-related event is reported) and a PSRQ eCRF (each time a serious suicidality-related event is reported). The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

6 For the last time point (60 months), data collection is extended by an additional 1 month and therefore can occur up to 63 months after enrollment (Day 0). This is to provide sites with additional time to contact patients before declaring them as lost-to-follow-up.

[7] The data collection time intervals of 6 months ±2 months are intended to align with routine standard of care visits for SLE patients. With the exception of the last time point at 60 months (for which data collection can only be extended up to 63 months), data collection occurring outside the time window (±2 months) should be assigned to the closest time point.

7 Adverse Events

7.1 Definitions

ADVERSE EVENT (EXPERIENCE): Any unfavorable or unintended sign, symptom, or disease that is temporally associated with the use of a study agent but is not necessarily caused by the study agent. This includes worsening (eg, increase in frequency or severity) of pre-existing conditions.

SERIOUS ADVERSE EVENT – an adverse event resulting in any of the following outcomes:

- death
- is life threatening (ie, an immediate threat to life)
- inpatient hospitalization*
- prolongation of an existing hospitalization
- persistent or significant disability / incapacity
- congenital anomaly / birth defect
- is medically important+

*An inpatient hospitalization is defined as an admission and inpatient stay for at least 24 hours. A hospitalization for administration of medication, for routine or planned clinical procedures, or for "social" reasons (not the result of any adverse change in the subject's condition) should not be considered an adverse event and should not be reported as a serious adverse event.

+Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or result in hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious. (ICH guidelines, March 1995)

UNEXPECTED ADVERSE EVENT: An adverse event, the nature or severity of which is not consistent with the applicable product information (eg, package insert/summary of product characteristics for an approved product). Expected means the event has previously been observed and is identified and/or described in the applicable product information. It does not mean that the event is expected with the underlying disease(s) or concomitant medications.

7.2 Reporting Adverse Events

7.2.1 Adverse Events of Special Interest

The following adverse events of special interest (AESI) will be collected in this registry:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)

- Non-melanoma skin cancers (NMSC)
- Selected serious psychiatric events (Appendix 2)
- Serious infections

All AESI identified from enrollment throughout the duration of the study will be recorded on the Adverse Event Case Report Form (AE eCRF). All data fields on the AE eCRF should be completed.

7.2.2 Serious AESI and Deaths

All AESI that meet the criteria of a serious adverse event and deaths must be recorded in the SAE section of the protocol database within 24 hours of site personnel becoming aware of a SAE. In the event the protocol database cannot be accessed, the SAE Worksheet should be used and information faxed to the Drug Safety Designee. All pages of the SAE Database/Worksheet should be completed and not held until all information is available. Additional information and corrections should be added to the protocol Database/Worksheet when available.

7.2.3 Other Adverse Events

Other adverse events (including serious adverse events) not collected as AESIs in this registry should be reported in accordance with the laws and regulations for marketed products in the country where the event occurred.

7.3 Suicidality

Some autoimmune diseases have an increased risk of suicidal behavior and/or ideation (Bachen, 2009; Timonen, 2003; Stenager, 1992). In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 occur, the investigator will be requested to complete the Possible Suicidality Related-History Questionnaire (PSRHQ) eCRF (only the first time a serious suicidality-related event is reported) and a Possible Suicidality-Related Questionnaire (PSRQ) eCRF (each time a serious suicidality-related event is reported). The PSRHQ collects past medical history in relation to SLE-related neuropsychiatric events prior to study enrollment. The PSRQ collects other information important for evaluating suicidality-related events such as use of illicit drugs, alcohol, other stressors, family history of suicidality and other psychiatric disorders. The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

7.4 Investigator Evaluation of Adverse Events

The Investigator will evaluate all AESI with respect to seriousness (criteria listed in Section 7.1), severity (intensity or grade) and causality (relationship to medicinal product) according to the following guidelines:

SEVERITY:

- **Mild** - causing no limitation of usual activities.
- **Moderate** - causing some limitation of usual activities.
- **Severe** - causing inability to carry out usual activities.
- **Life-threatening*** - potentially life-threatening or disabling; significant medical intervention is required.

*Note – a severity assessment of life-threatening is not necessarily the same as the seriousness criterion of life-threatening. (See "Serious" in Section 7.1). The former means that the event is a potential threat to life. The latter means that the event is an immediate threat to life.

CAUSALITY

Definitely Related	- reasonable temporal relationship to medicinal product administration - follows a known response pattern (eg, medicinal product is known to cause this AE) - there is no alternative etiology
Probably Related	- reasonable temporal relationship - follows a suspected response pattern (eg, based on similar drugs) - no evidence for a more likely alternative etiology
Possibly Related	- reasonable temporal relationship - little evidence for a more likely alternative etiology
Probably Not Related	- does not have a reasonable temporal relationship OR - good evidence for a more likely alternative etiology
Not Related	- does not have a temporal relationship OR - definitely due to alternative etiology

The causality assessment must be made by the investigator based on information available at the time that the AE eCRF or SAE worksheet is completed. The initial causality assessment may be revised as new information becomes available.

7.5 Follow-Up of Adverse Events of Special Interest

AESI (Section 7.2.1) and Serious AESI (Section 7.2.2) that occur from study entry are followed until the final outcome is known or until the end of patient participation.

7.6 Reporting Serious Adverse Events to the Regulatory Authorities and Institutional Review Board/Ethics Committee

The Sponsor or its designee, will follow all applicable local and national regulatory requirements regarding safety reporting. Each investigator must also comply with the applicable regulatory requirements related to the reporting of serious AESI to the IRBs/IECs responsible for reviewing the study at their site, as well as the regulatory authority(ies) (if applicable).

AESI that are study endpoints (as defined in Section 7.2.1) generally will not be submitted as expedited reports to regulatory authorities or participating investigators. However, serious AESIs related to belimumab will be reported by GSK to regulatory authorities as expedited individual case safety reports (ICSRs).

8 Data Analysis

8.1 General Statistical Considerations

This registry will observe mortality and AESI as well as effectiveness outcomes on patients with diverse treatment experience both during the registry and prior to enrollment. Some patients may enter the study already receiving BENLYSTA therapy (current user) and some patients may initiate BENLYSTA therapy within the last 2 months prior to study entry (treatment initiator). During the study, some patients receiving BENLYSTA therapy may stop and potentially restart therapy, and some comparison cohort patients may elect to initiate BENLYSTA therapy at some point subsequent to enrollment. Because of these complexities, a variety of analyses will be employed, some of which consider time periods of switching on and off BENLYSTA treatment. Since the initiation of this registry, a SC formulation of belimumab has been submitted for marketing authorization. The protocol database has been modified to capture formulation of BENLYSTA but reporting and analyses will not be separated by formulation.

Patients will be considered evaluable in the BENLYSTA cohort upon receiving a single, full or partial dose administration of BENLYSTA and collection of enrollment data (Section 6.1) and at least 1 post baseline assessment (Section 6.2). Patients will be considered evaluable in the comparison cohort if there is collection of enrollment data (Section 6.1) and at least 1 post baseline assessment (Section 6.2).

8.2 Sample Size Consideration

This registry will enroll approximately 3,000 patients approximately 2,000 receiving or initiating BENLYSTA plus standard of care (BENLYSTA cohort) and 1,000 standard of care only (comparison cohort). Each patient will be followed for 5 years, contributing a total of approximately 7,773 patient years in the BENLYSTA cohort and 3,886 patient years in the

comparison cohort, respectively, assuming a 10% annual patient drop-out rate and not accounting for crossover.

The registry will allow the difference in mortality rate in the BENLYSTA cohort and comparison cohort to be established with a 95% CI of +/-0.30 per 100-subject years, based on an estimated mortality rate of 0.68 per 100-subject years in both treatment groups (Table 8-1). The estimated mortality rate was based on the mortality rate in the pooled IV primary safety database in SLE subjects derived from 3 randomized, double-blind, IV placebo-controlled trials, referred to as IV SLE CRD studies (ie, integrated database of LBSL02 [placebo-controlled treatment phase only], HGS1006-C1056, and HGS1006-C1057) for all subjects (IV belimumab and placebo) adjusted for subject years. The precision of the rates of the AESI are provided in the table below:

Table 8-1 Precision of differences in AE rates estimated from a total of 7773 patient years in the BENLYSTA cohort and 3886 patient years in the comparison cohort, respectively

Adverse Events	Reference Rate[1] (per 100-patient years)	95% Confidence Interval for difference in AE rates[2] (per 100-patient years)
All Deaths	0.68	±0.32
Serious infection	5.80	±0.93
Opportunistic infection	0.136	±0.14
Malignancy excl. NMSC	0.226	±0.19
NMSC	0.226	±0.19
Serious Psychiatric Events	0.410	±0.25

[1] The reference AE rates were based on the AE rates in the pooled IV primary safety database derived from 3 IV SLE CRD studies (LBSL02, HGS1006-C1056, HGS1006-C1057) and adjusted for subject years.

[2] Assuming that the AE rates in BENLYSTA and the control groups were the same as the reference rate.

8.3 Endpoints and Analysis

8.3.1 Primary Endpoints

The primary endpoints are the incidence of the following AESI:

- Malignancies (excluding NMSC)
- Mortality
- Opportunistic infections and other infections of interest (Appendix 1)
- NMSC
- Serious psychiatric events (Appendix 2)
- Serious infections

8.3.2 Analysis of Primary Endpoints

In addition to analyses that consider initial treatment group (BENLYSTA cohort vs. comparison cohort), analyses that specifically account for changes in therapy (in either group) by considering a variety of risk windows will be employed. These analyses will attribute events to BENLYSTA treatment if they occur within the designated risk windows for BENLYSTA exposure and to comparison treatment otherwise. These analyses will allow for a registry patient to contribute person-time to both BENLYSTA treatment, and comparison treatment and as a result, will specifically account for treatment switching to BENLYSTA or from BENLYSTA. Switching between BENLYSTA and comparison treatment will be taken into account in a number of ways in the analysis and will be further defined within the statistical analysis plan. No new analyses for changing between BENLYSTA formulation or stratifying by BENLYSTA formulation are planned. Planned analyses are outlined below; all analyses will be detailed in the statistical analysis plan.

- Analysis by initial treatment group of rate per person years of observation time.
- Analysis by initial treatment group of rate per person years of exposure where BENLYSTA exposure ends 14 weeks (approximately 5 half-lives) after cessation of treatment.
- For serious psychiatric events, BENLYSTA exposure is all time on treatment with BENLYSTA ending 14 weeks (approximately 5 half-lives) after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For serious infections, opportunistic infections and other infections of interest, BENLYSTA exposure is all time on treatment with BENLYSTA ending 6 months after cessation of treatment, with all remaining treatment time attributed to the comparison cohort.
- For NMSC and malignancies excluding NMSC, analysis will be performed where all events will be attributed to BENLYSTA if the patient was ever exposed to BENLYSTA treatment prior to the event and attributed to the comparison cohort otherwise (ie, once exposed, always at risk).
- Mortality will be analyzed applying all the above-mentioned risk windows (eg, 14 weeks, 6 months, and ever-exposed).
- Other risk windows (including risk windows for comparison treatment) may also be assessed and defined in the statistical analysis plan.

Additional safety analysis will be performed comparing BENLYSTA treatment initiators with patients from the comparison cohort that start or switch an immunosuppressant and that have comparable background medication and treatment history. Subgroup analysis will be performed that will include but not be limited to analysis of patients with positive anti-dsDNA and low complement at baseline, patients with SLEDAI 2000 score at baseline (< 10 vs ≥ 10), SDI (0 vs ≥ 1), steroid use (yes vs no; ≤ 7.5 mg/day vs > 7.5 mg/day), immunosuppressant use (yes vs no; mycophenolate vs immunosuppressant other than mycophenolate), region (US/Canada vs Europe vs other), and race (black race vs other). Safety analyses will be adjusted for potential confounding factors (Appendix 7) through propensity score methods or other appropriate statistical methods. No new analyses for changing between BENLYSTA formulation or

stratifying by BENLYSTA formulation are planned. Further details of the safety analyses will be described in the statistical analysis plan.

8.3.3 Effectiveness Endpoints and Analysis

Additional endpoints include the following:

- Organ damage as assessed by SLICC/ACR Damage Index (Appendix 5)
- Concomitant SLE medications including steroids
- Hospitalizations

For any effectiveness endpoint analyses performed, methods to reduce the potential impact of confounding may be employed. These methods could include subgroup analysis, modeling adjusting for baseline and/or other confounding variables, or patient matching techniques like propensity score analysis. Furthermore, analyses considering changes in BENLYSTA use over time (eg, on or off treatment, but not changes between BENLYSTA formulations) in order to assess BENLYSTA effectiveness, as well as evaluate how these endpoints vary in response to BENLYSTA treatment will be assessed and further explored as appropriate. These analyses will be described in the statistical analysis plan.

9 Scientific Advisory Committee (SAC)

A Scientific Advisory Committee (SAC) consisting of global clinical experts, along with GSK staff (clinical, statistics, epidemiology) will be formed. The SAC will meet as needed to review the data collected.

10 Study Limitations

This is a registry and, as such, participants are not randomized into study arms. Due to the lack of randomization, there is a significant risk of confounding (ie, imbalance in important baseline characteristics between the BENLYSTA cohort and the comparison cohort where these characteristics are also risk factors for the outcomes). The present study attempts to minimize such confounding by selecting comparison patients that are as similar as possible to BENLYSTA cohort and will also attempt to account for confounding by further adjustment in the analysis using relevant statistical methods (such as propensity score matching or adjustment for baseline factors) (see Section 6.2). However, as with all non-randomized observational studies, residual unmeasured confounding may still exist. In addition, although the study is designed to specifically attempt to enroll a sample of SLE patients who are closely matched in both cohorts, it may be that the final enrolled study sample is not as well matched as desired due to multiple patient factors that can't be controlled for. The Sponsor will monitor enrollment for the proportion of patients who are treatment initiators versus current users and communicate to the sites the interest to achieve a reasonable balance for both groups.

Patients receiving commercially available belimumab may be seen more often by their medical care providers as compared to the bi-annual visits of standard of care patients. This may create

a reporting bias with increased reporting of events for some outcomes in the BENLYSTA group.

11 Study Administration

This study is sponsored by GlaxoSmithKline (GSK) LLC. They will lead on the operational conduct of this observational study world-wide working with contract research organizations.

11.1 Informed Consent

The consent form must be approved by the Institutional Review Board (IRB) or Institutional Ethics Committee (IEC) and contain all elements required by national, state, local, and institutional regulations or requirements. In the event that local regulations/laws require a Privacy Authorization this will be included as part of the informed consent process. Informed consent will be obtained by investigators for each patient whose data are included in this study. A copy of the signed informed consent must be given to each study patient.

11.2 Institutional Review Board Review/Independent Ethics Committee Review and Approval

Regulatory approval or notification will be obtained or performed, respectively, in countries where this is required. IRB/IEC approval will be obtained by participating investigators or a representative thereof; however, application will be made to central IRBs/IECs governing regions or countries wherever this is feasible.

11.3 Protocol Revisions

Protocol amendments will be prepared and approved by the sponsor. All protocol amendments will be signed by the investigator and submitted to the IRB/IEC for review prior to implementation. Documentation of IRB/IEC approval must be forwarded to the sponsor or designee. If an amendment significantly alters the study design or affects statements in the informed consent form, the informed consent form must be revised accordingly and submitted to the IRB/IEC for review and approval. The approved consent form must be used to obtain informed consent from new patients prior to enrollment and must be used to obtain informed consent from patients already enrolled if they are affected by the amendment.

11.4 Data Management

The investigator is responsible for maintaining accurate, complete, and up-to-date records for each patient. The investigator is also responsible for maintaining any source documentation related to the study, including any films, tracings, computer discs, or tapes.

The anonymity of participating patients must be maintained. For data collection and management purposes, patients are to be identified by a patient number only. Documents that identify the patient beyond patient number will not be submitted to the sponsor (eg, the signed informed consent document; patient initials) and must be maintained in strict confidence by the

investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Site personnel record all data for each study patient through electronic case report forms (eCRFs) using an Electronic Data Capture (EDC) system provided and approved by the sponsor. Sites must complete the eCRFs in a timely manner and the investigator must promptly review the completed eCRFs for each patient. As the person ultimately responsible for the accuracy of all eCRF data, the investigator must sign the Investigator's Statement in each patient's eCRF.

The EDC system automatically generates queries resulting from the computer checks embedded into the system, so as to ensure accuracy, quality, consistency, and completeness of the database. Manual queries resulting from review by monitors, medical coders, and other Data Management staff are also generated from within the EDC system, where they are tracked. Sites resolve the queries and correct the entered data when necessary. Every change to data is captured in the EDC system audit trail. Upon completion of the study, or after reaching a pre-specified point in the study, Data Management will lock the database and generate the SAS datasets necessary for data analysis and reporting. Upon completion of the study, each site will be provided with the eCRFs for each of their patients.

11.5 Study Conduct

The study sponsor or designee will monitor the conduct of the study. The sponsor may review eCRFs and compare them with source documents to verify accurate and complete collection of data and confirm that the study is being conducted according to the protocol. Monitors or auditors representing the sponsor may also similarly evaluate the study. For these purposes, the investigator will make eCRFs and source documents available when requested.

In addition, the study may be evaluated by representatives of the national regulatory authorities, who will also be allowed access to study documents. The investigators should promptly notify GlaxoSmithKline of any audits they have scheduled with any regulatory authority.

11.6 Retention of Records

The investigator shall retain all records and source documents pertaining to the study, including any films, tracings, computer discs, or tapes. They will be retained for the longer of the maximum period required by the country and institution in which the study is conducted, or the period specified by the sponsor at the time the study is completed, terminated, or discontinued.

If the investigator leaves the institution, the records shall be transferred to an appropriate designee who accepts the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to the sponsor.

11.7 Publication Policy

Reports to regulatory authorities will be provided as appropriate and agreed with the relevant authorities.

This study is a multi-center observational research study. Data from all sites participating in the multi-center observational initiative will be pooled and analyzed. The investigators acknowledge that an independent, joint publication is anticipated to be authored by the investigators of the multi-center study and the sponsor's representatives. Neither the participating institutions nor the principal investigators shall publish or present the results of the study prior to the publication of the multi-center study publication. The investigators agree that the sponsor will be the coordinator and arbitrator of all multi-center study publications. For multi-center studies, no investigator will be authorized to publish study results from an individual center until the earlier of the multi-center study results are published or 12 months after the end or termination of the multi-center study at all sites.

The investigator shall submit a copy of any proposed publication, manuscript, abstract, presentation or other document with respect to this study to the sponsor for review and comment at least 60 days prior to its submission for publication or presentation. No publication or presentation with respect to the study shall be made unless and until all of the sponsor's comments on the proposed publication or presentation have been considered and any information determined by the sponsor to be confidential information has been removed. If requested in writing by the sponsor, the investigator shall withhold material from submission for publication or presentation for an additional 60 days to allow for the filing of a patent application or the taking of other measures to establish and preserve the sponsor's proprietary rights.

11.8 Study or Study Site Termination

If the sponsor, the investigator, IRB/IEC, or a regulatory authority discovers conditions arising during the study that indicate that the study should be halted or that the study center should be terminated, this action may be taken after appropriate consultation between the sponsor and the investigator. Conditions that may warrant termination of the study include, but are not limited to, the following:

- Sufficient information has accumulated to meet the primary scientific objectives of the observational study.
- Other methods of gathering appropriate information become achievable or are deemed preferable.
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow-up.

The study site may warrant termination under the following conditions:

- Failure of the investigator to enroll patients into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent regulatory authority regulations.
- Submission of knowingly false information from the research facility to GSK, study monitor, or the regulatory authority.
- Insufficient adherence to protocol requirements.

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Ward M. Prevalence of physician-diagnosed systemic lupus erythematosus in the United States: Results from the third National Health and Nutrition Examination Survey. J Womens Health (Larchmt) 2004; 13(6):713-8.

Zonana-Nacach A, Camargo-Coronel A, Yañez P, et al. Infections in outpatients with systemic lupus erythematosus: a prospective study. Lupus 2001;10:505–10.

List of Appendices

Appendix 1 Opportunistic Infections and Other Infections of Interest

Opportunistic infections and other infections of interest are a subset of infections that are caused by organisms that usually do not cause disease in immunocompetent individuals but which may cause illness, or more severe illness, when the immune system is suppressed. Since there are no general guidelines for labeling pathogens as opportunistic without considering the host's immune condition, identification of opportunistic infections and other infections of interest in this study is based on the following list of pathogens which when present may indicate immune suppression in a patient. Pathogens considered to cause opportunistic infections and other infections of interest include but are not limited to the following:

Acinetobacter infection

Aspergillosis

Blastomycosis, extrapulmonary

Candidiasis of esophagus, bronchi, trachea, or lungs

Coccidiomycosis, dissemintaed or extrapulmonary

Cryptococcosis, extrapulmonary

Cryptosporidiosis infection, chronic intestinal (> 1 month duration)

Cytomegalovirus disease (other than liver, spleen, or nodes)

Herpes simplex bronchitis, pneumonitis, or esophagitis

Disseminated herpes zoster or involving at least 2 distinct episodes

Herpes virus associated Kaposi's sarcoma

Histoplasmosis disseminated or extrapulmonary

Human polyomavirus infection

Isosporiasis, chronic intestinal (> 1 month’s duration)

Listeriosis

Mycobacterium avium complex or M. Kansasii, disseminated or extrapulmonary

Mycobacterium infections, other species or unidentified species, disseminated or extrapulmonary (eg, M. haemophilium, M. fortuitum, or M. marinum)

Nocardiosis

Polyomavirus (JC virus or BK virus)-associated nephropathy (including progressive multifocal leukoencephalopathy)

Pneumocystis jiroveci infection

Toxoplasmosis of brain

Other infections of interest that should be recorded in this registry, but which are not generally considered opportunistic, include:

Mycobacterium tuberculosis, any site, latent or active

Salmonella sepsis

Hepatitis B

Hepatitis C

All other (ie, non-disseminated or single episode) herpes zoster (shingles)

Appendix 2 Serious Psychiatric Events

The following events suggesting serious mood disorders (including suicidality) and anxiety will be collected if serious.

Adjustment disorder
Adjustment disorder with anxiety
Adjustment disorder with depressed mood
Adjustment disorder with disturbance of conduct
Adjustment disorder with mixed anxiety and depressed mood
Adjustment disorder with mixed disturbance of emotion and conduct
Affective disorder
Agitated depression
Anxiety
Anxiety disorder
Anxiety disorder due to a general medical condition
Bipolar I disorder
Bipolar II disorder
Bipolar disorder
*Completed suicide
Cyclothymic disorder
Depressed mood
Depression
Depression post-operative
*Depression suicidal
Depressive delusion
Depressive symptom
Dysthymic disorder
Generalised anxiety disorder
*Intentional overdose
*Intentional self-injury
Major depression
Menopausal depression
Mood disorder due to a general medical condition
*Multiple drug overdose intentional
*Poisoning deliberate
Postpartum depression
*Self injurious behaviour
*Self-injurious ideation
*Suicidal behaviour
*Suicidal ideation
*Suicide attempt

In order to collect additional information on potential suicidality-related events, should any of the events indicated with the asterisk occur, the investigator will be requested to complete the Possible Suicidality-Related History Questionnaire (PSRHQ, only the first time a serious suicidality-related event is reported) and a Possible Suicidality-Related Questionnaire (PSRQ) (each time a serious suicidality-related event is reported). The PSRHQ collects past medical history in relation to SLE-related neuropsychiatric events prior to study enrollment. The PSRQ collects other information important for evaluating suicidality-related events such as use of illicit drugs, alcohol, other stressors, family history of suicidality and other psychiatric disorders. The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4, respectively.

Appendix 3 Possible Suicidality-Related History Questionnaire (PSRHQ)

Date of Assessment: _____

(DDMMMYYYY)

Has the subject had any SLE-related neuropsychiatric events prior to study start? ❑Yes ❑No

If Yes, check all that apply and provide the most recent date of occurrence:

	Event	**Date** (DDMMMYYYY)
❑	Acute Confusional State	
❑	Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barré Syndrome)	
❑	Anxiety Disorder	
❑	Aseptic Meningitis	
❑	Autonomic Disorder	
❑	Cerebrovascular Disease	
❑	Cognitive Dysfunction	
❑	Demyelinating Syndrome	
❑	Headache	
❑	Mononeuropathy Single	
❑	Mononeuropathy Multiplex	
❑	Mood Disorders	
❑	Movement Disorder (Chorea)	
❑	Myasthenia Gravis	
❑	Myelopathy	
❑	Neuropathy, Cranial	
❑	Plexopathy	
❑	Polyneuropathy	
❑	Psychosis	
❑	Seizures and Seizure Disorders	

Appendix 4 Possible Suicidality-Related Questionnaire (PSRQ)

Is the subject currently using illicit drugs? ❑ Yes ❑ No

If Yes, check all that apply:
❑ Amphetamines ❑ Benzodiazepines ❑ Cannabinoids ❑ Cocaine ❑ Opiates
❑ Other, Specify: _____

Is the subject currently using alcohol? ❑ Yes ❑ No

If Yes, Average Unit(s) of Alcohol/Week:

Has the subject experienced any recent stress? ❑ Yes ❑ No

If Yes, check all that apply:
❑ Family Problems ❑ Relationships ❑ Employment/ Unemployment ❑ Finances
❑ Other Factors, Specify:

Any family history of suicidality? ❑ Yes ❑ No

If Yes, check ideation and/or behavior next to all that apply:
Father ❑ Ideation ❑ Behavior
Mother ❑ Ideation ❑ Behavior
Sibling ❑ Ideation ❑ Behavior
Other ❑ Ideation ❑ Behavior

Any family history of psychiatric disorders? ❑ Yes ❑ No

If Yes, specify disorder next to all that apply:

Father _____

Mother _____

Sibling _____

Other _____

Appendix 5 SLICC/ACR Damage Index (SDI)

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	1
Retinal change or optic atrophy	1
Neuropsychiatric	
Cognitive impairment (eg memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	1
Seizures requiring therapy for 6 months	1
Cerebrovascular accident ever (score 2 > 1)	1 (2)
Cranial or peripheral neuropathy (excluding optic)	1
Transverse myelitis	1
Renal	
Estimated or measured glomerular filtration rate < 50%	1
Proteinuria > 3.5 gm/24hours	1
Or	
End-stage renal disease (regardless of dialysis or transplantation)	3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	1
Pulmonary fibrosis (physical and radiograph)	1
Shrinking lung (radiograph)	1
Pleural fibrosis (radiograph)	1
Pulmonary infarction (radiograph)	1
Cardiovascular	
Angina or coronary artery bypass	1
Myocardial infarction ever (score 2 if > 1)	1 (2)
Cardiomyopathy (ventricular dysfunction)	1
Valvular disease (diastolic, murmur, or systolic murmur > 3/6)	1
Pericarditis for 6 months, or pericardiectomy	1
Peripheral vascular	
Claudication for 6 months	1
Minor tissue loss (pulp space)	1
Significant tissue loss ever (eg loss of digit or limb)(score 2 if > 1 site)	1 (2)
Venous thrombosis with swelling, ulceration, or venous stasis	1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for cause any (score 2 if > 1 site)	1 (2)
Mesenteric insufficiency	1
Chronic peritonitis	1
Stricture or upper gastrointestinal tract surgery ever	1

Musculoskeletal	
Muscle atrophy or weakness	1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	1
Avascular necrosis (score 2 if > 1)	1 (2)
Osteomyelitis	1
Skin	
Scarring chronic alopecia	1
Extensive scarring or panniculum other than scalp and pulp space	1
Skin ulceration (excluding thrombosis) for > 6 months	1
Premature gonadal failure	1
Diabetes (regardless of treatment)	1
Malignancy (exclude dysplasia) (score 2 if > 1 site)	1 (2)

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)

Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996a;39(3):363-9.

Appendix 6 SLEDAI 2000

Score if descriptor is present at time of visit or ± 30 days of enrollment visit.

Weight	SLEDAI Score	Descriptor	Definition
8	_____	Seizure	Recent onset, exclude metabolic, infectious or drug causes.
8	_____	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Excluded uremia and drug causes.
8	_____	Organic brain syndrome	Altered mental function with impaired orientation, memory or other intelligent function, with rapid onset fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus, and inability to sustain attention to environment, plus at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	_____	Visual disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serious exodate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection, or drug causes.
8	_____	Cranial nerve disorder	New onset of sensory or motor neuropathy involving cranial nerves.
8	_____	Lupus headache	Severe persistent headache: may be migrainous, but must be nonresponsive to narcotic analgesia.
8	_____	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	_____	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual, infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	_____	Arthritis	≥ 2 joints with pain and signs of inflammation (i.e. tenderness, swelling, or effusion).
4	_____	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/adolase or electromyogram changes or a biopsy showing myositis.
4	_____	Urinary casts	Heme-granular or red blood cell casts.
4	_____	Hematuria	> 5 red blood cells/high power field. Exclude stone, infection or other cause.
4	_____	Proteinuria	> 0.5 gm/24 hours.
4	_____	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	_____	Rash	Inflammatory type rash.
2	_____	Alopecia	Abnormal, patchy or diffuse loss of hair.
2	_____	Mucosal ulcers	Oral or nasal ulcerations.
2	_____	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	_____	Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation.
2	_____	Low complement	Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory.
2	_____	Increased DNA binding	Increased DNA binding by Farr assay above normal range for testing laboratory.
1	_____	Fever	> 38°C. Exclude infectious cause.
1	_____	Thrombocytopenia	< 100,000 platelets/ $x10^9$/L, exclude drug causes.
1	_____	Lenkopenia	< 3,000 White blood cell/ $x10^9$/L, exclude drug causes.
TOTAL SLEDAI SCORE	_____		

Adapted from:

Dafna D Gladman, Dominique Ibañez and Murray B Urowitz, Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29;288-291.

Appendix 7 Potential Confounders for Malignancies and/or Infections List

- **Demographic and other general characteristics**
  - Age
  - Gender
  - Weight
  - Height
  - Race/ethnicity
  - Smoking history
  - Family history of cancer – first degree relatives & grandparents
  - Alcohol history
  - Female only:
  - Parity
  - Hormonal status

- **SLE disease profile**
  - Age at diagnosis
  - Organ involvement (SLEDAI 2000 Domains)
  - Disease Severity (SLEDAI 2000)
  - Organ Damage (SDI)
  - ANA status
  - Anti-dsDNA status
  - Quantitative Immunoglobulins (IgG, IgA, IgM)
  - Complement levels (C3/C4)
  - Total white blood cell count
  - Neutrophil differential %
  - Lymphocyte differential %

- **SLE treatment**
  - Name and duration of current SLE medications: including anti-malarials, biologics, steroids, and immunosuppressants at baseline
  - In addition, for steroids add dose

- **Co-morbidities**
  - ESRD/dialysis
  - Hepatitis B
  - Hepatitis C
  - HIV
  - Sjogren's Syndrome (Secondary)
  - Neutropenia
  - Post-transplant (any transplant)
  - Diabetes
  - Splenectomy

- Chronic lung disease
- Known immunoglobulin deficiencies
- Tuberculosis (latent or active)
- History of cancer (including NMSC)
- History of serious infection

- **Vaccinations**
  - BCG
  - Pneumococcal
  - Influenza vaccine
  - Human papillomavirus (HPV)
  - Hepatitis
  - Varicella zoster
  - Any live vaccine received 30 days prior to enrollment

Signature Page for 116543 TMF-14148167 v2.0

Reason for signing: Approved	Name: PPD Role: A Date of signature: 25-May-2022 14:05:04 GMT+0000

Reason for signing: Approved	Name: PPD Role: A Date of signature: 25-May-2022 14:10:27 GMT+0000

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Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for BEL116543, a 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (Belimumab)
Compound Number	:	GSK1550188
Clinical Study Identifier		BEL116543
Effective Date	:	14 March 2025

Description:

This document describes the safety and effectiveness analysis and outputs required for Clinical Study Report BEL116543 [HGS10006-C1124].

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TABLE OF CONTENTS

1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses required for the final Clinical Study Report (CSR) for study BEL116543 [HGS10006-C1124] based on the study protocol amendment 5.

Protocol Revision Chronology:		
Global	14-Aug-2012	Original
Global	01-Nov-2012	Amendment No 01
Local 2013N183013_00	10-Dec-2013	Local Addendum No 01 for Sweden
Global 2017N316452_00	19-Jun-2017	Amendment No 02
Global 2017N316452_01	12-Mar-2018	Amendment No 03
Global 2017N316452_02	25-Nov-2020	Amendment No 04
GlobalTMF-14148167	25 May 2022	Amendment No 05

This RAP is based upon the following study documents:

- Study Protocol Amendment 05 (25 May 2022)
- Case Report Form (CRF) Version 7.0 (27 Jul 2020)

The protocol amendment 03 excludes collection of the following data: quality of life (as assessed by SF-12v2 Health Survey), fatigue (as assessed by the functional assessment of chronic illness therapy [FACIT]-Fatigue Scale) and limits collection of systemic lupus erythematosus (SLE) disease activity (as assessed by the SLEDAI 2000) to the baseline visit only. The protocol amendment 04 updated the General Medical Status (current status of medical condition and/or medical procedure/surgery since last reported) to be collected at 24 and 48 months. The data collection modifications for protocol amendments 3 and 4 are shown in Appendix 1.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Reporting Analysis Plan and Previous RAP

2.1.1. Changes to the Protocol Defined Reporting Analysis Plan

This RAP provides a more detailed elaboration of the high-level summary of statistical analysis provided in the protocol. There are no changes to the approach originally planned for statistical analysis. However, the following slight modifications have been made:

- Computation of rates (incidence and event) will be done separately for Opportunistic Infections and Other Infections of Interest (these were combined as one in the protocol).

2.1.2. Changes to the Previous RAP

This version of the RAP for final analysis includes amendments to the approved interim analysis 11 (IA11) RAP. Changes are listed below:

- Section 3.1: details on Interim analysis have been deleted as not applicable for final analysis
  Along the document, non relevant statements related to interim analysis have been deleted.
- Section 4.2: last version of Protocol Deviation Management Plan (PDMP) added
- Section 5.1: Table presented analysis strategy per endpoints: Correction added for hospitalization for “As-Exposed time varying”, that is applicable to the 14 weeks risk window (Y1) and 6-months risk window (Y2) was made applicable for Serious Psychiatric Events
- Sections 5.2 and 9.5.1: updated laboratory measurement reporting
- Section 5.4: “Ongoing” status deleted as RAP applies for final analysis
- Section 5.5: clarification added regarding reporting of subjects transferred to a new site in table of enrollement
- Section 7.2: Effectiveness analysis will not be conducted separately for the two study cohorts (Current users and treatment initiators). All link in the RAP deleted.
- Section 7.3: New section added to include propensity scores analysis
- Section 8: AESI work instruction reference added, , references regarding propensity scores analysis also added
- Section 9: first appendix presented in previous version was removed, impacting the numbering of the subsequent sections.
- Section 9.4: GSK standards updated
- Section 9.9: new appendix added.
- Section 9.10: new appendix added.
- Section 9.11: updated for final analysis (was previously section 9.10)
- Section 9.12: section renumbered (was previous section 9.11)

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	**Primary**
To evaluate the incidence of selected adverse events of special interest (AESI) over 5 years in adults with active autoantibody-positive systemic lupus erythematosus (SLE) who are treated with or without BENLYSTA	Comparison of incidence rates, over a 5-year period, of listed Adverse Events of Special Interest (AESI) among adult SLE subjects who are exposed or unexposed to BENLYSTA: 1. Malignancies (excluding non-melanoma skin cancers) 2. Mortality 3. Opportunistic infections (serious and non-serious)* 4. Other infections of interest (serious and non-serious)* 5. Non-melanoma skin cancers (NMSC) 6. Serious psychiatric events 7. Serious infections
Other	**Other**
To evaluate selected effectiveness measures in adults with active autoantibody-positive SLE who are treated with or without BENLYSTA	1. Comparison of mean change from baseline in SLICC/ACR Damage Index (SDI) score over a 5-year period in adult SLE subjects who are exposed or unexposed to BENLYSTA 2a. Comparison of proportions of subjects with concomitant SLE medication use, including steroids (as defined below), over a 5-year period in adult SLE subjects who are exposed or unexposed to BENLYSTA Over the past six months the daily dose was either: i. Always < 7.5 mg/day ii. >= 7.5 mg/day for <= 2 weeks iii. >= 7.5 mg/day for > 2 weeks 2b. Comparison of mean change from baseline in six-month average daily corticosteroid dose (prednisone equivalent, mg/day) assessed over 5-year period in adult SLE subjects who are exposed or unexposed to BENLYSTA 3. Comparison of incidence rates, over a 5-year period, of hospitalizations (as shown below) among adults SLE subjects who are exposed or unexposed to BENLYSTA: i. All hospitalizations ii. SLE-related hospitalization
Tertiary/Exploratory	**Tertiary/Exploratory**
NA	NA

* Computation of rates will be done separately for opportunistic infections and other infections of interest (these were combined as one in the protocol)

2.3. Study Design

Overview of Study Design and Key Features	
Design Features	• Multi-centre, prospective, observational cohort study (registry). • Subjects receiving or initiating BENLYSTA and/or other immunosuppressant SLE medications (e.g. azathioprine, methotrexate, cyclophosphamide, mycophenolate, and biologics) (all medication decisions are at the discretion of the subject and their healthcare provider, and are not mandated by study design or protocol). • Subjects are followed-up approximately every 6 months for 5 years for occurrence of AESI (primary endpoint) and assessment of secondary endpoints including SDI organ damage. • Assessments are intended to be performed every 6 months based on information gathered during routine care and hospital attendance as there are no protocol mandated study visits*
Time & Events	Appendix 1: Schedule of Activities provides details of study activity timelines and data collection.
Exposure Assignment	• No formal or protocol defined treatment assignment. • Subjects are enrolled into 1 of 2 exposure groups; those who, at baseline, are receiving or initiating BENLYSTA (BENLYSTA or Exposed group) or are not receiving BENLYSTA (Non-BENLYSTA or Unexposed group).
Interim Analyses	• Annual interim analyses were planned throughout the study life cycle until the end of study in 2025.The interims were done for monitoring the safety of BENLYSTA and for reporting study progress to the external Scientific Advisory Committee, Benlysta Safety Review Team and Regulators.
Final Analysis	• Final analysis is planned for 2025 such that the enrollment and 5-year follow-up of every subject will have been completed.

* Study setup to collect data during routine visits at approximately 6-month intervals ± 2months; this data collection interval is intended to align with routine standard of care visits for SLE subjects.

2.4. Statistical Hypotheses / Statistical Analyses

The purpose of the study is to evaluate the incidence of AESI over 5 years in adults with SLE being treated with and without BENLYSTA in a real-world setting. No formal statistical hypotheses testing will be conducted since there is no pre-specified hypothesis for any of the study endpoints.

Unless otherwise specified, the following measures will be used:

- Categorical variables will be summarized as the number of subjects and percentages (%) of subjects in each category. Percentages will not include the missing category and will be calculated over the number of subjects with available (non-missing) data.
- Continuous variables will be summarized using the mean, standard deviation (SD), median, first and third quartiles (Q1, Q3), minimum (min), maximum (max).
- Computed percentages will be presented with one decimal place. Percentages equal to 100 will be presented as 100% and no percentage will be presented for zero frequencies. In case of presenting CIs for categorical/qualitative data, exact methods for deriving these intervals will be used in case of descriptive statistics.
- The 95% CI will be computed for rates to contextualize the extent of random error but will not be used for formal statistical hypothesis testing.

3. PLANNED ANALYSES

3.1. Interim Analyses

Annual interim analyses were conducted throughout the study life cycle at a prospectively pre-determined data cut-off date until end of study reporting in 2025 for the monitoring and reporting of study progress to either the external Scientific Advisory Committee, Benlysta Safety Review Team and/or regulators.

3.2. Final Analyses

The final planned analyses will be performed after the completion of the following procedure:

1. All subjects have completed their 5-year follow-up (or early withdrawal assessment for subjects withdrawing prior to completion of the 5-year follow-up), i.e. the last subject last visit milestone.
2. All required database cleaning activities have been completed and final database lock (DBL) has been declared by Data Management.

Further details of the sequential steps above, along with the relevant timelines can be found in the Clinical Study Activity Plan (CSAP).

This RAP describes the planned statistical analyses to be conducted for the final reporting. The AE review/categorization process is detailed in Appendix 3 (Section 9.3). The descriptive summary of baseline characteristics will be produced by exposure group (i.e. Benlysta or Exposed vs Non-Benlysta or Unexposed) using the ‘Eligible’ analysis population (see Section 4). A separate descriptive summary may be produced for the two study cohorts (‘Current Users’ and ‘Treatment Initiators’, see Section 5.6.2).

Safety and effectiveness endpoints will be analysed using the ‘Evaluable’ population. Results will be summarized by subjects’ exposure group (i.e. Benlysta or Exposed vs Non-Benlysta or Unexposed) defined using the ‘Initial Exposure’, ‘Ever-Exposed’, and/or ‘As-Exposed (Time Varying)’ strategies (Section 9.2). In addition, separate summary display tables may be produced for the two study cohorts). The list of the planned data displays for each analysis population is provided in Appendix 11 (Section 9.11).

Description of the statistical methods to be used to minimize selection bias and confounding bias of safety analysis is also presented.

4. ANALYSIS POPULATIONS

4.1. Study analysis population

Population	Definition / Criteria	Analyses Evaluated
Enrolled	• All subjects who were enrolled irrespective of whether they meet the inclusion/exclusion criteria	• Study Progress
Eligible	• Subjects in the 'Enrolled' population who met the inclusion/exclusion criteria [1]	• Study Population • Other Covariates
Evaluable [3]	• Subset of the 'Eligible' population with a collection of enrollment data and at least 1 post-baseline assessment	• Safety • Effectiveness
Sensitivity Analysis		
Sensitivity	• Subjects in the 'Enrolled' population who are on combination of medications that include both anti-malarials and corticosteroids, or who are in the 'Eligible' population [2]	• Study Population
Evaluable Sensitivity [3]	• Subset of the 'Sensitivity' population with a collection of enrollment data and at least 1 post-baseline assessment	• Safety

Refer to Appendix 11: List of Tables, Listings and Figures (TLF) Data Displays for details of the population used for each analysis endpoint.

[*1] Based on medications reported in the SLE medications page and/or baseline corticosteroids page of the eCRF. In the SDTM data, eligible subjects who are taking Benlysta at enrollment (refer to section 9.5.2 for more details) will be assigned study exposure group = BENLYSTA. Subjects on immunosuppressants other than Benlysta at enrollment will be assigned exposure group = NON-BENLYSTA. Subjects who are only on anti-malarials or steroids at enrollment will not be included in any analyses. Moreover subjects who are on combination of medications at enrollment that include both anti-malarials and corticosteroids, but not immunosuppressants, will not be included in the 'Eligible' population.*

***Note for programming**: some medications recorded as "Other" in CRF are immunosuppresants and should be considered when confirming eligibility. The manual review and selection of immunosuppressants reported as free text in "Other" field is under the responsibility of the GSK clinical team. At each data cut, review of new medications will manually be done and reported in an external Excel file.*

[*2] Compared to the 'Eligible' population, the 'Sensitivity' population will also include subjects on combination of medications that include both anti-malarials and corticosteroids, without immunosuppressant at enrollment. These subjects will be assigned exposure group = NON-BENLYSTA and used only for a sensitivity analysis.*

*[3]. **Note for programming:** subjects are considered 'Evaluable' if i) study day > 91 and visit is not end of study or ii) if previous point is not satisfied, last date of Adverse Events, Hospitalization and Concomitant Medications datasets is "day > 1" and Exposure dataset "day > 4". If previous point is not satisfied, the last contact date (as defined in Section 9.5.3) > 91 will be considered.*

4.2. Protocol Deviations

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Management Plan (PDMP) [22 April 2024 Version 5.0]. If the PDMP is updated, the most current version of the PDMP will be used.

Data will be reviewed on an ongoing basis and prior to locking the database to ensure all important deviations are captured and categorized in the protocol deviations dataset. This dataset will be the basis for the table and listing of protocol deviations.

A summary of subjects who did not meet inclusion/exclusion criteria will also be provided.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Exposure & Sub-group Display Descriptors

Exposure Group Descriptions			
Study Exposure Group		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	BENLYSTA	BENLYSTA	2
B	NON-BENLYSTA	NON-BENLYSTA	1

Exposure group comparisons will be displayed using the following specified descriptors:

- BENLYSTA vs NON-BENLYSTA

BENLYSTA group is used for subjects who are exposed to Benlysta while NON-BENLYSTA group is used for subjects who are not exposed to Benlysta. For summary description of baseline characteristics, the exposure group represents subjects' exposure at enrollment (i.e 'Initial Exposure'). For summary of safety and effectiveness endpoints, the exposure group will be defined using the 'Initial Exposure', 'As-Exposed', and/or 'Ever- Exposed' strategies (see Appendix 2, Section 9.2). 'As-Exposed' is defined based on whether or not a subject is using Benlysta at specific period during the study follow-up time; thus a subject's exposure group can change over time depending on switching[1] to or off Benlysta. 'Ever-Exposed' is defined based on whether a subject was exposed to Benlysta at any point in time after enrollment, in this instance a subject's exposure can change only once over time if they were initially 'Unexposed' and then started using Benlysta; once a subject is exposed to Benlysta, they will always be considered as 'Exposed'.

The specific strategy for defining exposure group and the analysis approach for accrued data will be indicated on the TLFs titles and list of the planned data displays provided in Appendix 11 (Section 9.11).

[1] *Subjects are considered to have switched from BENLYSTA exposure group if they permanently discontinued Benlysta treatment or missed doses of Benlysta for more than 98 days and do not restart doses of Benlysta on or before day 99 after the last Benlysta medication end date. Subjects are considered to have switched from NON-BENLYSTA exposure group if they initiate or start receiving Benlysta dose anytime during the study follow-up period. Change of different study-qualifying Non-Benlysta Standard of Care (SOC) medications does not count as exposure switching.*

Primary analysis will be done on 'Initial Exposure' strategy for all endpoints while 'As--Exposed' and 'Ever-Exposed' will apply for some endpoints as exploratory analysis:

	Primary analysis		Exploratory analysis	
Endpoints	**Initial Exposure Intent-To-Treat (ITT)**	**While on Initial Exposure**	**As-Exposed Time varying***	**Ever-Exposed**
Primary endpoints (AESI)				
Serious Psychiatric events	Y	Y	Y1, Y2	
Serious infections, opportunistic infections and other infections of interest	Y	Y	Y1, Y2	
NMSC and malignancies excluding NMSC	Y	Y	Y1	Y
Mortality	Y	Y	Y1, Y2	Y
Effectiveness endpoints				
SLICC/ACR Damage index (SDI)	Y			
Concomitant SLE medications including steroids	Y			
Hospitalization	Y	Y	Y1	

** For As-Exposed strategy, 14 weeks risk window or 6-months risk window are defined depending on the endpoint (see Appendix 2, Section 9.2). Y=Yes. Y1 = applicable to the 14 weeks risk window, Y2 = applicable to the 6-months risk window.*

For some display Tables and Figures, the 'Total' for the two exposure groups combined may be presented, as shown on the TLFs mock-shell (Appendix 12). The format of Graphs/Figures will follow the graphical display standard and handling convention specified in Appendix 4Appendix 5.

The "Initial Exposure" strategy will be used to derive weights from the Propensity Scores model for the weighted analyses (see section 7.3). This exposure includes two different analysis approaches:

- 'Intent-To-Treat (ITT)' and
- 'While On Initial Exposure'.

Other subgroups will be described in more detail in Section 5.6.2.

5.2. Baseline Definition

The protocol specifies Day 0 as baseline, but the Clinical Data Interchange Standards Consortium (CDISC) standard refers to the baseline as Day 1; therefore, baseline date will be referenced as Day 1 in this document. Further information on the definition of study and SLE medication phases is presented in Section 9.5.2.

In general, the baseline value of a variable will be defined as the value of the variable measured at the enrollment visit per eCRF . The exceptions are:

i. For SLICC, and SLEDAI 2000, measurements done within ±30 days of enrollment day will be considered as baseline. If there are multiple records that meet this criteria for the same measurement, the worst-case value will be selected as the baseline value. If the values are equal, the measurement which takes place first will be selected as the baseline value.

ii. For laboratory, measurements done within ±30 days of enrollment day will be considered as baseline. If there are multiple records that meet this criteria for the same measurement, the measurement which takes place first will be selected as the baseline value.

iii. For SLE medications, a 3-day post enrollment rule is applied such that SLE medications started or initiated between study days 1-4 of enrollment (i.e. Study Day 1, 2, 3 or 4) are counted as baseline medication.

iv. All hospitalizations (SLE-related and non-SLE-related) which occurred (based on admission date) within 6 months prior to or on the enrollment visit date.

5.3. Visit/Assessment Time Window and Descriptor

Follow-up assessments are expected to be performed every six months ±2-month time window. Analysis visit will be created for mapping data assessments into correct visit time point. This variable will be used in all analyses that require a visit number, regardless of the collected visit in the eCRF. If there are multiple visits done within a expected visit time window, the visit with the worst-case value will be used. Further details are provided in Section 9.5.1.

Study Period	Analysis Visit Number (AVISITN)	Target Visit Time	Expected Visit Interval	Expected Assessment Interval (Days)[1]	Target Study Day (for events slotting)[2]	Table/Graph Descriptor (Months)
Enrollment	1	Day 1		<=91 days		
Baseline	1.5					
Follow-up	2	6 Months	4 to 8 Months	92 – 274[3]	183	6
	3	12 Months	10 to 14 Months	275 – 456	366	12
	4	18 Months	16 to 20 Months	457 – 639	548	18
	5	24 Months	22 to 26 Months	640 – 822	731	24
	6	30 Months	28 to 32 Months	823 – 1004	914	30
	7	36 Months	34 to 38 Months	1005 – 1187	1096	36
	8	42 Months	40 to 44 Months	1188 – 1369	1279	42
	9	48 Months	46 to 50 Months	1370 – 1552	1461	48
	10	54 Months	52 to 56 Months	1553 – 1735	1644	54

	11	60 Months	58 to 63 Months[4]	1736 – 1918	1827	60

[1]Expected study day interval for mapping data assessments date to visit. Lower limit = Target Study Day–91 (i.e. approximately 3 months). Upper limit = Lower limit of next interval–1, 60 months upper limit is calculated as Target Study Day+91.
[2]Target study day for slotting events (e.g. AESI and Hospitalization) to time point. Target day is calculated as 365.25/12*<xx months> rounding up to the nearest integer.
[3]Expected assessment days for 6 months visit for all clinical data except for AEs and Hospitalizations (which collection should start from Day 1 for AEs and Day 2 for hospitalizations and then slotted using the target study day), and SLE medications (which starts from Day 5).
[4]Visits and events collected after 63 months will not be summarised or analysed.

All new cases of AESIs, medications, and/or hospitalizations occurring since the last visit assessment will be collected. The analysis time point will be assigned using the target study day and will be used for all corresponding statistical analysis and data summary. The study day will be assigned based on the date of event, measurement, or assessment, if present. Else, study day will be assigned based on the date of the visit.

5.4. Subjects' Study Status

A "study completer" is defined as a subject who did not withdraw from the study, was not lost to follow-up or not deceased prior to the 5-year follow-up. Study subject's completion status will be presented and described as 'Completed' or 'Withdrawn'. 'Ongoing' status will remain for the final analysis dry-run. At that time, subjects with 'Ongoing' status will be further grouped by time since last contact date as at the data cut date. This will be categorized as: 0.5 year, 0.5 - < 1 year, 1 - < 2 years, 2 - < 3 years, < 4 years, 4+ years (see Section 9.5.3). For subjects who withdraw, the following reason for withdrawal will be reported as captured on the eCRF: adverse event including death, lost to follow-up, withdrew consent, investigator discretion and site closed/terminated. Subjects who were still ongoing as of last interim analysis will be considered lost to follow-up (LTFU) only at the final 60-month visit following completion of 5-years + 3 months since enrollment into the study. The last contact date (as defined in Section 9.5.3) will be taken as the date of LTFU.

5.5. Multicentre Studies

In this multicentre global study, enrollment will be presented by country and site. For subjects who switched study sites, the last site where study was completed will be reported. Study sites will be grouped into three regions (US/Canada vs Europe vs Other).

5.6. Examination of Covariates, Other Strata and Subgroups

5.6.1. Covariates and Other Strata

The list of potential confounding factors included in statistical analysis to minimize selection and confounding bias will be listed in Appendix 9.9.

Descriptive summary will be performed for the subject demographic characteristics and some other covariates:

i. Baseline SDI (0 vs ≥ 1)

ii. Hospitalization within 6 months prior to study enrollment (Yes vs No)

iii. SLEDAI 2000 score at baseline (<10 vs ≥ 10)

iv. Baseline Immunosuppressant use (Yes vs No; mycophenolate vs immunosuppressant other than mycophenolate)

v. Duration of prior/baseline medication (i.e. Immunosuppressants, anti-malarials or other) (<1, 1-2 or >2years)

vi. SLE diagnosis duration (<1, 1- <5, 5-<10, 10-<15, 15-<20 ≥20years)

vii. Oral corticosteroids dose (mg/day) use at baseline (Always <7.5mg/day, ≥7.5mg/day for ≤ 2 weeks or ≥7.5mg/day for > 2 weeks)

viii. Region (US/Canada vs Europe vs Other)

ix. Race (Black, White, Asian, Other)

x. Positive anti-dsDNA at baseline

xi. Low complement at baseline

For the elderly population, sub-group summary will be performed as part of the end of study reporting (to fulfil the Elderly analysis post-approval commitment). Any analysis for elderly sub-group will be restricted to subjects aged 65 yrs and older, grouped as ≥65 years and age ≥75 years if feasible.

5.6.2. Examination of Subgroups

Descriptive summaries and statistical analyses will be performed separately for the two study cohorts (Current Users and Treatment Initiators).

Study Cohort	Definition / Criteria
Current Users	• Subjects who have received or started qualifying medication(s) for ≥ 2 months (≥ 62 days) prior to enrollment (Day 1)
Treatment Initiators	• Subjects who have initiated or started qualifying medication(s) in the last 2 months (< 62 days) prior to enrollment into the study (i.e Baseline SLE medication initiation < 62 days from study Day 1)

Study cohort can be determined for 'Eligible' subjects only (see section 4)

For the purpose of study cohort assignment to either a current user or a treatment initiator, the following rules will be used to determine when a subject first received Benlysta and/or Non-Benlysta SLE medications:

- For BENLYSTA subjects: this will be the start date of earliest baseline Benlysta medication.

- For NON-BENLYSTA subjects: this will be the start date of study-qualifying non-benlysta SLE medications or the most recently added immunosuppressant if they are on multiple medications at baseline.

5.7. Multiple Comparisons and Multiplicity

No adjustments for multiple comparisons are planned. There will be no formal statistical testing, analyses including comparison of estimates will be descriptive only..

5.8. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data summaries, analyses and data handling conventions are outlined in the following appendices:

Section	Component
9.2	**Appendix 2:** Exposure Strategy, Analysis Approach and Individual's Subject-Years Calculation
9.3	**Appendix 4Appendix 3:** Review and Categorization of Adverse Events of Special Interest
9.4	**Appendix 4:** Data Display Standards & Handling Conventions
9.5	**Appendix 5:** Derived and Transformed Data
9.6	**Appendix 6:** Reporting Standards for Missing Data
9.7	**Appendix 7:** Laboratory Tests

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

Study population analyses will be based on the 'Eligible' population. These analyses will include descriptive summaries of subject's disposition, demographic and baseline characteristics, SLE concomitant medications, historical and baseline medical/disease condition, baseline SLEDAI 2000 (S2K composite score) and SLE diagnosis. All baseline characteristics summaries will be presented by exposure group (BENLYSTA or NON-BENLYSATA) for the two study cohorts ('Current Users' and 'Treatment Initiators').

Table 1 provides an overview of the planned baseline study population analyses. Details of data displays to be generated are presented in Appendix 11 (Section 9.11.1). Frequency (numbers and percentages) and summary statistics including number of observations, mean, SD, median, range (min; max) and interquartile range (Q1; Q3) will be reported as necessary.

Of note, baseline SLEDAI 2000 descriptive summaries will include:

- Summary statistics of continuous SLEDAI score
- Frequency of each SLEDAI 2000 component (see Section 9.5.5)
- Frequence of SLEDAI 2000 score category and SLEDAI 2000 score grouped (<10 vs. ≥ 10)

Table 1 Overview of Planned Study Population Analyses

Display Type	Data Displays to be Generated		
	Table	Figure	Listing
Subjects Disposition			
Subject Population Disposition	Y		
Subject Study Status & Withdrawal Reason	Y		
Inclusion/Exclusion Criteria	Y		
Enrollment	Y		
Subjects Demographic and Baseline Characteristics			
Demographic Characteristics	Y		Y
History of Tobacco Use and Alcohol Use	Y		
Pregnancy**	Y		
SLEDAI 2000	Y		
Disease Condition			
Medical History	Y		
SLE Diagnosis Duration	Y		
Laboratory Tests			
Laboratory Test Parameters*	Y		
Treatment Switching relative to Initial Cohort			
Exposure switching (BENLYSTA start/stop)	Y		Y
Reasons for switching (starting or stopping Benlysta)	Y		Y
Withdrawal and Reason for Withdrawal			
Withdrawal from study	Y		
Reason for withdrawal	Y		Y

NOTES: Y = Yes; implies display type (Table, Figure, Listing) generated. Empty cells implies 'No' display type generated. * See list of tests in Appendix 7 (Section 9.7); ** female participants only

The following statistical analyses to describe the rate and risk/probability of study withdrawal will be performed:

- Study Withdrawal rate (see details of methodology in Section 7.1.5)
- The rate of Study Withdrawal using Kaplan–Meier (KM) estimator (see details of methodology in Section 7.1.5)
- Survival Probability (the probability of not withdrawing from the study)

7. STATISTICAL ANALYSES

The data displays of the final analysis are shown in Appendix 11. Unless otherwise specified, analyses will be performed using 'Evaluable' analysis population, and presented separately for 'Current Users' and 'Treatment Initiators' study cohorts.

7.1. Safety Analyses

For all primary endpoint analyses (AESIs) comparison is by exposure group (BENLYSTA and NON-BENLYSTA) defined based on exposure assignment strategies described in Appendix 2 (Section 9.2): 'Initial Exposure', 'As-Exposed' (Time Varying), and/or 'Ever-Exposed'. The exposure strategy used for each endpoint will be indicated on the data displays list (Appendix 11) and on the actual Tables, Listings and Figures (TLFs).

An overview of planned safety analyses is presented in Table 2. Details of the data displays for the planned analyses are presented in Appendix 11: List of TLF Data Displays (Section 9.11.2).

Table 2 Overview of Planned Safety Analyses

Endpoint	Absolute						Change from Baseline			
	Stats Analysis		Summary		Individual		Summary		Individual	
	T	F	T	F	F	L	T	F	F	L
Adverse Events of Special Interest (AESI)										
Overall and specific AESIs experienced during follow-up (section 2.2)	Y		Y			Y[1]				

[1]Listing will include individual's subject study ID, adverse event's (AE's) & AE system organ classes, preferred terms and verbatim text.

NOTES:

- T = Table, L = Listing, F = Figure, Y = Yes display type generated. Empty cells implies 'No' display type generated.
- Stats Analysis = display type for statistical analysis (i.e. modelling and computation of rates) of event count data.
- Summary = display type for any summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = display of individual subject observed raw data.

7.1.1. Endpoint / Variables

The primary safety endpoint is each category of AESI (listed in Section 2.2) experienced by subjects during study follow-up period.

7.1.2. Summary Measure

The summary measures for the safety endpoints specified in Table 2 are:

AESI endpoints

- Cumulative count of all AESI combined and count of subjects (number and percentage) experiencing at least one AESI.
- Cumulative count of each specific AESI category and count of subjects (number and percentage) experiencing at least one occurrence of each specific AESI category.
- Incidence proportion (expressed as a %) for each specific AESI category.
- Incidence rate (Section 7.1.5.1) for each specific AESI category.
- Event rate (Section 7.1.5.1) for each specific AESI category (except mortality).

7.1.3. Population of Interest

The primary safety analyses will be based on the “Evaluable” analysis population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Not applicable.

7.1.5. Statistical Analyses / Methods

Unless otherwise specified, endpoints/variables displayed in Section 7.1.1 will be summarised as specified in Section 7.1.2. Details of the planned displays for each endpoint are provided in Appendix 11: List of TLF Data Displays.

The statistical analysis method for estimation of rate and 95% CI are described below.

7.1.5.1. Statistical Methodology Specification Related to AESI Endpoints

Endpoint / Variables
Incidence and event rates will be calculated for the following endpoints/variables (unless otherwise specified): • Each category of AESI experienced by subjects as listed in Section 2.2
Endpoint Specification
1. Incidence rate will be calculated for each exposure group as follows: $$Incidence\ \ Rate = \frac{\sum at\ risk\ subjects\ with\ at\ least\ one\ event}{\sum subject\ years\ at\ risk}\ X\ 100$$ - Incidence rate is defined as the number of 'at-risk' subjects experiencing first event (i.e. number of new cases) during the specified follow-up period divided by total subject-years at-risk of that event for all subjects at risk. - Although the categorization of study follow-up time to Benlysta (Exposed) or Non-Benlysta (Unexposed) depends on the exposure assignment strategy (see Appendix 2, Section.9.2.1 for further discussion), the follow-up time included in the subject-years at-risk calculation, for each month xx time period, starts from enrollment date and ends at the earliest of the following: o First event date o Last contact date (as defined in Section 9.5.3) o Month xx target date (Section 5.3) o Censored date (for While on Initial Exposure strategy; see Section 9.2.1.1) o Data cut-off date Additionally, for some exposure strategies (e.g. 'As-Exposed' strategy; see Appendix 2, Section 9.2.1.2), time to treatment switch and risk windows are also considered when categorizing follow-up time into 'Exposed' and 'Unexposed' period. - Calculation of an individual's subject-years at-risk for each exposure strategy is shown in Section 9.2. - Subject-years at-risk will be calculated for each event type separately. - Only the first experience of the event (i.e. new cases) or first primary diagnosis (in the case of a malignant event) which occurred during the 'at-risk' period are counted (see Section 9.2.1 for time period considered for each exposure strategy). - For summary of each specific AESI category, subjects experiencing events in multiple AESI categories will be counted in more than 1 AESI category. 2. Event rate will be computed for each exposure group as follows: $$Event\ rate = \frac{\sum all\ AESI\ events}{\sum subject\ years\ of\ follow\text{–}up} X\ 100$$ - Event rate is estimated for potentially recurrent events and represents the average number of events per unit time of follow-up. It is defined as the total number of events experienced by all subjects during the specified study period divided by subject-years of follow-up. The categorization of study follow-up time depends on the exposure strategy (see Appendix 2, Section 9.2.1). The subject-years of follow-up for each month xx time period takes the same definition above for the subject-years at-risk, however, follow-up does not stop at the time of first event. - Additionally, for some exposure strategies (e.g. 'As-Exposed' strategy), time to treatment switch and risk windows are also considered when categorizing follow-up time into exposed and unexposed period (Section 9.2.1.2) - All events experienced during the follow-up period including recurrent events are counted (see Section 9.2.1 for time period considered for each exposure strategy).

- Calculation of an individual's subject-years of follow-up for each exposure strategy is shown in Appendix 2 (Section 9.2). Incidence and event rates will be calculated and reported per 100 subject-years. The 95% CI for the rate will be calculated assuming an exact Poisson distribution method [Stokes, 2012].
Model Checking & Diagnostics
• No model-based statistical analysis will be performed; hence there is no model checking and diagnostics to be conducted.
Results Presentation
Total number of events, number and % of subjects with events, total subject-years at-risk, and total subject-years of follow-up will be reported. In addition, incidence proportion (where applicable), incidence rate, event rate and their 95% CI will be presented. The mock-shell tables showing details of data displays are presented in Appendix 12.
Subgroup Analyses
This analysis may be conducted for each study cohort separately (Current Users and Treatment Initiators; Section 5.6.2) . The list of TLF Data Displays is presented in Appendix 11.
Sensitivity Analyses
This analysis will also be conducted using the 'Evaluable Sensitivity' population. Details of the planned displays are provided in Appendix 11: List of TLF Data Displays.

7.1.5.2. Statistical Methodology Specification related to study withdrawal event

Endpoint / Variables
• Study Withdrawal event
Endpoint Specification
1. The percentage of subjects withdrawing from the study at the time of the final analysis data cut will be calculated for each exposure group, using the Kaplan-Meier product-limit estimator for the survival probability (the probability of not withdrawing from the study), as follows: $$\hat{S}(t) = \prod_{t_i \le t} (1 - \frac{d_i}{n_i})$$ - t_i is the specific time of interest when at least one event occurred - d_i is the number of dropout events at time t_i. - n_i is the number of subjects at-risk up to time t_i. 2. Withdrawal rates at time *t* will be computed at time *t*, denoted as $\hat{F}(t)$: $$\hat{F}(t) = 1 - \hat{S}(t)$$ The probabilites of survival and study withdrawal will be expressed in percentage (%), along with 95% CI, for the following time points: 12, 24, 36, 48, 60 months. Additionally the cumulative number of withdrawals will be presented, along with percentage (calculated as cumulative number of withdrawals/N). For the following time periods: 0-12, 12-24, 24-36, 36-48, 48-60 months, the number at-risk at the start of each time period, along with number of withdrawals during each time period will be presented. Percentage is calculated as <number of withdrawals during time point> / <the number at risk at the start of time period>
Model Checking & Diagnostics
• No model-based statistical analysis will be performed; hence there is no model checking and diagnostics to be conducted.
Results Presentation
The mock-shell tables showing details of data displays are presented in Appendix 12.
Subgroup Analyses
This analysis may be conducted overall and for each study cohort separately (Current Users and Treatment Initiators; Section 5.6.2) and by relevant clinical covariate listed in Section 5.6.1. The list of TLF Data Displays is presented in Appendix 11.
Sensitivity Analyses
N/A

7.2. Effectiveness Analyses

Overview of planned selected effectiveness measures is shown in Table 3. The analyses will be conducted using 'Evaluable' analysis population and by study exposure defined using the 'Initial Exposure' strategy (see section 9.2.1.1) and/or by strata of clinical covariates listed in Section 5.6.1. Appendix 11: List of TLF Data Displays provides details of the analyses to be conducted.

Table 3 Overview of Planned Effectiveness Analyses

Mock shell Endpoint	Absolute							Change from Baseline						
	Stats Analysis			Summary		Individual		Stats Analysis			Summary		Individual	
	T	F	L	T	F	F	L	T	F	L	T	F	F	L
Clinical														
SLICC/ACR Damage Index (SDI)				Y							Y			
Hospitalizations experienced	Y			Y										
Average Corticosteroid dose (mg/day)				Y							Y			
Concomitant SLE medications and corticosteroid use				Y			Y							

NOTES:

- T = Table, F = Figure, L = Listing, Y = Yes display type generated. Empty cell implies 'No' display type generated.
- Stats Analysis = display type for statistical analysis (i.e. modelling and computation of rates) of event count data.
- Summary = display type for summaries (i.e. descriptive statistics) of the observed raw data.
- Individual = display of individual subject observed raw data.

7.2.1. Endpoints

The effectiveness (other) endpoints assessed include:

- Organ damage as assessed by SLICC/ACR Damage Index (SDI)
    - Absolute and change from baseline for SDI composite score
    - Count of subjects with each SDI domain component
    - Count of subjects with no change in SDI, and SDI worsening (i.e. change from baseline ≥0) as SDI score change 0, 1, 2 and >=3
    - Count of subjects in each permutation of baseline score and subsequent follow-up scores , to quantify how the scores change from baseline (0 to 0, 0 to 1, 0 to 2, etc) over the follow-up period
- Concomitant SLE medication and corticosteroid use

- Use of concomitant SLE medication (Yes or No)
- Use of concomitant immunosuppressants (Yes or No)
- Use of concomitant corticosteroids (Yes or No)
- If concomitant corticosteroid use is 'Yes':
  - Concomitant corticosteroid dose (mg/day) (Always <7.5mg/day, ≥7.5mg/day for ≤ 2 weeks or ≥7.5mg/day for > 2 weeks)
  - Absolute and change from baseline of average corticosteroids dose (mg/day)

- Hospitalization events
  - Count of events and subjects hospitalized for All-cause
  - Count of events and subjects hospitalized for SLE-related reasons

7.2.2. Summary Measure

The following measures will be used to summarize endpoints listed on Table 3 and in Section 7.2.1 above.

- Continuous endpoints such as absolute and change from baseline SDI score, absolute and change from baseline average corticosteroids dose (mg/day)
  - Summary statistics including number of observations, mean, SD, median, range (min; max) and interquartile range (Q1; Q3)
- Categorical binary, nominal and/or ordinal endpoints such as SLE medication use (immunosuppressants vs. others), use of corticosteroids (Yes or No), oral corticosteroids dose (mg/day) use (Always <7.5mg/day, ≥7.5mg/day for ≤ 2 weeks or ≥7.5mg/day for > 2 weeks), presence or absence of each SDI domain item, and SDI worsening (change from baseline ≥1)
  - Proportion or frequency (number and percentage) of subjects
- Count of events such as hospitalizations
  - Incidence and events rates with 95% CI (see Section 7.2.4 below for detailed methodology)

7.2.3. Population of Interest

The effectiveness analyses will be based on the "Evaluable" analysis population.

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7.2.4. Statistical Analyses / Methods

Endpoints listed in Section 7.2.1 will be summarised and presented as specified in Section 7.2.2. Details of the planned displays are provided in Appendix 11: List of TLF Data Displays.

Incidence and event rates of hospitalizations will be computed with 95% CI following the same approach described in Section 7.1.5.

7.3. Propensity Score Analysis

This section describes statistical methods to be used to control for confounding bias of the BEL116543 study final analysis.

Of note, statistical methods presented in this section will apply to primary objectives only.

7.3.1. Statistical Considerations

Analysis will be conducted on the evaluable population defined in section 4 as: Subset of the 'Eligible' population with a collection of enrollment data and at least 1 post baseline assessment.

First step of analysis: Inverse probability of treatment weighting (IPTW)

Propensity scores will be computed as the probability of being exposed to Benlysta at enrollment given an individual's baseline characteristics. Logistic regression will be used to derive the PS. Non-stabilized weights (i.e. IPTW) for each individual will be calculated as the inverse of the probability of receiving the actual exposure: 1/PS for the Benlysta arm and 1/(1-PS) for the Non-Benlysta arm.

Inverse probability of treatment weighting (IPTW) (Rosenbaum, 1983) will be used to adjust for differences in covariates balance between exposure groups, Benlysta versus Non-Benlysta. To reduce likelihood of extreme weights being assigned in the analysis, stabilized weights will be computed by multiplying the non-stabilized weight of each individual by the proportion of subjects who were exposed to Benlysta at enrollment : p/PS for the Benlysta arm and (1-p)/(1-PS) for the Non-Benlysta arm., (Chesnaye, 2021). For the remainder of the document, references to "weight" refer to stabilized weights.

These weights will create a *pseudopopulation* whereby confounding factors are balanced among Benlysta and non-Benlysta arms. The weights' distributions will be checked to identify extreme weights which might impact results (see section 7.3.1.3). If the balance assessment reveals that adequate balance cannot be achieved between the Benlysta and non-Benlysta arms (section 7.3.1.2.2), no further analysis using propensity scores will be conducted.

Second step of analysis: Outcome analysis

The primary outcome model will be a weighted Poisson regression based on stabilized weights. Weighted incidence rates and event rates will be calculated and presented. Further details presented in section 7.3.1.5.

7.3.1.1. General Assumptions for Causal Inference

Observational research relies on causal inference methods when deriving unbiased estimates. Hernán & Robins (2019) list 3 conditions to be met, for the valid use of methods like IPTW: conditional exchangeability, positivity and consistency. Additionally, the no interference assumption between subjects should be met. These conditions make

underlying assumptions about the data to be analyzed and violations of the underlying assumptions can bias the estimates, leading to inaccurate conclusions.

7.3.1.1.1. Conditional Exchangeability

The conditional exchangeability assumption allows an observational study to be conceptualized as a conditionally randomized trial, where the probability to receive the treatment depends on the covariates, but not on unmeasured variables. Essentially, this assumption leads to the postulation of no unmeasured confounding, and potential outcomes can be treated as Missing at Random (MAR). In practice, verifying the validity of the conditional exchangeability assumption is not possible. While we assume conditional exchangeability within specific groups (such as treatment arms or covariate levels), it's important to recognize that unmeasured factors may still exist. Therefore, we proceed with caution, acknowledging that perfect validation of this assumption is unattainable.

7.3.1.1.2. Positivity

The positivity assumption specifies that every subject has a probability > 0 to receive either treatment, otherwise no causal inference would be possible. The assumption of positivity will be checked by examining the overlap of the propensity score distribution for both treatment groups graphically. The SAS option WCLOUD will be used within the CAUSALTRT procedure to display weights, and if weights > 10 are observed, the potential for non-positivity will be investigated (see section 7.3.1.4).

7.3.1.1.3. Consistency

The assumption of treatment consistency specifies that there is no ambiguity defining a treatment (Hernán and Robins, 2020). This assumption is also known by the term "treatment variation irrelevance".

7.3.1.1.4. Interference

The assumption of no interference specifies that a potential outcome for any subject does not vary with the treatment assigned to other subjects, i.e., a subject's outcome is not affected by other subjects' exposure to the treatment. In the current study interference is not expected due to the characteristics of the studied disease.

7.3.1.2. IPTW Estimation

7.3.1.2.1. Propensity Score Variables Selection

A PS model will be defined for IPTW estimation.

The pre-specified variables collected at baseline, considered by medical experts to be potentially important covariates, with respect to both treatment assignment and likelihood of experiencing outcome, are presented in Section 9.9 (Table 4).

Firstly, multicollinearity assumption will be assessed by verifying that there are no two or more variables which are highly collinear. Variance Inflation Factor (VIF) will be

computed by specifying the 'vif' option in a PROC REG in SAS (see section 9.10). A VIF higher than 10 indicates co-linearity regarding the concerned covariates. The decision of which covariate(s) to drop, if applicable, will be made based on clinical importance.

Secondly, selected variables will be used as covariates in the SAS CAUSALTRT procedure to fit a logistic regression model and compute propensity scores. The response variable will be the probability of receiving Benlysta at enrollment.

In case the model does not converge, multi-level covariates with sparse counts will be collapsed. If any issues remain thereafter, covariates which generate non-convergence will be removed from the model. In either such case, a corresponding footnote will be added to the corresponding statistical tables.

The propensity score model will be finalized prior to proceeding to estimation of weighted incidence and event rates. An evaluation of all variables used in the PS will be made to allow adjustment prior to the final analysis, considering:

- overlap of the predicted probability of exposure initiation through inspection of graphical and distributional summaries (see section 7.3.1.1.2);
- balancing exposure cohorts through IPTW (Robins et al 2000; see section 7.3.1.2.2);

In addition, the odds ratios of the covariates in the PS model will be reported along with 95% CI and p-value using PROC LOGISTIC to identify PS covariates more associated with the treatment assignment and potentially influencing the weight.

7.3.1.2.2. Balance Assessment of the Propensity Score Model

As described in Rosenbaum and Rubin (1983), the propensity score is also a balancing score. To assess the balance that is produced by a propensity score model, standardized mean differences (SMDs), variance ratios and weighted density plots for the continuous covariates will be displayed using the 'CovDiffPS' and 'PSCovDen' options in the SAS PROC CAUSALTRT statement in SAS.

The resultant table and plots will be provided as supplementary outputs, presenting SMDs and variance ratios before and after weighting (per SAS ODS table name 'PSCovDiff') in order to assess covariate balance after weighting.

An improvement in the covariate balance after weighting would be indicated by the following two observations when the unweighted and weighted columns in the table are compared:

- Smaller SMDs in the weighted column than in the unweighted column
- Variance ratios between 0.5 to 2 in the weighted column

Although there is no universally agreed criterion as to what threshold of the standardized difference can be used to indicate important imbalance, it is commonly agreed that a standardized mean difference of less than 0.1 indicates a negligible difference in the mean

or prevalence of a covariate between treatment groups (Austin, 2011). Of note, variance ratio will be assessed but the main criterion of balance will be based on SMDs.

7.3.1.3. Handling of Extreme Weights

Following satisfaction of positivity assumptions as per section 7.3.1.1.2, if there is evidence of extreme weights (> 10) that cannot be resolved by adjusting the PS model then subjects in the tails of the propensity score distributions will have their propensity score truncated at the 99th percentile value (i.e.: large weight will be replaced with the 99th percentile).

7.3.1.4. Missing Data on Covariates

Considering the background of the study, missingness is known for the baseline confounders. Among variables listed in Table 4, Body Mass index (BMI), Race, Ethnicity, SDI and SLEDAI 2000 score are reported with missing values. The rules below will apply:

- The missing data for individual variables will be coded into a "missing" category for categorical variables to allow all subjects to be used in the analysis; for continuous measures, missing data will be set to a fixed value (i.e. median) and an indicator variable will be added in the model.

- However, in the case of very few missing cases (<10):
  - The modal category will be assumed for categorical variables.
  - The indicator variable will be omitted from the model for continuous variables

- Specific case of baseline SLEDAI 2000 (S2K composite score):
  The Assessments of SLEDAI 2000 score consist of 24 individual items (see section 9.5.5) in which signs and symptoms, laboratory tests, and physician's assessment for each of 9 organ systems are given a weighted score and summed if present (marked 'Yes').
  - A "Clinical SLEDAI 2000 score" (CS2K) will be computed considering all items except "Low Complement" and "Increased DNA Binding". The CS2K is computed based on the remaining 22 items, with either "absent" or "not done" being regarded as 0.

  - A corresponding variable "total not-done points" calculating the sum of not done weights is also included in the model. "Total not done points" = 0 for subjects who were assessed for all items. "Total not done points" = 18 for subjects with maximum (6) not done items. The variable's inclusion is to allow the model to differentiate between subjects who have scored x points/101 available compared to subjects who have score x points/83 available, or anywhere in between.

- If the SLEDAI 2000 form is completely missing, then median CS2K (based on subjects who answered >0 questions) and median "total not done points" will be assumed, and an indicator variable will be added in the model.

7.3.1.5. Incidence and event rate analysis

Weighted incidence rate per 100 person-years and weighted event rate per 100 person years will be presented for 'ITT' and 'While-On-Initial Exposure' treatment strategies. The 95% CI for the rates will be calculated assuming an exact Poisson distribution method.

Incidence rates will be calculated as total weighted incidence divided by total weighted subject years at risk with corresponding weighted exact Poisson CI:

$$Lower = \frac{(quantile('CHISQ', 0.025, 2 * \sum weight * \ subject\ with\ at\ least\ \ one\ event)/2)}{\sum weight * \ subject\ years\ at\ risk}$$

$$Upper = \frac{(quantile('CHISQ', 0.975, 2 * (\sum weight * \ subject\ with\ at\ least\ \ one\ event + 1))/2)}{\sum weight * \ subject\ years\ at\ risk}$$

Event rates will be calculated as total weighted number of events divided by total weighted follow up time. with corresponding weighted exact Poisson CI:

$$Lower = \frac{(quantile('CHISQ', 0.025, 2 * \ \sum weight * \ events)\ /2)}{\sum weight * \ subject\ years\ of\ follow\text{–}up}$$

$$Upper = \frac{(quantile('CHISQ', 0.975, 2 * (\sum events\ + 1))/2)}{\sum weight * \ subject\ years\ of\ follow\text{–}up}$$

7.3.2. Baseline Characteristics

Baseline characteristics (i.e. variables included in the PS-model) will be presented for the evaluable population and appropriate statistical tests will be used for group comparison. P-values, for descriptive purpose only, will be presented.

- For categorical variables:
  - Fisher's exact test will be used for 2*2 frequency tables (FISHER option in TABLES statement of PROC FREQ)
  - Otherwise, Chi-Square test will be used (CHISQ option in TABLES statement of PROC FREQ)
- For continuous variables, t-test will be used (PROC TTEST), normality assumed considering sample.
- Standardized mean differences (SMDs), variance ratios and weighted density plots for the continuous covariates will be displayed before and after weighting as described in section 7.3.1.2.2.

7.3.3. Safety Endpoints with confounding adjustment

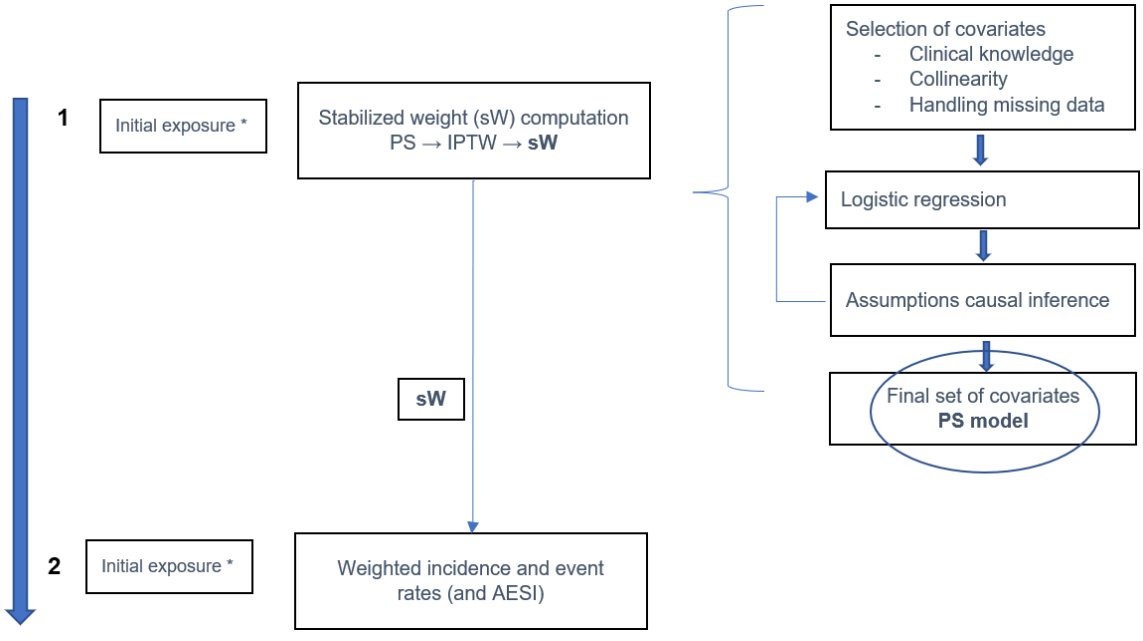
The primary endpoint analysis with confounding adjustment, (weighted incidence rates) will be conducted using ITT and While On Initial Exposure strategies only for the below safety endpoints:

- Malignancies (excluding non-melanoma skin cancers)
- Mortality
- Opportunistic infections (serious and non-serious)
- Other infections of interest (serious and non-serious)
- Non-melanoma skin cancers (NMSC)
- Serious psychiatric events
- Serious infections

For all endpoints, details about outcome-specific baseline covariates, distributions are displayed in the below table:

Analysis	Endpoints	Dependent variable	Distribution	Baseline covariates
Primary	- Weighted Incidence rate	Number of first event	Poisson	Not adjusted
Primary	- Weighted Event rate	Number of all events	Poisson	Not adjusted

7.3.4. Summary



** Initial exposure: ITT strategy and while on initial treatment.*

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9. APPENDICES

9.1. Appendix 1: Schedule of Activities

9.1.1. Protocol Defined Schedule of Events

	Time Points										
Data Collection[7]	Enrollment[1] (Day 1)	6 months (±2months)	12 months (± 2 months)	18 months (± 2 months)	24 months (±2 months)	30 months (±2 months)	36 months (±2 months)	42 months (±2 months)	48 months (± 2 months)	54 months (± 2 months)	60 months (-2/+3 months)[6]
Informed Consent	X										
Demographics	X										
Medical History (including SLE History)/General Medical Status	X				X[3]				X[3]		
Potential Confounders for Malignancies and/or Infections List	X										
Historical SLE Medications	X										
SLEDAI 2000[2]	X										
Verify Eligibility Criteria	X										
SLICC/ACR Damage Index	X	X	X	X	X	X	X	X	X	X	X
Record of Current SLE Medications (including corticosteroids)[4]	X	X	X	X	X	X	X	X	X	X	X
Record of Hospitalizations	X	X	X	X	X	X	X	X	X	X	X
Record of AEs of Special Interest[5]		X	X	X	X	X	X	X	X	X	X

1. Data collection for enrollment may occur over more than one day.
2. Laboratory values should not be attributed on the SLEDAI 2000 unless laboratory values were obtained within 30 days of the assessment.
3. Only General Medical Status (current status of medical condition and/or medical procedure/surgery since last reported) is collected at 24 and 48 months.
4. SLE Medications include immunosuppressants, biologics, antimalarials, corticosteroids, and investigational agents for SLE. If a subject currently using BENLYSTA changes formulation, the original BENLYSTA record must be updated with a stop date and a new BENLYSTA record needs to be created with a start date for the new formulation. The new BENLYSTA record should also include formulation (IV or SC).
5. AEs of special interest for this study include mortality, serious infections, opportunistic infections and other infections of interest, selected serious psychiatric events, and malignancies (including NMSC). In order to collect additional important information on potential suicidality-related events, should any of the events marked with an asterisk in Appendix 2 of the protocol occur, the investigator will be requested to complete the PSRHQ eCRF (only the first time a serious suicidality-related event is reported) and a PSRQ eCRF (each time a serious suicidality-related event is reported). The PSRHQ and PSRQ are provided in Appendix 3 and Appendix 4 of the protocol, respectively.
6. For the last time point (60 months), data collection is extended by an additional 1 month and therefore can occur up to 63 months after enrollment (Day 1). This is to provide sites with additional time to contact subjects before declaring them as lost-to-follow-up.

7. The data collection time intervals of 6 months ±2 months are intended to align with routine standard of care visits for SLE subjects. With the exception of the last time point at 60 months (for which data collection can only be extended up to 63 months), data collection occurring outside the time window (±2 months) should be assigned to the closest time point.

9.2. Appendix 2: Exposure Strategy, Analysis Approach and Individual's Subject-Years Calculation

9.2.1. Exposure Strategy

For the purpose of statistical analysis, subjects' exposure arm (BENLYSTA vs NON-BENLYSTA) will be assigned using the following exposure strategies: 'Initial Exposure', 'As-Exposed (Time Varying)' with Benlysta risk windows of 14 weeks (98 days) and 6 months, and 'Ever-Exposed'. Hypothetical scenarios for each strategy are represented in Section 9.2.2.

Programming Hints for assignment of fatalities applicable to all exposure strategy (see also Section 9.3.2**):**

- For mortality events: the fatal SAE onset date should be used as the 'Event Date' when slotting the death to the relevant analysis time period, and as a result corresponding exposure group. In the case of multiple fatal SAEs, the latest onset date should be used.
- For individual's subject-years at-risk computation, the date of death should be used as the 'Event Date'.

9.2.1.1. Initial Exposure

This is defined as subjects' exposure arm assignment (Benlysta or Non-Benlysta) at the time of enrollment (Baseline). Due to potential for one or more treatment switching during the follow-up, two different analysis approaches will be used for 'Initial Exposure' strategy; namely, 'ITT' and 'While On Initial Exposure'.

1. ITT approach will use all accrued data during the whole follow-up period irrespective of treatment switching. Subjects entering the study on Benlysta medication will be considered 'Exposed' and those on Non-Benlysta SLE medications are considered 'Unexposed' throughout the study period.

A limitation of the ITT is potential bias from mismatch of events to exposure arm since events occurring after exposure switching are attributed to that Initial Exposure. This will attribute events to Benlysta exposure when subjects are no longer exposed and vice-versa (i.e. Non-Benlysta initial cohort switched to Benlysta). See Section 9.2.1.2 for details of 'As-Exposed' (Time Varying) approach to address this limitation

Programming Hints for derivation of essential variables needed for computation of incidence and event rates (presented in Section 7.1.5.1**) under the ITT approach:**

- Compute individual's subject-years at-risk as:

  [(minimum (Event Date, Last Contact Date*) – Study Enrollment Date) +1]/365.25

- Compute individual's subject-years of follow-up as:

  [(Last Contact Date* – Study Enrollment Date) +1]/365.25

- Consider events experienced during the whole study period:

  Study Enrollment Date ≤ Event Date ≤ Last Contact Date*

  - For incidence rate calculation only count new cases (i.e. first onset) of the event experienced during the period
  - For events rate calculation count all the events experienced during the period

  NOTE:

  i. Individual's subject-years at-risk will be calculated for each event type separately and if required for each time period (i.e. for analysis by time period)

  ii. Individual subject-years of follow-up may be required for each time period (i.e. for analysis by time period)

  * Last Contact Date as defined in section 9.5.3

2. While On Initial Exposure analysis approach will be used to analyze all data accrued up to the first treatment switch. Any events and follow-up time accrued after the first exposure switching (switching from Initial Exposure) will be censored (i.e. excluded from analysis) at first exposure switch date (see Section 5.14 for the definition of exposure/medication switching).

A limitation of this analysis approach is potential bias introduced by underreporting of events experienced during the study since data from only a subset of the study period and events collected before the first treatment switch are included in the analysis. The results only present risk of exposure prior to first treatment switch. See Section 9.2.1.2 for details of 'As-Exposed' (Time Varying) approach to address this.

Programming Hints for derivation of essential variables needed for computation of incidence and events rates (presented in Section 7.1.5.1**) under the While On Initial Exposure approach:**

- Compute First Switch Date as:

  Baseline Benlysta Medication End Date + 98 days (for switching from Benlysta to Non-Benlysta) or

  First Post-Baseline Benlysta Start Date – 1) (for switching from Non-Benlysta to Benlysta)

- Compute individual's subject-years at-risk as:

  [(minimum (Event Date, First Switch Date, Last Contact Date*) – Study Enrollment Date) +1]/365.25

- Compute individual's subject-years of follow-up as:

  [(minimum (First Switch Date, Last Contact Date*) – Study Enrollment Date) +1]/365.25

- Consider events experienced up to First Switch Date (if switching from Initial Exposure) or whole study period (if no switch):

  Study Enrollment Date ≤ Event Date ≤ minimum(First Switch date-1, Last Contact Date*)

  - For incidence rate calculation only count new cases (i.e. first onset) of the event experienced during the period
  - For events rate calculation count all the events experienced during the period

  NOTE:

  i. Individual's subject-years at-risk will be calculated for each event type separately and if required for each time period (i.e. for analysis by time period)

  ii. Individual subject-years of follow-up may be required for each time period (i.e. for analysis by time period)

  * Last Contact Date as defined in section 9.5.3

An illustration of follow-up to be counted in each exposure group defined by the two 'Initial Exposure' analysis approaches is shown in Section 9.2.2.

9.2.1.2. As-Exposed (Time Varying)

This exposure strategy specifically accounts for treatment switching to or from BENLYSTA throughout the study. It dynamically assigns subjects' exposure group based on Benlysta/non-Benlysta use at time of event, during study follow-up. Therefore, a subject's exposure group can change over time (time varying) depending on the SLE medication in use at specific time during study follow-up. For Benlysta, exposure does not end on the date when Benlysta stops. Instead, two different risk windows will be used to determine when Benlysta exposure ends:

- 14 weeks: Benlysta exposure ends 14 weeks (98 days) after Benlysta treatment stops.
- 6 months: Benlysta exposure ends 6 months (183 days) after Benlysta treatment stops.

- Subjects may contribute events and follow-up time (i.e. subject-years) to either one or both exposure periods depending on the medication switch pattern (see Section 9.2.2). Data summary and analysis will be done by exposure group assigned using the 'As--Exposed' strategy.

In contrast to the 'Initial Exposure' or 'While on Initial Exposure' strategies, which may only utilize subject level exposure group at Enrollment, the 'As-Exposed' strategy (time--varying) will assign and use exposure group at the time of the event.

Programming Hints for derivation of essential variables needed for computation of incidence and events rates (presented in Section 7.1.5.1**) under the 'As-Exposed' approach:**

- Each subject's follow-up time will be split into different exposure periods categorized as 'Exposed' (when the subject is on Benlysta medication) or 'Unexposed' (when the subject is off Benlysta). Each exposure period will have a distinct *'Period Start Date'* and a distinct *'Period end date'.*
    - Note that for each subject, number of exposure periods = number of switches + 1 (see Section 5.1 4 for definition of switching)
- Identify the start of each period as follows:
    - The first exposure period (i.e. period=1) starts from enrollment date (i.e. ***Period Start Date*** = Enrollment Date). First period exposure status is same as baseline exposure group assignment
    - For subsequent exposure periods, ***Period$_{n+1}$ Start Date*** is ***Period$_n$ End Date*** + 1
- Identify the end of each period as follows:
    - For all exposure periods except the last, ***Period End Date*** = ***Switch Date***

      Switch Date is

      Benlysta End Date + 98 days or 183 days when switching from Benlysta to Non-Benlysta (i.e. Exposed to Unexposed) period. *Period with this end date will be assigned 'Benlysta' or 'Exposed' group.*

      Next Benlysta Start Date – 1 when switching from Non-Benlysta to Benlysta (i.e. Unexposed to Exposed) period. *Period with this end date will be assigned 'Non-Benlysta' or 'Unexposed' cohort*
    - For last or final exposure period, ***Period End Date*** is the ***Last Contact Date****.
- Identify or map events experienced during the study to the specific exposure period satisfying:

  Follow-up Period Start Date ≤ Event Onset Date ≤ Follow-up Period End Date

  NOTE: for incidence rate calculation, first event is retained for each exposure group (i.e. Benlysta and Non-Benlysta).
- Calculate individual's subject-years of follow-up for time spent in each exposure group *j* (where *j* =1(Exposed), 2(Unexposed)) as follows:

- For overall or 60-Month+ time period, calculate '*period follow-up time*' ($pFUt$) in days for each period *i* (i =1, 2, …., n) as:

  (Period End Date – Period Start Date) +1

- For other xx-Month time periods (xx = 12, 24, 36, 48), calculate '*period follow-up time*' ($pFUt$) in days as follows:

  - Calculate cumulative follow-up duration for each exposure period i (CM_FUD[i])
  - Identifying qualifying exposure period for each xx-Month time specific computation as period where previous CM_FUD value is less than xx-Month target visit day (i.e. CM_FUD[i-1] < xx-Month target visit day for i= 1, 2,…n; where CM_FUD[0] = 0)
  - For each qualifying exposure period for xx-Month time, calculate xx-M_pFUt =

    CM_FUD[i] – CM_FUD[i-1] if CM_FUD[i] ≤ xx-Month target visit day

    xx-Month target visit day – CM_FUD[i-1] if CM_FUD[i] > xx-Month target visit day

    where CM_FUD[0] = 0

- Calculate each individual subject-year of follow-up $(syFU_j)$ as follows:

  - For each exposure group *j* (j =1(Exposed), 2(Unexposed)), sum $pFUt$ over all periods *i* with the same exposure group and divided by 365.25

    $syFU_j = \left(\sum_{i=1}^{n} pFUt_{i(j)}\right)/365.25$ (for overall or 60+Month time period)

    $xxM\_syFU_j = \left(\sum_{i=1}^{n} xxM\_pFUt_{i(j)}\right)/365.25$ (for time period specific computation)

(NOTE: For time period analysis, the above computation will be done for the following time periods: 12-month, 24-month, 36-Month, and 48-Month).

- Individual's subject-years 'at-risk' ($syAR_j$) will be calculated for each exposure group *j* (j = 1(Exposed), 2(Unexposed)) as follows:

  - Calculate *period 'at-risk' time* ($pARt_i$) for each exposure period *i* (i=1, 2,….,n) or qualifying exposure period for xx-Month time as:

    - if no event occurred in the exposure period (for overall or 60-Month+ time period calculation) or event day > xx-Month target visit day (for xx-Month time period specific calculation)

      $pARt_i$ = *period follow-up time*' ($pFUt$) or

xxM_$pARt_i$ = xxM_pFUt (for time specific calculation)

- for period where first event occurred (per exposure group) or event day <= xx-Month target visit day

  $pARt_i$ = *event day – CM_FUD[i-1]*

  xxM_$pARt_i$ = *event day – CM_FUD[i-1]* (in case of time specific calculation)

  where CM_FUD[0] = 0

- For each exposure group *j* (*j* =1(Exposed), 2(Unexposed)) separatedly compute individual subject-year at-risk $syAR_j$ thus:

  - For subjects with no events in exposure group j, sum $pARt_i$ for all periods *i(j) (i.e. periods occurring while on exposure group j)*

    $syAR_j = \left(\sum_{i=1}^{n} pARt_{i(j)}\right)/365.25$

    $xxM\_syAR_j = \left(\sum_{i=1}^{n} xxM\_pARt_{i(j)}\right)/365.25$ (for time period specific computation)

  - For subjects with at least one event in exposure group j, sum $pARt_i$ for all periods *i(j)* up to period where the first event in exposure group j occurred

    $syAR_j = \left(\sum_{i=1}^{n*} pARt_{i(j)}\right)/365.25$

    $xxM\_syFU_j = \left(\sum_{i=1}^{n*} xxM\_pFUt_{i(j)}\right)/365.25$ (for time period specific computation)

    where *n** is the period where the first event was experienced (NOTE: Time spent in subsequent exposure periods for the same exposure group after an event had occurred will not be counted)

  NOTE: Individual's subject-years at-risk will be calculated for each event category separately

* Last Contact Date as defined in Section 9.5.3

9.2.1.3. Ever-Exposed

This exposure strategy accounts for whether a subject was ever-exposed to Benlysta at any point during the follow-up period, once exposed to Benlysta they will always be considered at risk. Any events accrued and all follow-up time after first Benlysta treatment has started will be allocated to Benlysta exposure. Follow-up time before first Benlysta exposure will be allocated to the comparison cohort. Therefore, a subject's exposure group will only change once if a subject moves from a comparison treatment ('Not exposed' onto Benlysta).

A limitation of this strategy is bias from mismatch of events to exposure arm since events occurring after switching off Benlysta are attributed to Benlysta exposure when subjects are no longer exposed.

Programming Hints for derivation of essential variables needed for computation of incidence and events rates (presented in Section 7.1.5.1**) under the 'Ever-Exposed' approach:**

- Subjects on Benlysta at enrollment will only have one exposure period (period=1) and Period Start Date = Enrollment Date (as ITT strategy).
- Subjects not on Benlysta at enrollment who do not switch on to Benlysta will only have one exposure period (period=1) and Period Start Date = Enrollment Date (as ITT strategy).
- Subjects not on Benlysta at enrollment who do switch on to Benlysta will have two exposure periods:
    - For period = 1, Period Start Date = Enrollment date, Exposure = Non-Benlysta and Period End Date = Benlysta start date -1
    - For period = 2, Period Start Date = Benlysta start date, Exposure = Benlysta and Period End Date = Last contact date*.
- Identify or map events experienced during the study to a specific exposure period by checking the event onset within the period start and end interval.

  Follow-up Period Start Date ≤ Event Date ≤ Follow-up Period End Date

  NOTE: for incidence rate calculation, first event is retained for each exposure group (i.e. Benlysta and Non-Benlysta). This is only applicable for subjects with two exposure periods, i.e. subjects not on Benlysta at enrollment who do switch on to Benlysta.

- Calculate individual's subject-years of follow-up for time spent in each exposure group as follows:

a) Subjects on Benlysta at enrollment:

   Exposed subject-years = (Last contact date* - Enrollment Date+1)/365.25.

b) Subjects not on Benlysta at enrollment who do not switch on to Benlysta:

   Unexposed subject-years = (Last contact date* - Enrollment Date+1)/365.25.

c) Subjects not on Benlysta at enrollment who do switch on to Benlysta:

   Unexposed subject-years = (Benlysta start date – Enrollment date)/365.25

   Exposed subject-years = (Last contact date* - Benlysta start date +1)/365.25

- For other xx-Month time periods (xx = 12, 24, 36, 48), calculate period follow-up years as follows:

a) Subjects on Benlysta at enrollment:

Exposed period follow-up years = (xx-Month period end date - Enrollment Date+1)/365.25.

where xx-Month period end date = earliest of xx-Month target visit date and Last contact date*

b) Subjects not on Benlysta at enrollment who do not switch on to Benlysta before xx-Month target visit date:

Unexposed period follow-up years = (xx-Month period end data - Enrollment Date+1)/365.25.

where xx-Month period end data = earliest of xx-Month target visit date and Last contact date*

c) Subjects not on Benlysta at enrollment who do switch on to Benlysta before xx-Month target visit date:

Unexposed period follow-up years = (Benlysta start date – Enrollment date) /365.25

Exposed period follow-up years = (xx-Month period end date - Benlysta start date +1)/365.25

where xx-Month period end data = earliest of xx-Month target visit date and Last contact date*

- An individual's subject-years 'at-risk' will be calculated for each exposure group as follows:

a) Subjects on Benlysta at enrollment:

Exposed subject-years at-risk = [(minimum (Event Date, Last Contact Date*) – Study Enrollment Date) +1]/365.25

b) Subjects not on Benlysta at enrollment who do not switch on to Benlysta before xx-Month target visit date:

Unexposed subject-years at-risk = [(minimum (Event Date, Last Contact Date*) – Study Enrollment Date) +1]/365.25

c) Subjects not on Benlysta at enrollment who do switch on to Benlysta before xx-Month target visit date:

i) If no event happens in period:

Unexposed subject-years at-risk = (Benlysta start date - Enrollment Date) /365.25.

Exposed subject-years at-risk = (Last contact date* - Benlysta start date+1) /365.25

ii) If event happens in period:

Unexposed subject-years at-risk = (minimum (Event date, Benlysta start date) - Enrollment Date)/365.25

Exposed subject-years at-risk =

If Event date ≥ Benlysta start date: (Event date – Benlysta start date+1) /365.25

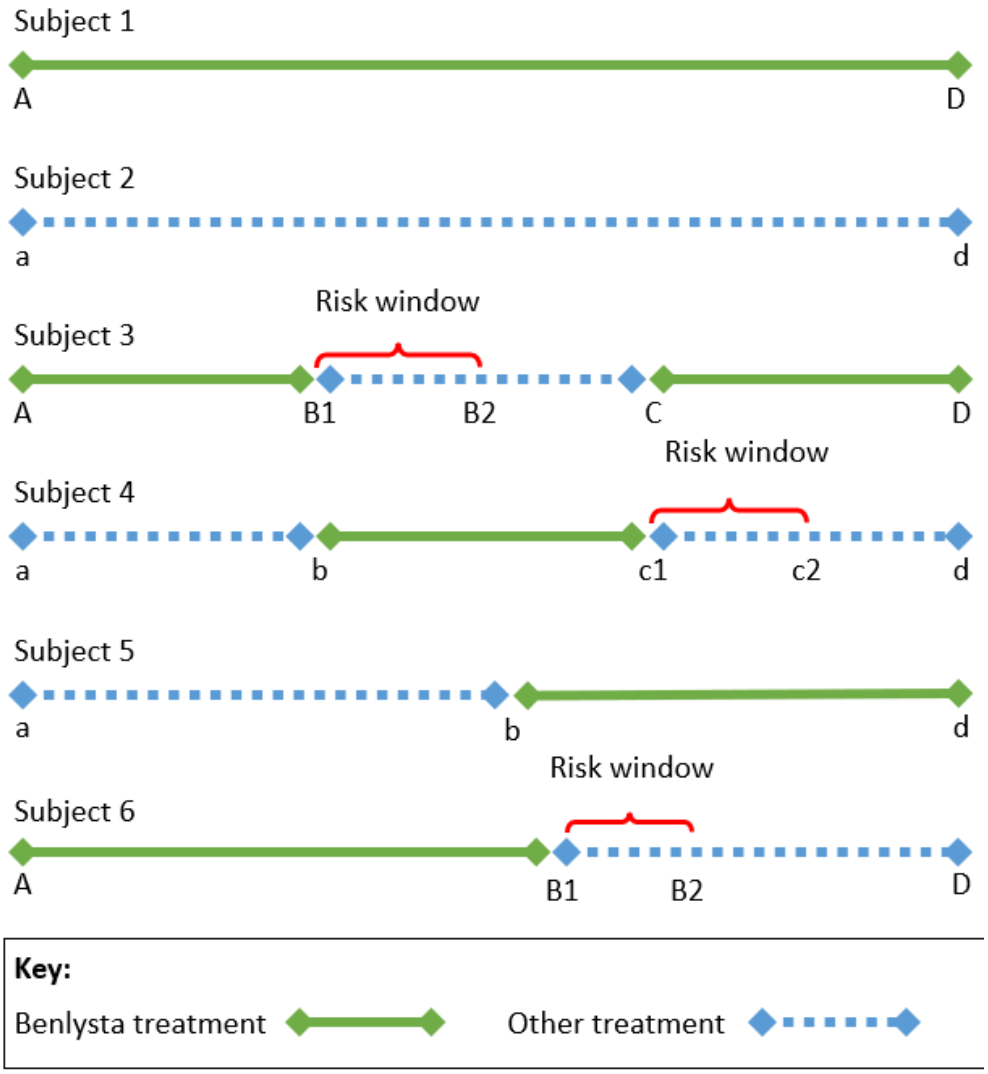
If Event date < Benlysta start date: 0

NOTE: An individual's subject-years at-risk will be calculated for each event category separately

* Last Contact Date as defined in Section 9.5.3

9.2.2. Exposure Strategy Hypothetical Illustration

The exposure status strategies described in Section 9.2.1 are illustrated in the chart below showing treatment profile of six hypothetical subjects.



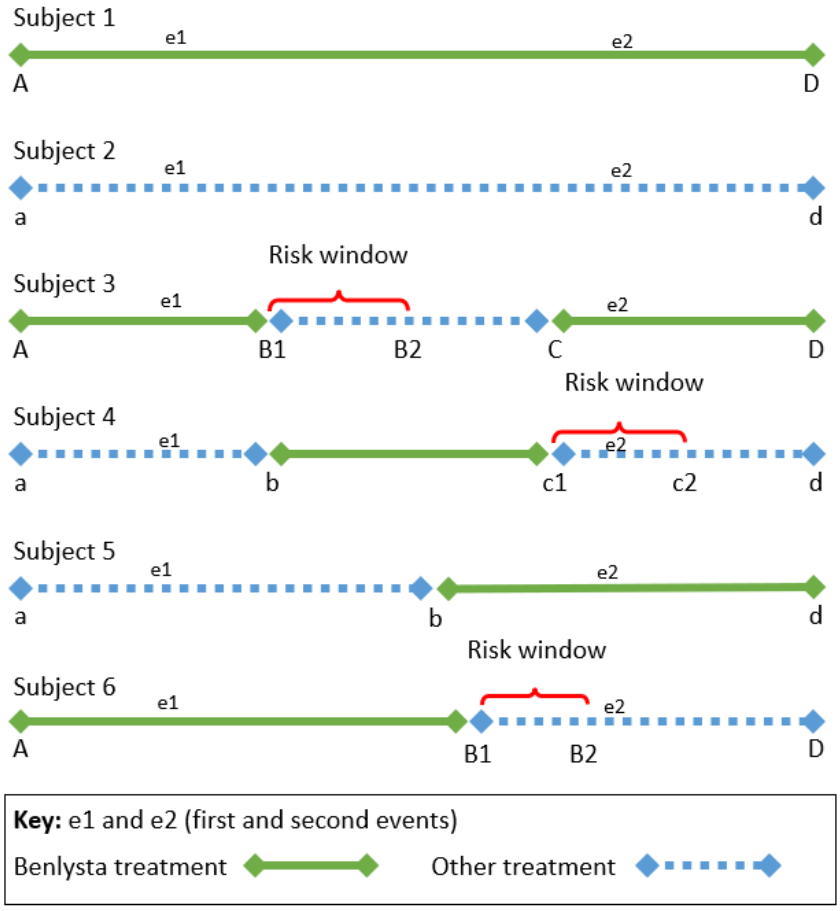
NOTE: The risk windows are only applicable when switching from Benlysta medication to Non-Benlysta Standard of Care (SOC) medication(s). There are two possible risk windows: (1) 14 weeks (98 days) which assumes that Benlysta exposure ends 14 weeks (98 days) after cessation (End Date) of Benlysta medication; and (2) 6 months.

The events and exposure time contributed by each subject to the two exposure status cohorts (Benlysta or Non-Benlysta) depend on the analysis strategy as shown in the Table below.

Exposure Strategy	Highlights	Exposure Time/Events Attribution per risk windows*	
		BENLYSTA	NON-BENLYSTA
Initial Exposure: - Intent-To-Treat (ITT)	ITT • Assign exposure status based on baseline (enrollment) SLE medication • Include all events and exposure time during FU irrespective of switching	D – A (subjects 1, 3, 6)	d – a (subjects 2, 4, 5)
- While On-Initial Exposure	While On-Initial Exposure • Assign exposure status based on baseline (enrollment) SLE medication • Censor (exclude) events and exposure time post switching	D – A (subject 1) B2 – A (subjects 3 & 6)	d – a (subject 2) b - a (subjects 4 & 5)
As-Exposed (Time varying)	• Allows subjects to switch treatment exposure status based on treatment use • Assign time varying treatment exposure group • Subjects treatment exposure group change over follow-up time depending on switch on and off Benlysta medication • Treatment exposure status is assigned at event and visit data level • Used all data since no censoring of events or follow-up exposure time after switching • Subjects can contribute person-year exposure time to any of treatment exposure groups	D – A (subject 1) B2 – A & D – C (subject 3) c2 – b (subject 4) d - b (subject 5) B2 – A (subject 6)	d – a (subject 2) C – B2 (subject 3) b – a & d – c2 (subject 4) b – a (subject 5) D – B2 (subject 6)
Ever-Exposed	• Assigns exposure status based on ever being exposed to Benlysta • Considers whether subject was exposed to Benlysta at any point during the follow up period • When subject has not been exposed to Benlysta at any point in time, the subject is considered as 'Unexposed'. Once a subject is exposed to Benlysta even once, they will be considered as always exposed • Treatment exposure status is assigned at event and visit data level • Uses all data • Subjects who start as 'Unexposed' can contribute person-year exposure time to both of the treatment exposure groups if they start taking Benlysta	D – A (subject 1) D – A (subject 3) d – b (subject 4) d – b (subject 5) D – A (subject 6)	d – a (subject 2) b – a (subject 4) b – a (subject 5)

*** Assume at-risk window is only applicable after switching from Benlysta**

The same chart could be used to illustrate how events are considered to compute incidence rate. Let's note e1 and e2, two events of same AESI occurring for a subject.



- For initial exposure (i.e. ITT and while on initial exposure), events only contribute to the subject's initial exposure assignement, and only the first event will be considered for the incidence rate computation:
    - Subjects 1, 3 and 6: one event for Benlysta group (e1-A)
    - Subjects 2, 4 and 5: one event for Non-Benlysta group (e1-a)

- For the 'As-Exposed' and 'Ever-Exposed' strategies, subjects can contribute subject-years and events to either one or both exposure groups. The following events will be considered for the incidence rate computation:
    - For subjects 1 and 2, there is no medication (exposure) switching, therefore computation remains as per initial exposure.
    - For subject 3, only the first event is considered for Benlysta group and therefore computation remains as per initial exposure.
    - Subject 4:

- For the as-exposed strategy, one event for Non-Benlysta group (e1-a) and one event for Benlysta group (e2-b) as the event occurred during risk-window of Benlysta period.
- The same applies for the ever-exposed strategy, as subject was not on Benlysta at enrollment and switch on to Benlysta.

- Subject 5:
  - For the as-exposed strategy, one event for Non-Benlysta group (e1-a) and one event for Benlysta group (e2-b).
  - The same applies for the ever-exposed strategy, as subject was not on Benlysta at enrollment and switch on to Benlysta.
- Subject 6:
  - For the as-exposed strategy, one event for Benlysta group (e1-a) and one event for Non-Benlysta group (e2-B2).
  - For the ever-exposed strategy, one event for Benlysta group (e1-A) and none for non-Benlysta group. The subject was on Benlysta at enrollment and is always considered as exposed, therefore computation remains as per initial exposure.

9.3. Appendix 3: Review and Categorization of Adverse Events of Special Interest

9.3.1. Semi-Automated Adverse Events of Special Interest Coding Process

A programming process will be performed for the creation of AE flags and adjudication variables for assigning each AE to at least a specific AESI category using the current version of Benlysta Program Safety Analysis Plan (PSAP) term of interest (TOI) and the GSK Medical Dictionary for Regulatory Activities (MedDRA) dictionary in effect at the time of reporting. The automated categorization of the reported AE into AESIs will be based on the following Benlysta pre-specified custom MedDRA queries (CMQ) variables:

- Neoplasms, hematological (CQ02NAM)
- Neoplasms, skin (CQ03NAM)
- Non-melanoma skin cancer-NMSC (CQ03NMFL)
- Neoplasms, solid (CQ01NAM)
- Neoplasms, unspecified (CQ04NAM)
- Opportunistic Infections (CQ06NAM)
- Herpes Zoster (CQ07NAM)
- Pneumonia (CQ10NAM)
- Sepsis (CQ08NAM)
- Tuberculosis (CQ11NAM)
- Suicide/self-injury (SMQ01NAM)
- Depression (CQ09NAM)

Any AEs that cannot be automatically categorized into AESI by the automatic process will be flagged for manual review by the GSK Study Medical Monitor and GSK Safety Evaluation and Risk Management (SERM) physician to adjudicate. The manual review process is as described in Section 9.3.2. The working instruction provided by GSK showing details of the automated steps is available on request from the GSK SABLE Study Lead Programmer or Statistician.

9.3.2. Review and Categorization of Adverse Events of Special Interest

All reported AE terms will be reviewed at the subject level by GSK Medical Monitor. The review and categorization of AEs are used to flag AESIs. The reviewers will categorize each AE into one of the following AESI category.

- Malignancies (excluding non-melanoma skin cancer - NMSC)
- Opportunistic infections (see protocol Appendix 1)
- Other infections of interest (see protocol Appendix 1)
- NMSC
- Serious psychiatric events (see protocol Appendix 2)
- Serious infections

Cases of mortality (death) are reported as all the events captured as fatal SAEs in the eCRF. All other AESI types are assigned based on the review outcome described above. For summary and reporting purpose, the eCRF field for reporting SAE will be used to separate serious and non-serious Opportunistic Infections and Other Infections of Interest AESI.

In addition to review by the GSK Medical Monitor, an independent review and categorization will be performed by safety physician for concurrence with the initial review using the same data and following the same convention of the main review. Identified discrepancies will be discussed and reconciled between the GSK clinical representatives (Medical Monitor and study Clinical Science Lead or designee) and the SERM physician. The reconciled record of categorization will be utilized in study reporting.

The identification, classification and categorization of AESI is planned to occur at least annually prior to the clinical database cut-off date for the scheduled annual post-approval European Medicines Agency (EMA) submission. It is anticipated that since this is an ongoing study and in-stream query process, categorization may change from one report to another, as additional information becomes available on safety events.

9.4. Appendix 4: Data Display Standards & Handling Conventions

9.4.1. Reporting Process

Software	
• All analyses will be conducted using SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA).	
Reporting Area: • Datasets and TLF outputs received from FSO will be uploaded to	
Domino Project	16267_116543_EOS
Compound/Study	GSK1550188\BEL116543
Analysis Datasets	
• Analysis datasets will be created according to CDISC standards (SDTM IG Version 3.2 & Analysis Data Model (ADaM) IG Version 1.1).	
Generation of RTF Files	
• RTF files will be generated for each Table, Listing and Figure.	

9.4.2. Reporting Standards

General
The current GSK Statistical Display Principles will be applied for reporting, unless otherwise stated. I GSK Statistical Display Principles location: https://myteams.gsk.com/sites/IDSLLibrary/PublishingImages/Combined%20Statistical%20Displays%20Principles%20v2.docx). Below sections from "Combined Statistical Displays Principles v2.docx" will be applied: • 4.3 to 4.24: Principles for All Displays • 5.1 to 5.9: Principles for Data Listings • 6.1 to 6.11: Principles for Summary Table • 7.1 to 7.13: Principles for Graphics
Formats
• GSK Statistical Displays Principles (4.24, 6.8.3, & 6.9) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the GSK statistical displays principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for Tables, Figures and formal statistical analyses:
  • Target visit dates will be used for slotting events. The analysis visit dates will be used for any displays with time point analysis and derivations.
• Reporting for Data Listings:
  • Unless otherwise stated, planned/scheduled time relative to study assessment will be shown for TLF (Refer to Statistical Displays Principle 5.5).

Unscheduled Visits
• No unscheduled visit in the study

9.5. Appendix 5: Derived and Transformed Data

9.5.1. General

Multiple Measurements at One Analysis Time Point
• All AESIs, SLE medications or hospitalizations reported since the last visit will be reported and analysed. • If there are multiple values available within a visit window, then the worst case will be used for analysis. If the worst-case values are equal, the visit with the earliest date will be selected. For laboratory, the measurement which takes place first will be selected as the value. • For SLICC and SLEDAI 2000, the worst-case value will be that which increases the total score.

9.5.2. Study and Concomitant Medication Phases

Study Phase	Definition
Historical	Date < Enrollment Date
Baseline	Enrollment Date
Follow-up	Date > Enrollment Date

Medication Phase	Definition	
Historical	Medications stopped prior to enrollment date (Day 1). For BENLYSTA only: With regards to interruptions (i.e. stopping & restarting the medication), medications that stop within the 98 days window before enrollment, and don't restart within 98 days of the medication end date, will be classified as historical.	Medication End Date < Study Enrollment Date, excluding interruptions in medications for BENLYSTA only (as defined in the baseline medication phase)
Baseline	Medications started on or prior to enrollment date (Day 1) and still ongoing at or after enrollment, or for BENLYSTA only: Benlysta that stops within 98 days before enrollment and restarts, such that restart date – stop date ≤98 days and subsequent Benlysta end date is ongoing or after enrollment date. Such cases are considered interruptions, the medication is classified as baseline.	Medication Start Date ≤ Enrollment Date* ≤ Medication End Date, or accounting for interruptions for BENLYSTA only: Enrollment Date -98 ≤ Medication(A) End Date < Enrollment Date* and Subsequent Medication(B) Start Date ≤ Medication(A) End Date + 98 and ((Subsequent Medication(B) End date ≥ Enrollment Date) or (Subsequent Medication(B) End Date is missing))
Post-Baseline	Medication is still ongoing after enrollment day or medications end date is after enrollment.	Medication End Date is missing or Medication End Date> Enrollment Date

* Consider SLE medication(s) started within 3 days following the enrollment date (i.e Medication started or initiated at Day 1, 2, 3, or 4) as Baseline Medication (i.e Enrollment Date ≤ Medication Start Date ≤ Enrollment Date +3)

Study Day

• Calculated as the number of days from Enrollment Date (Day 1):
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Enrollment Date → Study Day = Ref Date – Enrollment Date
  • Ref Data ≥ Enrollment Date → Study Day = Ref Date – (Enrollment Date) + 1

For all parameters, changes from baseline will be derived as follows:

Definition	Reporting Details
Change from Baseline	= FU Visit Value – Baseline Value
% Change from Baseline	= 100 x [(FU Visit Value – Baseline Value) / Baseline Value]

9.5.3. Study Population

Demographics
Age
• GSK standard integrated data standards library (IDSL) algorithms will be used for calculating age where birth date will be imputed as follows: 1. Any subject with a missing day will have this imputed as day '15'. 2. Any subject with a missing date and month will have this imputed as '30th June'. • Birth Year will be presented in listings as 'YYYY'.
Body Mass Index (BMI)
• Calculated as Weight (kg) / [Height (m)]^2
Baseline Characteristics
Time since SLE Diagnosis
• Calculated as: $\frac{(Enrollment\ date - Diagnosis\ date + 1)}{365.25}$ ○ Partial dates will be imputed as described in Section 9.6.2.1: Handling of Missing and Partial Dates
Exposure Duration
• Duration or extent of exposure (days) = (Medication End Date – Medication Start Date) +1 ○ Last contact Date (as defined in Section 9.5.3) will be used as Medication End Date if medication is ongoing at the time of data cut ○ May be calculated for historical, at baseline and post (follow-up) enrollment ○ For multiple medication records within each medication predefined category (i.e anti-malarial, Mycophenolate Mofetil etc): • the start date of earliest and end date of latest medications will be used when there is overlap in days of use • total of all durations of exposures will be used when there is no overlap in days of use
Disposition Duration
• Duration since last known visit or last contact date ○ Subject who has an 'Ongoing' status on the database (applicable to final analysis dry-run) will be categorized by duration since last contact calculated as: (DataCut Off Date (DCO) – Last Contact Date +1)/365.25 ○ The following categories will be used: - Last contact date to DCO is < 0.5 year

- Last contact date to DCO is 0.5 - < 1 year - Last contact date to DCO is 1 - < 2 years - Last contact date to DCO is 2 - < 3 years - Last contact date to DCO is 3 - < 4 years - Last contact date to DCO is 4+ years
• Last contact date definition: o maximum (death date [supersedes all other dates], last data assessment date, last visit date, last AE or hospitalization date) o in the case that the above date is greater than the reference end date (date of completion or withdrawal from end of study disposition CRF page), then the last contact date will be replaced with the reference end date. This is equivalent to the risk end period for each subject, and will be used for the subject-years calculations.

9.5.4. Safety

Adverse Events of Special Interest
• Duration of AESI (days) = Date of AESI resolution – AESI start date + 1 (If the AE is ongoing the duration will be left blank and no imputation will be done)

9.5.5. Effectiveness

Effectiveness endpoints
SLICC/ACR Damage Index (SDI) score
• SDI is designed to capture items of irreversible organ damage (present for at least 6 months) occurring in subjects with SLE. It consists of 12 organ system (listed below) scales each having subscales comprised of up to six components. • Scoring will be performed for the following items as per Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index. • Total scores used for analysis will not be obtained directly from the eCRF electronic data capture (EDC), but instead calculated by summing the scores of each domain. • If any item is missing, the total score should be set to missing (see Section 9.6.2.3 for exceptions).

Item	Score
Ocular (either eye, by clinical assessment)	
Any cataract ever	0,1
Retinal change or optic atrophy	0,1
Neuropsychiatric	
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance levels) or major psychosis	0,1
Seizures requiring therapy for 6 months	0,1
Cerebrovascular accident ever (score 2 if >1)	0,1,2
Cranial or peripheral neuropathy (excluding optic)	0,1
Transverse myelitis	0,1
Renal	
Estimated or measured glomerular filtration rate <50%	0,1
Proteinuria >3.5 g/24hours	0,1
Or	

Effectiveness endpoints	
End-stage renal disease (regardless of dialysis or transplantation)	0,3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	0,1
Pulmonary fibrosis (physical and radiograph)	0,1
Shrinking lung (radiograph)	0,1
Pleural fibrosis (radiograph)	0,1
Pulmonary infarction (radiograph)	0,1
Cardiovascular	
Angina or coronary artery bypass	0,1
Myocardial infarction ever (score 2 if >1)	0,1,2
Cardiomyopathy (ventricular dysfunction)	0,1
Valvular disease (diastolic, murmur, or systolic murmur >3/6)	0,1
Pericarditis for 6 months, or pericardiectomy	0,1
Peripheral vascular	
Claudication for 6 months	0,1
Minor tissue loss (pulp space)	0,1
Significant tissue loss ever (e.g. loss of digit or limb) (score 2 if >1 site)	0,1,2
Venous thrombosis with swelling, ulceration, or venous stasis	0,1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver, or gall bladder ever, for any cause (score 2 if >1 site)	0,1,2
Mesenteric insufficiency	0,1
Chronic peritonitis	0,1
Stricture or upper gastrointestinal tract surgery ever	0,1
Musculoskeletal	
Muscle atrophy or weakness	0,1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	0,1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	0,1
Avascular necrosis (score 2 if >1)	0,1,2
Osteomyelitis	0,1
Skin	
Scarring chronic alopecia	0,1
Extensive scarring or panniculum other than scalp and pulp space	0,1
Skin ulceration (excluding thrombosis) for >6 months	0,1
Premature gonadal failure	0,1
Diabetes (regardless of treatment)	0,1
Malignancy (exclude dysplasia) (score 2 if >1 site)	0,1,2
From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996 (Gladman, 1996)	

Effectiveness endpoints

SLEDAI**, 2000 (S2K) score**

- Assessments consist of 24 individual items (listed below) in which signs and symptoms, laboratory tests, and physician's assessment for each of 9 organ systems are given a weighted score and summed if present (marked 'Yes') at the time of the visit or ±30 days of enrollment visit.
- The maximum theoretical score is 105 (all 24 descriptors present simultaneously) with 0 indicating inactive disease (marked 'No'), but in practice few subjects have scores >45.
- Total Scores used for analysis are derived based on the sum of the weighted value for each organ system component (see Gladman, 2002).

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

Effectiveness endpoints		
Fever (move to hematologic)	1	>38 degrees C (38ºC). Exclude infectious cause.
Thrombocytopenia	1	<100,000 platelets/mm^3, exclude drug causes.
Leukopenia	1	<3,000 white blood cells/mm^3, exclude drug causes.

Adapted from: Gladman D Dafna, Ibañez Dominique and Urowitz B Murray. Systemic lupus erythematosus disease activity index 2000. J Rheumatol 2002;29;288-29 [Gladman, 2002]

9.6. Appendix 6: Reporting Standards for Missing Data

9.6.1. Study Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as completion of the 5-year follow-up following enrollment into study. • Withdrawn subjects will not be replaced in the study. Subjects who develop AESI will still remain in the study except for fatality event, withdrawal of consent or withdrawal at physician discretion. • All available data from subjects who were withdrawn from the study will be listed and all available data will be included in summary Tables and Figures.

9.6.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument: ○ These data will be indicated using a "blank" in subject listing displays, unless all data for a specific timepoint are missing in which case the data are excluded from the Table. ○ Answers of "Not applicable" (i.e. within the section 'Serious Adverse Event of Special Interest [SAE-SI]') are not considered to be missing data and should be displayed as such.
Data Collection Stopped	• For effectiveness endpoints where collection of the underlying data have been stopped as per protocol amendment 3. Data collected for these endpoints prior to their removal from the protocol are available in the previous interim analysis reports.

9.6.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in subject listing displays
Adverse Events Concomitant Medications Medical History Hospitalization	• The eCRF allows for the possibility of partial dates (i.e. only month and year) to be recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the imputation will follow the conventions shown in Section 9.6.2.2. In the event the end date is after to the last contact date, the last contact date (section 9.5.3) will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing (where applicable). • The recorded partial date will be displayed in listings; so, should not be overwritten.

9.6.2.2. Imputation Convention for Missing and Partial Dates

Start date	Stop Date	Imputation
Complete date available	Complete date available	Not applicable
Complete date available	Only day is missing	Impute day of stop date with last day of the same month
Complete date available	Month and day are missing	1. Impute stop date with 'Jun30' 2. If (year of start date=year of stop date) then stop date =max (start date + 1, stop date)
Day is missing	Complete date available	Impute the day part of start date with "01" of the same month
Day is missing	Only day is missing	Impute day of start date with '01' and day of stop date with last day of the same month
Day is missing	Month and day are missing	1. Impute day of start date with '01' and 'Jun 30' for day and month of stop date 2. If (year of start date=year of stop date) then stop date =max (start date + 1, stop date)
Day and Month missing	Complete date available	1. Impute start date with 'Jun01' 2. If (year of start date=year of stop date) then start date =min (start date, stop date-1)
Day and Month missing	Only day is missing	1. Impute day of stop date with '30' and 'Jun 01' for day and month of start date 2. If (year of start date=year of stop date) then start date =min (start date, stop date-1)
Day and Month missing	Month and day are missing	Impute start date with 'Jun01' and stop date with 'JUN30'

9.6.2.3. Handling of Missing Data for Statistical Analysis

Element	Reporting Detail
General	• For endpoints not relying on multiple questionnaire items, missing values will not be imputed • Data will be analysed only for the time point at which they were collected.
SDI Domains	• If any item is missing, the total score should be missing. However, if the missing item has previously been score in previous visits, the worst observation can be carried forward for that item. • If the SDI is scored inconsistently (a decrease score at subsequent follow-up relative to previous visit has occurred) and the data are unable to be queried and/or corrected, the previous score (before the decrease) will be carried forward at the item level for the SLICC/Damage Index questions, this corresponds to worst observation carried forward (WOCF). These carried forward values at items level will then be used to calculate the total score which will be the value summarized and displayed for reporting.
S2K Score	For the calculation of S2K score, all items will be taken from the completed SLEDAI 2000 CRF page; no imputation will be performed. Scores for any S2K items will be used as observed. Subjects with at least one missing i.e. 'not done' value at baseline assessment will be excluded from the analysis of S2K total score.

9.7. Appendix 7: Laboratory Tests

Laboratory Parameter	Units
ANA status	
Anti-dsDNA	
C3	
C4	
CH50	
Lymphocyte differential % / count	
IgA	
IgM	
IgG	
White blood cell (WBC) count	mm^3
Neutrophil differential Count	mm^3
Thrombocytopenia (<100,000 platelets/10^9/L)	
Urinary Casts (Heme-granular or red blood cell casts)	
Hematuria (>5 red blood cells/high power field)	[Units]
Proteinuria (>0.5mg/24 hours)	
Pyuria (>5 white blood cells/high power field)	

9.8. Appendix 8: Abbreviations & Trade Marks

9.8.1. Abbreviations

Abbreviation	Description
ACR	American College of Rheumatology
ADaM	Analysis Data Model
AE	Adverse Event
AESI	Adverse Event of Special Interest
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CSAP	Clinical Study Activity Plan
CSR	Clinical Study Report
DBL	Database Lock
DCO	Data Cut Off date
eCRF	Electronic Case Record Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FACIT	Functional Assessment of Chronic Illness Therapy
IA	Interim Analysis
IDSL	Integrated Data Standards Library
IPTW	Inverse Probability of Treatment Weighting
ITT	Intent-To-Treat
MAR	Missing at Random
Max	Maximum
Min	Minimum
NMSC	Non-melanoma skin cancers
PDMP	Protocol Deviation Management Plan
PS	Propensity score
Q1	First Quartile
Q3	Third Quartile
RAP	Reporting & Analysis Plan
PSRHQ	Possible Suicidality-Related History Questionnaire
PSRQ	Possible Suicidality-Related Questionnaire
S2K	SLEDAI 2000
SABLE	Safety And effectiveness of Belimumab in Systemic Lupus Erythematosus Registry
SAC	Statistical Analysis Complete
SAE	Serious Adverse Event
SD	Standard Deviation
SDI	SLICC/ACR Damage Index
SDTM	Study Data Tabulation Model
SERM	Safety Evaluation and Risk Management
SLE	Systemic Lupus Erythematosus

Abbreviation	Description
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLICC	Systemic Lupus International Collaborating Clinics
SMDs	standardized mean differences
TLF	Tables, Listings & Figures
VIF	Variance Inflation Factor

9.8.2. Trademarks

Trademarks of the GSK Group of Companies
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Trademarks not owned by the GSK Group of Companies
MedDRA
SAS® version 9.4 or higher (SAS Institute, Cary, NC, USA)
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9.9. Appendix 9: Treatment Propensity Score Models Covariates

Table 4: Treatment Propensity Score Models Covariates

Variables	Categories/Units	Key covariates*
Year of entry in the study	2013/2014 2015/2016 2017/2018 2019/2020	
Age at baseline	Years	Yes
Sex	Female Male	Yes
BMI	Underweight (<18.5) Normal (18.5 - <25) Overweight (25 - <30) Obese (30 - <40) Extremely obese (>=40)	
Race	Black White Asian Other	Yes
Ethnicity	Hispanic/Latino Not Hispanic/Latino	
Region	US/Canada Europe Other	Yes
Baseline Clinical SLEDAI 2000 score	Score	Yes
Baseline SDI	Score	
SLE duration since diagnosis	Years	
Used corticosteroids for SLE in the past six months	Yes No	Yes
Cardiovascular risk factors	Yes No	
Allergic reactions	Yes No	
Interstitial lung disease	Yes No	
Chronic Obstructive Pulmonary Disease (COPD)	Yes No	
Opportunistic Infection	Yes No	

Variables	**Categories/Units**	**Key covariates***
Any other infection	Yes No	
Autoimmune disorders	Yes No	
Hypogammaglobulinaemia	Yes No	
Cancer	Yes No	
Non-Melanoma Skin Cancer (NMSC)	Yes No	
Family history of cancer	Yes No	
End stage renal failure	Yes No	
Depression and/or anxiety disorder	Yes No	
Suicidal ideation and/or suicidal depression and/or suicidal behavior	Yes No	
Attempted suicide	Yes No	
Dialysis	Yes No	
Transplant	Yes No	
Splenectomy	Yes No	

Treatment propensity score models covariates are collected at baseline.
* Key covariates will be included in PS models. They are selected based on clinical judgment. If during building the PS model, there is a need to simplify the model specification, retention of key variables will be given priority. Any model simplification involving removal of these key covariates, will require further discussions and alignment with study team prior to implementation.

9.10. Appendix 10: SAS example code

Assessing co-linearity:

The option VIF gives the variance inflation factor in SAS REG procedure:

```
PROC REG data=out ;
  MODEL Y= X Z / VIF ;
RUN;
```

Categorical covariates with at least 3 categories will be transformed into dummy variables to be used in the SAS REG procedure.

Example:

The covariate Z could take the 3 categories values: 1, 2 and 3. Three dummy variables will be created:

Z1=1 if Z =1 else Z1=0;
Z2=1 if Z =2 else Z2=0;
Z3=1 if Z =3 else Z3=0;

If we choose the Z=1 as the reference category, the regression will be:

```
PROC REG data=out ;
  MODEL Y= X Z2 Z3 / VIF ;
RUN;
```

Propensity score model(s) definition:

```
proc causaltrt data= ADPS method=IPW noeffect;
   class  X1 X2 Xn ;
   psmodel TRT01Pn(descending) = X1….. Xn;
   model outcome;
   output out=PS ps=PS1 ipw=IPTW1;
run;
```

Note: the CAUSALTRT code contains both PSMODEL (to specify the propensity model) and MODEL (to specify the outcome model) statements. Anyway, the NOEFFECT option will allow finalization of the propensity model prior to conducting any outcome analysis.

9.11. Appendix 11: List of TLF Data Displays

9.11.1. Subjects and Study Characteristics Tables

Subjects and Study Characteristics Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
Subject Disposition			
1.000	Enrolled	Summary of Subjects Population by Study Cohort, Visit Attendance and Benlysta Medication (Exposure) Switch	
2.000	Eligible	Subject Completion Status	
3.000	Enrolled	Inclusion/Exclusion Criteria Deviations	
4.000	Eligible	Enrollment by Country	
5.000	Eligible	Enrollment by current Site	
Demographic			
6.000	Eligible	Demographic and Baseline Characteristics	
6.001	Sensitivity	Demographic and Baseline Characteristics – Sensitivity Analysis	
6.010	Eligible	Demographic and Baseline Characteristics – Current Users	
6.020	Eligible	Demographic and Baseline Characteristics – Treatment Initiators	
7.000	Eligible	Tobacco Use and Alcohol Abuse History at Baseline	
7.010	Eligible	Tobacco Use and Alcohol Abuse History at Baseline – Current Users	
7.020	Eligible	Tobacco Use and Alcohol Abuse History at Baseline – Treatment Initiators	

Subjects and Study Characteristics Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
Pregnancy Status			
8.000	Eligible	Baseline Pregnancy Status	
8.010	Eligible	Baseline Pregnancy Status – Current Users	
8.020	Eligible	Baseline Pregnancy Status – Treatment Initiators	
Historical and Current Medical History			
9.011	Eligible	Summary of Past Medical History at Baseline	
9.012	Eligible	Summary of Past Medical History at Baseline – Current Users	
9.013	Eligible	Summary of Past Medical History at Baseline – Treatment Initiators	
9.021	Eligible	Summary of Current Medical History at Baseline	
9.022	Eligible	Summary of Current Medical History at Baseline – Current Users	
9.023	Eligible	Summary of Current Medical History at Baseline – Treatment Initiators	
9.111	Eligible	Summary of Past General Medical Status at Month 24 and 48 Visits [Initial Exposure - ITT Strategy]	
9.112	Eligible	Summary of Past General Medical Status at Month 24 and 48 Visits [Initial Exposure - ITT Strategy] – Current Users	
9.113	Eligible	Summary of Past General Medical Status at Month 24 and 48 Visits [Initial Exposure - ITT Strategy] – Treatment Initiators	
9.121	Eligible	Summary of Current General Medical Status at Month 24 and 48 Visits [Initial Exposure - ITT Strategy]	
9.122	Eligible	Summary of Current General Medical Status at Month 24 and 48 Visits [Initial Exposure - ITT Strategy] – Current Users	

Subjects and Study Characteristics Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
9.123	Eligible	Summary of Current General Medical Status at Month 24 and 48 Visits [Initial Exposure - ITT Strategy] – Treatment Initiators	
SLEDAI 2000			
10.011	Eligible	Summary of SLEDAI 2000 at Baseline	
10.012	Eligible	Summary of SLEDAI 2000 at Baseline – Current Users	
10.013	Eligible	Summary of SLEDAI 2000 at Baseline – Treatment Initiators	
SLE Disease Duration			
12.000	Eligible	Summary of SLE Disease Duration at Baseline by Study Cohort	

Subjects and Study Characteristics Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
Laboratory Values			
19.000	Eligible	Summary of Baseline Laboratory Values	
19.010	Eligible	Summary of Baseline Laboratory Values – Current Users	
19.020	Eligible	Summary of Baseline Laboratory Values – Treatment Initiators	
Vaccinations			
20.000	Eligible	Summary of Baseline Vaccination Status by Study Cohort	
Exposure Switching			
17.000	Eligible	Summary of Medication Switching During Study Follow-up Period	
17.010	Eligible	Summary of Medication Switching During Study Follow-up Period – Current Users	
17.020	Eligible	Summary of Medication Switching During Study Follow-up Period – Treatment Initiators	
Withdrawal from Study			
50.000	Eligible	Time to Study Withdrawal [Initial Exposure - ITT Strategy]	
50.001	Eligible	Time to Study Withdrawal [Initial Exposure - ITT Strategy] – Current Users	
50.002	Eligible	Time to Study Withdrawal [Initial Exposure - ITT Strategy] – Treatment Initiators	
Protocol Deviations			
52.000	Eligible	Protocol Deviations	

9.11.2. Safety Endpoints Tables

Safety Endpoints Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
AESI			
23.000	Evaluable	Summary of Adverse Events of Special Interest by Time Period [Initial Exposure - ITT Strategy]	
23.001	Evaluable Sensitivity	Summary of Adverse Events of Special Interest by Time Period [Initial Exposure - ITT Strategy] – Sensitivity Analysis	
23.010	Evaluable	Summary of Adverse Events of Special Interest by Time Period [Initial Exposure - ITT Strategy] – Current Users	
23.020	Evaluable	Summary of Adverse Events of Special Interest by Time Period [Initial Exposure - ITT Strategy] – Treatment Initiators	
23.100	Evaluable	Summary of Adverse Events of Special Interest by Time Period [While On Initial Exposure Strategy]	
23.101	Evaluable Sensitivity	Summary of Adverse Events of Special Interest by Time Period [While On Initial Exposure Strategy] – Sensitivity Analysis	
23.110	Evaluable	Summary of Adverse Events of Special Interes by Time Period [While On Initial Exposure Strategy] – Current Users	
23.120	Evaluable	Summary of Adverse Events of Special Interest by Time Period [While On Initial Exposure Strategy] – Treatment Initiators	
23.200	Evaluable	Summary of Fatal AESI by SOC, PT and Study Cohort	
23.201	Evaluable Sensitivity	Summary of Fatal AESI by SOC, PT and Study Cohort – Sensitivity Analysis	
24.110	Evaluable	Overall Proportion and Rates of Adverse Events of Special Interest [Initial Exposure - ITT Strategy]	
24.1101	Evaluable Sensitivity	Overall Proportion and Rates of Adverse Events of Special Interest [Initial Exposure - ITT Strategy] – Sensitivity Analysis	

Safety Endpoints Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
24.111	Evaluable	Overall Proportion and Rates of Adverse Events of Special Interest [Initial Exposure - ITT Strategy] – Current Users	
24.112	Evaluable	Overall Proportion and Rates of Adverse Events of Special Interest [Initial Exposure - ITT Strategy] – Treatment Initiators	
24.120	Evaluable	Overall Proportion and Rates of Adverse Events of Special Interest [While On Initial Exposure Strategy]	
24.1201	Evaluable Sensitivity	Overall Proportion and Rates of Adverse Events of Special Interest [While On Initial Exposure Strategy] – Sensitivity Analysis	
24.121	Evaluable	Overall Proportion and Rates of Adverse Events of Special Interest [While On Initial Exposure Strategy] – Current Users	
24.122	Evaluable	Overall Proportion and Rates of Adverse Events of Special Interest [While On Initial Exposure Strategy] – Treatment Initiators	
24.210	Evaluable	Rates of Adverse Events of Special Interest by Time Period [As-Exposed – Time Varying Strategy with 14 Weeks Risk Window]	
24.211	Evaluable	Rates of Adverse Events of Special Interest by Time Period [As-Exposed – Time Varying Strategy with 14 Weeks Risk Window] – Current Users	
24.212	Evaluable	Rates of Adverse Events of Special Interest by Time Period [As-Exposed – Time Varying Strategy with 14 Weeks Risk Window] – Treatment Initiators	
24.310	Evaluable	Rates of Mortality, Serious Infections, Opportunistic Infections, Other Infections of Interest and Serious Psychiatric Events by Time Period [As-Exposed - Time Varying Strategy with 6 Months Risk Window]	
24.311	Evaluable	Rates of Mortality, Serious Infections, Opportunistic Infections, Other Infections of Interest and Serious Psychiatric Events by Time Period [As-Exposed – Time Varying Strategy with 6 Months Risk Window] – Current Users	

Safety Endpoints Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
24.312	Evaluable	Rates of Mortality, Serious Infections, Opportunistic Infections, Other Infections of Interest and Serious Psychiatric Events by Time Period [As-Exposed – Time Varying Strategy with 6 Months Risk Window] – Treatment Initiators	
24.410	Evaluable	Rates of Mortality, NMSC and Malignancies by Time Period [Ever-Exposed Strategy]	
24.411	Evaluable	Rates of Mortality, NMSC and Malignancies by Time Period [Ever-Exposed Strategy] – Current Users	
24.412	Evaluable	Rates of mortality, NMSC and Malignancies by Time Period [Ever-Exposed Strategy] – Treatment Initiators	

9.11.3. Effectiveness Endpoints Tables

Effectiveness Endpoints Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
SLICC/ACR Damage Index (SDI)			
11.000	Eligible	Summary of Baseline SLICC/ACR Damage Index (SDI)	
11.100	Evaluable	Change from Baseline in SLICC/ACR Damage Index (SDI) by Visit [Initial Exposure – ITT Strategy]	
Hospitalizations			
13.000	Eligible	Summary of Hospitalizations at Baseline by Study Cohort	
13.110	Evaluable	Summary of Hospitalizations Rate by Time Period [Initial Exposure – ITT Strategy]	
13.210	Evaluable	Summary of Hospitalizations Rate by Time Period [While On Initial Exposure Strategy]	
13.310	Evaluable	Summary of Hospitalizations Rate by Time Period [As-Exposed – Time Varying Strategy with 14 Weeks Risk Window]	
SLE Medications			
14.000	Eligible	Duration of Prior SLE Medications Not in Use at Baseline (Historical) by Study Cohort	
14.100	Eligible	Duration of Prior SLE Medications in Use at Baseline by Study Cohort	
14.200	Eligible	Frequency of Prior SLE Medications in Use at Baseline by Study Cohort	
14.300	Eligible	Frequency of Concomitant SLE Medications by Study Cohort	

Corticosteroids Use			
15.000	Eligible	Summary of Corticosteroids Usage at Baseline	
15.101	Evaluable	Change from Baseline in Average Corticosteroids Dose by Visit [Initial Exposure – ITT Strategy]	
15.201	Evaluable	Summary of Corticosteroids Usage by Visit [Initial Exposure – ITT Strategy]	

9.11.4. Propensity Scores Tables

Propensity Scores Tables			
Table No	**Analysis Population**	**Title**	**Programming Note**
53.011	Evaluable	Baseline Characteristics Included in the Propensity Score Model as Covariates	
53.012	Evaluable	Propensity Score Model Building: Associations between Baseline Characteristics and Treatment Initiation	
53.020	Evaluable	Standardized Mean Differences before and after IPTW Adjustment [Initial Exposure]	
53.031	Evaluable	IPTW Distribution [Initial Exposure]	
53.032	Evaluable	Stabilized IPTW Distribution [Initial Exposure]	
54.010	Evaluable	Weighted Rates of Adverse Events of Special Interest [Initial Exposure - ITT Strategy]	
54.020	Evaluable	Weighted Rates of Adverse Events of Special Interest [While On Initial Exposure Strategy]	

9.11.5. Listings

Listings			
No.	**Population**	**Title**	**Programming Notes**
1.000	Eligible	Subjects Demographic Characteristics	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
2.000	Eligible	SLE Medication	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
3.010	Eligible	All Adverse Events	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
4.000	Eligible	Exposure Switching (BENLYSTA Start/Stop) Information	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators

Listings			
No.	**Population**	**Title**	**Programming Notes**
5.000	Eligible	Baseline General Medical History - Other Specify Medical Conditions	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
6.000	Eligible	Medical Conditions Relevant to AESI	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
7.000	Eligible	Fatality by Initial Exposure Group and Study Cohort	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
8.000	Eligible	Serious Psychiatric AESI	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators

Listings			
No.	**Population**	**Title**	**Programming Notes**
8.100	Eligible	Possible Suicidality-Related Questionnaire	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
9.000	Eligible	Study Withdrawal	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
10.000	Eligible	Protocol Deviations	Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators

9.11.6. Figures

Figures			
Table No	**Population**	**Title**	**Programming Notes**
1.000	Eligible	Baseline Medication Groupings	
2.000	Eligible	Plot of Projected vs. Observed Withdrawal Probabilities	
53.020	Evaluable	Supplementary Results (Original SAS Output) - [Initial Exposure]	Figure referred to the table 53.020 (Proposensity Score Table)

9.11.7. Elderly Study (Subjects ≥ 65 years old) Data Display Tables

Study Population Tables			
Table No	**Population**	**Title**	**Programming Notes**
Subject Disposition			
2.0001	Eligible	Subject Completion Status (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)
Demographic			
6.0001	Eligible	Demographic and Baseline Characteristics (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)

Effectiveness Endpoints Tables			
Table No.	**Population**	**Title**	**Programming Notes**
SLICC/ACR Damage Index (SDI)			
11.0001	Eligible	Summary of Baseline SLICC/ACR Damage Index (SDI) (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)
SLE Disease Duration			
12.0001	Eligible	Summary of SLE Disease Duration at Baseline by Study Cohort (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)
Historical and Baseline Concomitant SLE Medications			
15.0001	Eligible	Summary of Corticosteroids Usage at Baseline (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)
Safety Endpoints Tables			
23.0001	Eligible	Summary of Adverse Events of Special Interest by Time Period (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)

9.11.8. Elderly Study (Subjects ≥ 65 years old) Data Display Listings

Listings			
No.	**Population**	**Title**	**Programming Notes**
Subject Disposition			
1.0001	Eligible	Subjects Demographic Characteristics (subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old)
2.0001	Eligible	SLE Medication (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old) Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiators
Adverse Events of Special Interest (AESI)			
3.0101	Eligible	All Adverse Events (Subjects ≥65 Years Old)	Repeat for ≥75 years and change population label to Elderly (Subjects ≥75 Years Old) Separate page by Initial Exposure Group [ITT Strategy]/Study Cohort: NON-BENLYSTA/Current Users BENLYSTA/Current Users NON-BENLYSTA/Treatment Initiators BENLYSTA/Treatment Initiator

9.12. Appendix 12: Example Mock Shells for Data Displays

TLF displays mock shells is on a separate file and available on request.

Certificate Of Completion

Envelope Id: PPD
Status: Completed
Subject: Complete with Docusign: SABLE FA Merged RAP_20250314_Final_Clean.pdf
Source Envelope:
Document Pages: 85 Signatures: 12
Certificate Pages: 6 Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC+01:00) Brussels, Copenhagen, Madrid, Paris

Envelope Originator:
PPD
PPD
PPD
IP Address: PPD

Record Tracking

Status: Original
14-Mar-2025 | 19:35
Holder: PPD
PPD
Location: DocuSign

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 17-Mar-2025 | 05:11 Signed: 17-Mar-2025 | 05:11
Electronic Record and Signature Disclosure: Accepted: 17-Mar-2025 | 05:11 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 17-Mar-2025 | 17:35 Signed: 17-Mar-2025 | 17:36
Electronic Record and Signature Disclosure: Accepted: 17-Mar-2025 | 17:35 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 17-Mar-2025 | 13:58 Signed: 17-Mar-2025 | 13:58
Electronic Record and Signature Disclosure: Accepted: 17-Mar-2025 | 13:58 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Resent: 19-Mar-2025 | 13:16 Viewed: 19-Mar-2025 | 13:17 Signed: 19-Mar-2025 | 13:17
Electronic Record and Signature Disclosure: Accepted: 13-Oct-2023 | 16:20 ID: PPD		

Signer Events	Signature	Timestamp
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Resent: 19-Mar-2025 | 13:16 Viewed: 19-Mar-2025 | 13:36 Signed: 19-Mar-2025 | 13:36
Electronic Record and Signature Disclosure: Accepted: 19-Mar-2025 | 13:36 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 14-Mar-2025 | 19:44 Signed: 14-Mar-2025 | 19:45
Electronic Record and Signature Disclosure: Not Offered via Docusign		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Resent: 19-Mar-2025 | 13:16 Viewed: 20-Mar-2025 | 12:29 Signed: 20-Mar-2025 | 12:29
Electronic Record and Signature Disclosure: Accepted: 20-Mar-2025 | 12:29 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Resent: 19-Mar-2025 | 13:16 Viewed: 20-Mar-2025 | 19:23 Signed: 20-Mar-2025 | 19:23
Electronic Record and Signature Disclosure: Accepted: 20-Mar-2025 | 19:23 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 17-Mar-2025 | 05:24 Signed: 17-Mar-2025 | 05:24
Electronic Record and Signature Disclosure: Accepted: 17-Mar-2025 | 05:24 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Resent: 19-Mar-2025 | 13:16 Viewed: 20-Mar-2025 | 18:07 Signed: 20-Mar-2025 | 18:08
Electronic Record and Signature Disclosure:		

Signer Events	Signature	Timestamp
Accepted: 20-Mar-2025 | 18:07 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Drawn on Device Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 17-Mar-2025 | 10:55 Signed: 17-Mar-2025 | 10:56
Electronic Record and Signature Disclosure: Accepted: 17-Mar-2025 | 10:55 ID: PPD		
PPD PPD Security Level: Email, Account Authentication (None)	PPD Signature Adoption: Pre-selected Style Using IP Address: PPD	Sent: 14-Mar-2025 | 19:44 Viewed: 17-Mar-2025 | 13:20 Signed: 17-Mar-2025 | 13:20
Electronic Record and Signature Disclosure: Accepted: 06-Apr-2022 | 16:01 ID: PPD		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	14-Mar-2025 | 19:44
Certified Delivered	Security Checked	17-Mar-2025 | 13:20
Signing Complete	Security Checked	17-Mar-2025 | 13:20
Completed	Security Checked	20-Mar-2025 | 19:23

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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To contact us by email send messages to: PPD

To advise Real World Solutions – Standard of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at PPD and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

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i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to PPD and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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GlaxoSmithKline

Human Genome Sciences

SABLE

SAfety and effectiveness of Belimumab in sLE

SABLE

A 5-Year Prospective Observational Registry to Assess Adverse Events of Interest and Effectiveness in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Treated with or without BENLYSTA™ (belimumab)

PROTOCOL No.: BEL116543 (HGS1006-C1124)

Case Report Forms

Version 8.0

27 MAY 2022

Prepared By:

IMS Health & Quintiles are now IQVIA™

GlaxoSmithKline / Human Genome Sciences

SABLE

Protocol No.: BEL 116543 (HGS1006-C1124)

CRF Revision History

Document Version	Version Date	Author	Description
1.0	22 Jan 2013	PPD PPD	Initial Release
1.1	13 Feb 2013	PPD PPD	A. ENROLLMENT Form: Corticosteroids -- added new questions at beginning of page to include historical data. B. ENROLLMENT & FOLLOW-UP Forms: Vaccinations: Added "Not Known" to Yes/No choices. Also broke out Hepatitis to Hep A and Hep B. C. SAE-SI and NON-SERIOUS AESI Forms: Added Corticosteroid to the list of suspect therapies that may have caused the event. D. SAE-SI and NON-SERIOUS AESI Forms: Removed Ongoing checkbox after Event Stop Date. Stop date will be Queried if Resolved or Fatal is selected, but will assume ongoing if Resolving or Not Resolved is selected. E. NON-SERIOUS AESI Form: Removed question, "*Was the AE caused by activities related to study participation other than*
1.2	14 May 2013	PPD PPD	A. ENROLLMENT & FOLLOW-UP Form: Labs - added format MMMYYYY B. FOLLOW-UP Form: Vaccinations - question changed to "Has the patient received any of the following vaccinations since it was last reported?"
1.3	06 Jun 2013	PPD PPD	ENROLLMENT & FOLLOW-UP Form: Corticosteroids - added <2.5 and > 60 in the average dose in the past 6 months drop list
2.0	28 Oct 2013	PPD PPD	RF changes further sponsor requests: A. ENROLLMENT form: - SLE Historical Medications page removed - Corticosteroids: average dose in the past 6 months codelist replaced by numeric field, Oral label removed, "≥ 7.5 mg/day but ≤ 2 weeks" radio button added, List of daily dose option label changed, ">= 7.5 mg /day but <20mg / day" radio button added. List of daily dose >= 7.5 mg option label changed, Parenteral and Intramuscular dose changed to >= 40mg, At any time during the pas 6 months, has there been an increase in Prednisone (or equivalent) to > 0.5 mg/kg/day due to SLE activity" question removed -Laboratory value: Lab parameters order change, new lab parameters added (CH50, Thrombocytopenia, Urinary Casts, Hematuria, Proteinuria, Pyuria), Due to SLE flag column added, IgG and Total White Blood cell count result codelist changed. Neutrophil label changed.

Document Version	Version Date	Author	Description
			-Modified SLE flare index: New questions added, Page changed as Repeat group Tobacco history: New question added -General Medical History: Column SLE related removed, Not assessed removed for other medical condition -Vaccinations: Changed as repeat group, Other, specify added - SLEDAI 2000: Not done removed on top and for fever - SLICC: Score changed to radio button, Not done/Assessed, patient has no damage removed on top - SF-12: Language code added - FACIT: Language code added B. FOLLOW UP form: - SLICC: Score changed to radio button, Not done/Assessed, patient has no damage removed on top - SLE Medications page removed - Corticosteroids: No corticosteroids since last visit box replaced by question with Yes/No answer, average dose since last visit codelist replaced by numeric field, Oral label removed, "≥ 7.5 mg/day but ≤ 2 weeks" radio button added, List of daily dose option label changed, ">= 7.5 mg /day but <20mg / day" radio button added. List of daily dose >= 7.5 mg option label changed, Parenteral and Intramuscular dose changed to >= 40mg, At any time during the pas 6 months, has there been an increase in Prednisone (or equivalent) to > 0.5 mg/kg/day due to SLE activity" question removed -Laboratory value: Lab parameters order change, new lab parameters added (CH50, Thrombocytopenia, Urinary Casts, Hematuria, Proteinuria, Pyuria), Due to SLE flag column added, IgG and Total White Blood cell count result codelist changed. Neutrophil label changed. Required at all visits. - Tobacco use: section moved to a separate page as should be present for all visits, questions modified. -General Medical Status: Column SLE related removed. Other, specify added for procedures -Vaccinations: section moved to a separate page as should be present for all visits, Changed as repeat group, Other, specify added, date of vaccination added -Modified SLE flare index: New questions added, Page changed as Repeat group - SLEDAI 2000: Not done removed on top and for fever - SF-12: Language code added - FACIT: Language code added - End of study: Other removed, Please specify added fro Withdrew consent and for Investigator discretion -SLE medications: new page as Log
3.0	11 Nov 2013	PPD PPD	SLE Medications: Added Other specify to Reason for starting medication and for stopping medication
4.0	21 Aug 2017	PPD PPD	SLE Medications: Added new field "Route of Administration with options - Intravenous - Subcutaneous
5.0	14 Jun 2018	PPD PPD	**The data fields will no-longer be collected effective 18JUL2018 due to WO-22 eCRF Modification:** - **Enrollment:** ▪ MODIFIED SLE FLARE INDEX (SLE FLARE) ▪ SF-12 (Hide all fields from this section) ▪ FACIT FATIGUE SCALE v4.0 (Hide all fields from this section) - **Follow-up** ▪ LABS (LABORATORY VALUES - all fields in this section) ▪ MEDICAL STATUS (PREGNANCY - all fields in this section) ▪ TOBACCO USE (Hide all fields in this section) ▪ ALCOHOL USE (Hide all fields in this section) ▪ VACCINATIONS (Hide all fields in this section)

Document Version	Version Date	Author	Description
			▪ SLEDAI 2000 (Hide all fields in this section) ▪ SLE Flare (MODIFIED SLE FLARE INDEX - hide all fields in this section) ▪ SF-12 (Hide all fields in this section) ▪ FACIT FATIGUE SCALE v4.0 (Hide all fields in this section)
6.0	10 Jun 2020	PPD PPD	Addition of Coding Fields (Modified Term, MedDRA LLT Code, MedDRA Dictionary Synonym) for: Enrollment - Other Medication Enrollment - Other Medical Procedure/Surgery Follow-up – Other Medical Procedure/Surgery Hospitalization Log
7.0	27 Jul 2020	PPD	Addition of Follow-up Visit Tracker
8.0	27 May 2022	PPD PPD	<u>Enrollment Medical History Form:</u> Added help-text for Hospitalization [*Note: An admission for administration of medication or for routine or planned clinical procedures should not be considered a hospitalization.*] <u>Follow-up Visit Info Form:</u> Added help-text for Hospitalization Question [*Note: An admission for administration of medication or for routine or planned clinical procedures should not be considered a hospitalization.*] Replaced help-text for PSRQ Question: [*If YES, and the event is SERIOUS, please complete the SAE Form and PSRQ Form for each occurrence.*] <u>Follow-up General Medical Status Form:</u> For Auto-immune disorders, [Diabetes] corrected to [Type 1 Diabetes]

Enrollment **Patient ID:** **Created:** 27-May-2022 07:48:44 **Last Updated:** 27-May-2022 07:48:44

Legend: Clear Selection Show Warnings Show History

[+] Errors

Date of Enrollment: DD MMM YYYY

Date of Original SLE Diagnosis: DD-MMM-YYYY DD MMM YYYY

INCLUSION / EXCLUSION CRITERIA

Has the patient met all of the inclusion and exclusion criteria? Yes No

If No, please select all boxes corresponding to violations of any of the inclusion/exclusion criteria:

Inclusion Criteria

- 1. Males or females age 18 or older.
- 2. Have a clinical diagnosis of active SLE.
- 3. Current or history of autoantibody-positive SLE.
- 4. Must be treated with SLE therapy including BENLYSTA and/or immunosuppressant (e.g., azathioprine, methotrexate, cyclophosphamide, mycophenolate and biologics).
- 5. Have the ability to understand the requirements of the study, provide written informed consent, including consent for the use and disclosure of research-related health information, and comply with the study data collection procedures.

Exclusion Criteria

- 1. Treatment with an investigational drug within one year of enrollment. Investigational drug applies to any drug not approved for sale in the country in which it is being used.
- 2. Currently enrolled in a placebo-controlled BENLYSTA (belimumab) clinical trial or a continuation protocol where belimumab is used as an investigational agent.
- 3. Patient who has a history of BENLYSTA exposure, but is not currently receiving BENLYSTA.
- 4. Patient only receiving an anti-malarial for SLE.
- 5. Patient only receiving steroids for SLE.

DEMOGRAPHICS

Date of Birth: DD MMM YYYY

Sex: Male Female

Ethnicity: Hispanic or Latino Not Hispanic or Latino

Race (Select all that apply):

- White/Caucasian - European Heritage
- White/Caucasian - Middle Eastern/North African Heritage
- Asian - East Asian Heritage
- Asian - South East Asian Heritage
- Asian - Central/South Asian Heritage
- Asian - Japanese Heritage

- [ ] Black - African American or African Heritage
- [ ] Alaska Native or American Indian from North/Central/South America
- [ ] Native Hawaiian or Other Pacific Islander

CORTICOSTEROIDS

Please use the corticosteroid calculator located at http://www.globalrph.com/corticocalc.htm to convert all doses to an equivalent Prednisone dose.

Has the patient ever taken corticosteroids for SLE? *(If NO, go to next page)* ◯ Yes ◯ No

If YES, how long was the patient taking corticosteroids for SLE? _____ Year(s) _____ Month(s)

Is the patient currently taking corticosteroids for SLE? ◯ Yes ◯ No

If NO, please enter the date the patient stopped taking corticosteroids for SLE: DD-MMM-YYYY (DD MMM YYYY)

Has the patient taken any corticosteroids for SLE in the past 6 months? *(If NO, go to next page)* ◯ Yes ◯ No

If YES, please complete the following:

Average dose of all corticosteroids in the past 6 months (Include all routes of administration and convert all doses to an equivalent oral prednisone dose) _____ mg/day

In the past 6 months:

- ◯ Always < 7.5 mg/day
- ◯ >= 7.5 mg / day for <= 2 weeks
- ◯ >= 7.5 mg / day for > 2 weeks

The section below is to evaluate excursions above the daily dose in the past 6 months

If >= 7.5 mg/day for > 2 weeks is checked above , check which category best describes the highest average dosage excursion over 2 consecutive weeks in the past 6 months:

- ◯ >= 7.5 mg/day but < 20 mg/day
- ◯ >= 20 mg/day but < 40 mg/day
- ◯ >= 40 mg/day but < 60 mg/day
- ◯ >= 60 mg/day

- [ ] Parenteral: At least one dose of intravenous steroids (i.e., Solumedrol) >= 40 mg in the past 6 months.
- [ ] Intramuscular: At least one dose of intramuscular steroids >= 40 mg in the past 6 months.

LABORATORY VALUES

Date Collected	Laboratory Test Name	ND (No Results Available / Not Done)	Result	Due to SLE (if applicable)
DD-MMM-YYYY (DD MMM YYYY)	IgA	☐	<1>	
DD-MMM-YYYY (DD MMM YYYY)	IgM	☐	<1>	
DD-MMM-YYYY (DD MMM YYYY)	IgG	☐	<1>	
DD-MMM-YYYY (DD MMM YYYY)	ANA Status	☐	<2>	
DD-MMM-YYYY	Anti-ds DNA	☐		If Positive, is it due SLE?

DD MMM YYYY			<2>	Yes No
DD-MMM-YYYY DD MMM YYYY	C3		<1>	If Low, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	C4		<1>	If Low, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	CH50		<1>	If Low, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Lymphocyte Differential % / Count		<1>	
DD-MMM-YYYY DD MMM YYYY	Total White Blood Cell Count		<3> /mm^3	If < 3,000 / mm^3, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Neutrophil Differential Count		<4> /mm^3	
DD-MMM-YYYY DD MMM YYYY	Thrombocytopenia (< 100,000 platelets/10^9/L)		<2>	If Positive, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Urinary Casts (Heme-granular or red blood cell casts)		<2>	If Positive, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Hematuria (>5 red blood cells / high power field)		<2>	If Positive, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Proteinuria (>0.5 gm / 24 hours)		<2>	If Positive, is it due to SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Pyuria (>5 white blood cells / high power field)		<2>	If Positive, is it due to SLE? Yes No

Note: If unit conversion is required, please refer to the AMA Manual of Style located at:

http://www.amamanualofstyle.com/page/si-conversion-calculator

MODIFIED SLE FLARE INDEX

Did the subject experience a flare in the last 6 months? Yes No

If yes, please p

If multiple flares

Any increase in P

New cyclophosph
mycophenolate d

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Inpatient hospitalization due to SLE? Yes No

New/Worse of the below conditions due to SLE requiring doubling of prednisone to >0.5 mg/kg/day or hospitalization? Yes No

If yes, indicate the new/worse condition and the criteria (questions 1 and 2) which was met

Condition	Are any of the following New or Worse? (If yes, please answer questions 1 and 2)	1. Was doubling of Prednisone to > 0.5mg/ kg/day required for this condition?	2. Was hospitalization required for this condition?

Seizures	Yes No	Yes No	Yes No
Psychosis	Yes No	Yes No	Yes No
Organic Brain Syndrome	Yes No	Yes No	Yes No
Visual Disturbance	Yes No	Yes No	Yes No
Cranial Nerve Disorder	Yes No	Yes No	Yes No
Lupus Headach			
CVA			
Other CNS-SLE			
Vasculitis			
Nephritis	Yes No	Yes No	Yes No
Myositis	Yes No	Yes No	Yes No
Hemolytic Anemia with Hb < 70g/L or decrease in Hb > 30g/L	Yes No	Yes No	Yes No
Platelets <60,000 /10^9/L	Yes No	Yes No	Yes No

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Done | Delete Entry

Create Next Entry

Height: cm

Weight: kg

Was the patient hospitalized within the previous 6 months? Yes No

If YES, complete the Hospitalization Log Form
Note: An admission for administration of medication or for routine or planned clinical procedures should not be considered a hospitalization.

Does the patient have a history of alcohol abuse? Yes No

TOBACCO HISTORY

1. History of all tobacco use:
   - Never used
   - Current user
   - Former user

2. History of smoking use:
   - Never used
   - Current user
   - Former user

   Average number of cigarettes smoked per day*:

3. History of smokeless tobacco use:
   - Never used
   - Current user
   - Former user

4. Total number of years smoked: years

5. Total number of years used tobacco (smoking and smokeless): years

**1 cigar = 7 cigarettes*

1 gram (or 0.03 oz.) of tobacco = 1 cigarette

PREGNANCY

Is the patient pregnant? ◯ Yes ◯ No

Parity:

(Gravida)	(Para)	(Full-Term)	(Pre-Term)	(Spontaneous Miscarriage)	(Elective Abort

Is the patient taking oral contraceptives? ◯ Yes ◯ No

Is the patient menopausal? ◯ Yes ◯ No

If Yes, is the patient on hormone replacement therapy? ◯ Yes ◯ No

GENERAL MEDICAL HISTORY

Does the patient currently or historically have a relevant diagnosis or medical condition other than SLE? ◯ Yes ◯ No

If Yes, please specify below:

CARDIOVASCULAR RISK FACTORS	
	Status
Angina Pectoris:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Myocardial Infarction:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Stroke:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Diabetes:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Hypertension:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Hyperlipidemia:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Thromboembolic Event:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed

ALLERGIC REACTIONS	
	Status
Food Allergy:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Drug Allergy:	◯ Current ◯ Past ◯ No Medical Condition ◯ Not Assessed
Hypersensitivity:	◯ Current ◯ Past

	○ No Medical Condition ○ Not Assessed
Infusion-Related Reaction:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

RESPIRATORY DISORDERS	
	Status
Interstitial Lung Disease:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Chronic Obstructive Pulmonary Disease:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

INFECTION	
	Status
Cellulitis:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Fungal Infection:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Herpes Virus Infection:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Respiratory Tract Infection:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Opportunistic Infection:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Sepsis:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Hepatitis B:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Hepatitis C:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
HIV Infection:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Active Tuberculosis:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Latent Tuberculosis:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

AUTO-IMMUNE DISORDERS	
	Status
Asthma:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Celiac Disease:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Type I Diabetes:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Sjorgren's Syndrome:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

IMMUNE SYSTEM DISORDERS	
	Status
Hypogammaglobulinaemia:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

NEOPLASMS: Benign, Malignant and Unspecified (including cysts and polyps)	
	Status
Cancer:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Non-Melanoma Skin Cancer:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Family History of Cancer:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

RENAL and URINARY DISORDERS	
	Status
End Stage Renal Failure:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

BLOOD and LYMPHATIC SYSTEM DISORDERS	
	Status
Neutropenia:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

PSYCHIATRIC DISORDERS

	Status
Depression:	Current Past No Medical Condition Not Assessed
Anxiety Disorder:	Current Past No Medical Condition Not Assessed
Suicidal Ideation:	Current Past No Medical Condition Not Assessed
Suicidal Depression:	Current Past No Medical Condition Not Assessed
Suicidal Behavior:	Current Past No Medical Condition Not Assessed
Attempted Suicide:	Current Past No Medical Condition Not Assessed

OTHER MEDICAL CONDITIONS

Form Name:

Medical Condition Sequence:

	Status
If Other, specify: Modified term: MedDRA lower level term code: MedDRA dictionary synonym:	Current Past

Done Delete Entry

Create Next Other Medical Condition

Medical Procedure/Surgery	Has the Patient had Procedure/Surgery	Date
Dialysis:	Yes No	DD-MMM-YYYY DD MMM YYYY
Transplant:	Yes No	DD-MMM-YYYY DD MMM YYYY
Splenectomy:	Yes No	DD-MMM-YYYY DD MMM YYYY

Form Name:

Surgical History Sequence:

Other, specify: Modified term:	Yes No	DD-MMM-YYYY DD MMM YYYY

MedDRA lower level term code:

MedDRA dictionary synonym:

Done | Delete Entry

Create Next Other Surgery/Procedure

VACCINATIONS

Has the patient received any of the following vaccinations? ◯ Yes ◯ No

Please select all relevant vaccinations.

<5> Specify:

Done | Delete Entry

Create Next Entry

SLEDAI 2000

Date of Assessment: DD - MMM - YYYY

Check box if descriptor is present at the time of visit or in the preceding month.

Weight	Check if Present	Check if Not Done* (for select items only)	Descriptor	Defintion
8	☐		Seizure	Recent onset, exclude metabolic, infectious or drug cause.
8	☐		Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.
8	☐		Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐		Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection or drug causes.
8	☐		Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐		Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	☐		CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	☐		Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐		Arthritis	> 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4			Myositis	Proximal muscle aching/weakness associated with

	☐			elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	○	○ Not Done	Urinary Casts	Heme-granular or red blood cell casts.
4	○	○ Not Done	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	○	○ Not Done	Proteinuria	> 0.5 gm/24 hours.
4	○	○ Not Done	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	☐		Rash	Inflammatory type rash.
2	☐		Alopecia	Abnormal, patchy or diffuse loss of hair.
2	☐		Mucosal Ulcers	Oral or nasal ulcerations.
2	☐		Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening.
2	☐		Pericarditis	Pericardial pain with at least 1 of the following: rub, effusion or electrocardiogram or echocardiogram confirmation.
2	○	○ Not Done	Low Complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
2	○	○ Not Done	Increased DNA Binding	Increased DNA Binding by FARR assay above normal range for testing laboratory.
1	☐		Fever	>38 degrees C (38^{o} C). Exclude infectious cause.
1	○	○ Not Done	Thrombocytopenia	<100,000 platelets/ x 10^{9}/L, exclude drug causes.
1	○	○ Not Done	Leukopenia	<3,000 white blood cells/ x 10^{9}/L, exclude drug causes.
	TOTAL SCORE *(Sum of weights next to descriptors marked present)*			

* Not Done is only available for the following assessments: Urinary Casts, Hematuria, Proteinuria, Pyuria, Low Complement, Increased DNA Binding, Fever, Thrombocytopenia and Leukopenia.

Adapted from the original source: Dafna D Gladman, Dominique Ibanez and Murray B Urowitz, Systemic lupus erythematosus disease activity index 2000. *J Rheumatol 2002;29;288-291.*

SLICC/ACR DAMAGE INDEX (SDI)

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Date of Assessment: DD - MMM - YYYY

Item	Score
Ocular (Either eye, by clinical assessment)	
Any cataract ever	○ 0 ○ 1
Retinal change OR optic atrophy	○ 0 ○ 1
Neuropsychiatric	
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR major psychosis	○ 0 ○ 1
Seizures requiring therapy for 6 months	○ 0 ○ 1
Cerebral vascular accident ever (Score 2 if >1)	○ 0 ○ 1 ○ 2
Cranial OR peripheral neuropathy (excluding optic)	○ 0 ○ 1
Transverse myelitis	○ 0 ○ 1

Renal	
Estimated or measured GFR < 50%	○ 0 ○ 1
Proteinuria > 3.5 g /24 hours	○ 0 ○ 1
OR	
End-stage renal disease (regardless of dialysis or transplantation)	○ 0 ○ 3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	○ 0 ○ 1
Pulmonary fibrosis (physical and radiograph)	○ 0 ○ 1
Shrinking lung (radiograph)	○ 0 ○ 1
Pleural fibrosis (radiograph)	○ 0 ○ 1
Pulmonary infarction (radiograph)	○ 0 ○ 1
Cardiovascular	
Angina OR coronary artery bypass	○ 0 ○ 1
Myocardial infarction ever (score 2 if > 1)	○ 0 ○ 1 ○ 2
Cardiomyopathy (Ventricular dysfunction)	○ 0 ○ 1
Valvular disease (diastolic murmur, or a systolic murmur > 3/6)	○ 0 ○ 1
Pericarditis x 6 months OR pericardiectomy	○ 0 ○ 1
Periperhal Vascular	
Claudication x 6 months	○ 0 ○ 1
Minor tissue loss (pulp space)	○ 0 ○ 1
Significant tissue loss ever (e.g. loss of digit or limb) (Score 2 if > one site)	○ 0 ○ 1 ○ 2
Venous thrombosis with swelling, ulceration, OR venous stasis	○ 0 ○ 1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver or gall bladder ever, for whatever cause (score 2 if > one site)	○ 0 ○ 1 ○ 2
Mesenteric insufficiency	○ 0 ○ 1
Chronic peritonitis	○ 0 ○ 1
Stricture OR upper gastrointestinal tract surgery ever	○ 0 ○ 1
Musculoskeletal	
Muscle atrophy or weakness	○ 0 ○ 1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	○ 0 ○ 1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	○ 0 ○ 1
Avascular necrosis (score 2 if > 1)	○ 0 ○ 1 ○ 2
Osteomyelitis	○ 0 ○ 1
Skin	
Scarring chronic alopecia	○ 0 ○ 1
Extensive scarring of panniculum other than scalp and pulp space	○ 0 ○ 1
Skin ulceration (not due to thrombosis) for more than 6 months	○ 0 ○ 1
Premature gonadal failure	○ 0 ○ 1
Diabetes (regardless of treatment)	○ 0 ○ 1
Malignancy (exclude dysplasia) (score 2 if > one site)	○ 0 ○ 1 ○ 2
TOTAL SCORE *(Sum of weighted value for all checked items)*	

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)

Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996a;39(3):363-9.

SF-12

Please use Pre-Printed Forms Included in the Investigator Study Package to Complete the SF-12 Questionnaire

Date of Assessment DD MMM YYYY ☐ Assessment Not Done

Language code: <6>

1. In general, w

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:
- ◯ Yes, limited a lot
- ◯ Yes, limited a little
- ◯ No, not limited at all

b. Climbing several flights of stairs:
- ◯ Yes, limited a lot
- ◯ Yes, limited a little
- ◯ No, not limited at all

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Accomplished less than you would like:
- ◯ All of the time
- ◯ Most of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

b. Were limited in the kind of work or other activities:
- ◯ All of the time
- ◯ Most of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Accomplished less than you would like:
- ◯ All of the time
- ◯ Most of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

b. Did work or other activities less carefully than usual:
- ◯ All of the time
- ◯ Most of the time
- ◯ Some of the time
- ◯ A little of the time
- ◯ None of the time

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?
- ◯ Not at all

- A little bit
- Moderately
- Quite a bit
- Extremely

6. These questi… question, please give the …

How much of th…

a. Have you fe…

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

- Some of the time
- A little of the time
- None of the time

b. Did you have a lot of energy?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

c. Have you felt downhearted and depressed?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

FACIT FATIGUE SCALE v4.0

Please use Pre-Printed Forms Included in the Investigator Study Package to Complete the FACIT-Fatigue Scale v4.0

Date of Assessment DD - MMM - YYYY ☐ Assessment Not Done

Language code: <7>

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

						Very much
HI7	I feel fat…					○ 4
HI12	I feel we…					○ 4
An1	I feel listless (''washed out'')	○ 0	○ 1	○ 2	○ 3	○ 4
An2	I feel tired	○ 0	○ 1	○ 2	○ 3	○ 4
An3	I have trouble starting things because I am tired	○ 0	○ 1	○ 2	○ 3	○ 4
An4	I have trouble finishing things because I am tired	○ 0	○ 1	○ 2	○ 3	○ 4
An5	I have energy	○ 0	○ 1	○ 2	○ 3	○ 4

An7	I am able to do my usual activities	0	1	2	3	4
An8	I need t					4
An12	I am to					4
An14	I need h					4
An15	I am fru to do					4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Please indicate the current status of the form: ○ Complete ◉ Incomplete

☐ **Sign Form** Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for Enrollment

<1> - IgA Result , IgM Result , IgG Result , C3 Result , C4 Result , CH50 Result , Lymphocyte Differential Result
Low
Normal
High

<2> - ANA Status Result , Anti-ds DNA Result , Thrombocytopenia Result , Urinary Casts Result , Hematuria Result , Proteinuria Result , Pyuria Result
Positive
Negative

<3> - Total White Blood Cell Count Result
< 2,000
2,000 - 2,999
3,000 - 3,999
>= 4,000

<4> - Neutrophil Differential Result
< 1,000
1,000 - 1,999
>= 2,000

<5> - Vaccination Status
BCG
Pneumococcal
Influenza
Human papillomavirus (HPV)
Hepatitis A
Hepatitis B
Varicella zoster
Other vaccination

<6> - SF-12 Language Code - Enrollment
Afrikaans
Arabic
Australian languages
Bengali
Bantu languages
Bosnian
Bulgarian
Catalan; Valencian
Cebuano
Chinese

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Czech
Danish
Dutch; Flemish
English
Estonian
Finnish
French
Georgian
German
Greek, modern (1453-)
Alemanic; Swiss German; Alsatian
Gujarati
Hebrew
Hiligaynon
Hindi
Croatian
Hungarian
Icelandic
Indonesian
Italian
Japanese
Kannada
Central Khmer
Korean
Latvian
Lithuanian
Macedonian
Malayalam
Marathi
Malay
Mandar
Ndebele, South
Ndebele, North
Norwegian
Pedi; Sepedi; Northern Sotho
Panjabi; Punjabi
Philippine languages
Polish
Portuguese
Romanian
Russian
Slovak
Slovenian
Sotho, Southern (Sesotho)
Spanish
Serbian
Swati
Swedish
Tamil
Telugu
Tagalog
Thai
Turkish
Ukrainian
Urdu
Vietnamese
Xhosa
Zulu

<7> - Facit-Fatigue Language Code

Afrikaans
Arabic
Australian languages
Bengali
Bantu languages
Bosnian
Bulgarian
Catalan; Valencian
Cebuano
Chinese
Czech
Danish
Dutch; Flemish

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

English
Estonian
Finnish
French
Georgian
German
Greek, modern (1453-)
Alemanic; Swiss German; Alsatian
Gujarati
Hebrew
Hiligaynon
Hindi
Croatian
Hungarian
Icelandic
Indonesian
Italian
Japanese
Kannada
Central Khmer
Korean
Latvian
Lithuanian
Macedonian
Malayalam
Marathi
Malay
Mandar
Ndebele, South
Ndebele, North
Norwegian
Pedi; Sepedi; Northern Sotho
Panjabi; Punjabi
Philippine languages
Polish
Portuguese
Romanian
Russian
Slovak
Slovenian
Sotho, Southern (Sesotho)
Spanish
Serbian
Swati
Swedish
Tamil
Telugu
Tagalog
Turkish
Thai
Ukrainian
Urdu
Vietnamese
Xhosa
Zulu

Follow-Up **Patient ID:** **Created:** 27-May-2022 07:48:48 **Last Updated:** 27-May-2022 07:48:48

Legend: Clear Selection Show Warnings Show History

[+] Errors

Visit Info | SLICC/ACR (SDI) | Corticosteroids | Labs | Medical Status | General Medical Status | Tobacco Use | Vaccinations | SLE Flare | SLEDAI 2000 | SF-12 | FACIT-Fatigue

Visit Date: DD MMM YYYY

Visit ID <1>

VISIT INFO

Was the patient hospitalized since the last visit? Yes No

If YES, please complete the Hospitalization Log Form for each occurrence.
Note: An admission for administration of medication or for routine or planned clinical procedures should not be considered a hospitalization.

Has the patient experienced a Serious Adverse Event of Special Interest (SAE-SI) since the last visit? Yes No

If YES, please complete the Serious Adverse Event of Special Interest Form for each occurrence.

Has the patient experienced a Non-Serious Adverse Event of Special Interest (AESI) since the last visit? Yes No

If YES, please complete the Non-Serious Adverse Event of Special Interest Form for each occurrence.

Has the patient experienced a Possible Suicidality-Related Event since the last visit? Yes No

If YES, and the event is SERIOUS, please complete the SAE Form and PSRQ Form for each occurrence.

SLICC/ACR DAMAGE INDEX (SDI)

System Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus

Date of Assessment: DD MMM YYYY

Item	Score
Ocular (Either eye, by clinical assessment)	
Any cataract ever	0 1
Retinal change OR optic atrophy	0 1
Neuropsychiatric	
Cognitive impairment (e.g. memory deficit, difficulty with calculation, poor concentration, difficulty in spoken or written language, impaired performance level) OR major psychosis	0 1
Seizures requiring therapy for 6 months	0 1
Cerebral vascular accident ever (Score 2 if >1)	0 1 2
Cranial OR peripheral neuropathy (excluding optic)	0 1
Transverse myelitis	0 1
Renal	
Estimated or measured GFR < 50%	0 1
Proteinuria > 3.5 g /24 hours	0 1
OR	

End-stage renal disease (regardless of dialysis or transplantation)	○ 0 ○ 3
Pulmonary	
Pulmonary hypertension (right ventricular prominence, or loud P2)	○ 0 ○ 1
Pulmonary fibrosis (physical and radiograph)	○ 0 ○ 1
Shrinking lung (radiograph)	○ 0 ○ 1
Pleural fibrosis (radiograph)	○ 0 ○ 1
Pulmonary infarction (radiograph)	○ 0 ○ 1
Cardiovascular	
Angina OR coronary artery bypass	○ 0 ○ 1
Myocardial infarction ever (score 2 if > 1)	○ 0 ○ 1 ○ 2
Cardiomyopathy (Ventricular dysfunction)	○ 0 ○ 1
Valvular disease (diastolic murmur, or a systolic murmur > 3/6)	○ 0 ○ 1
Pericarditis x 6 months OR pericardiectomy	○ 0 ○ 1
Periperhal Vascular	
Claudication x 6 months	○ 0 ○ 1
Minor tissue loss (pulp space)	○ 0 ○ 1
Significant tissue loss ever (e.g. loss of digit or limb) (Score 2 if > one site)	○ 0 ○ 1 ○ 2
Venous thrombosis with swelling, ulceration, OR venous stasis	○ 0 ○ 1
Gastrointestinal	
Infarction or resection of bowel below duodenum, spleen, liver or gall bladder ever, for whatever cause (score 2 if > one site)	○ 0 ○ 1 ○ 2
Mesenteric insufficiency	○ 0 ○ 1
Chronic peritonitis	○ 0 ○ 1
Stricture OR upper gastrointestinal tract surgery ever	○ 0 ○ 1
Musculoskeletal	
Muscle atrophy or weakness	○ 0 ○ 1
Deforming or erosive arthritis (including reducible deformities, excluding avascular necrosis)	○ 0 ○ 1
Osteoporosis with fracture or vertebral collapse (excluding avascular necrosis)	○ 0 ○ 1
Avascular necrosis (score 2 if > 1)	○ 0 ○ 1 ○ 2
Osteomyelitis	○ 0 ○ 1
Skin	
Scarring chronic alopecia	○ 0 ○ 1
Extensive scarring of panniculum other than scalp and pulp space	○ 0 ○ 1
Skin ulceration (not due to thrombosis) for more than 6 months	○ 0 ○ 1
Premature gonadal failure	○ 0 ○ 1
Diabetes (regardless of treatment)	○ 0 ○ 1
Malignancy (exclude dysplasia) (score 2 if > one site)	○ 0 ○ 1 ○ 2
TOTAL SCORE *(Sum of weighted value for all checked items)*	

(From the Systemic Lupus International Collaborating Clinics (SLICC) and the American College of Rheumatology Diagnostic and Therapeutic Criteria Committee, 1996)

Gladman EM, Ginzler E, Goldsmith C et al. SLICC/ACR damage index for SLE. Arthritis Rheum 1996a;39(3):363-9.

CORTICOSTEROIDS

Please use the corticosteroid calculator located at http://www.globalrph.com/corticocalc.htm to convert all doses to an equivalent Prednisone dose.

Has the patient taken any corticosteroids for SLE since the last visit? ◯ Yes ◯ No
(If NO, go to next page)

If YES, please complete the following:

Average dose of all corticosteroids since last visit _____ mg/day
(Include all routes of administration and convert all doses to an equivalent oral prednisone dose)

Since last visit:

- ◯ Always < 7.5 mg/day
- ◯ >= 7.5 mg / day for <= 2 weeks
- ◯ > =7.5 mg / day for > 2 weeks

The section below is to evaluate excursions above the daily dose since last visit

If >= 7.5 mg/day for > 2 weeks is checked above , check which category best describes the highest average dosage excursion over 2 consecutive weeks since last visit:

- ◯ >= 7.5 mg/day but < 20 mg/day
- ◯ >= 20 mg/day but < 40 mg/day
- ◯ >= 40 mg/day but < 60 mg/day
- ◯ >= 60 mg/day

☐ Parenteral: At least one dose of intravenous steroids (i.e., Solumedrol) >= 40 mg since last visit

☐ Intramuscular: At least one dose of intramuscular steroids >= 40 mg since last visit

LABORATORY VALUES

Date Collected	Laboratory Test Name	ND (No Results Available / Not Done)	Result	Due to SLE (if applicable)
DD-MMM-YYYY				
DD-MMM-YYYY				
DD-MMM-YYYY	IgG	☐	<2>	
DD-MMM-YYYY	ANA Status	☐	<3>	
DD-MMM-YYYY	Anti-ds DNA	☐	<3>	If Positive, is it due SLE? ◯ Yes ◯ No
DD-MMM-YYYY	C3	☐	<2>	If Low, is it due SLE? ◯ Yes ◯ No
DD-MMM-YYYY	C4	☐	<2>	If Low, is it due SLE? ◯ Yes ◯ No
DD-MMM-YYYY	CH50	☐	<2>	If Low, is it due SLE? ◯ Yes ◯ No
DD-MMM-YYYY	Lymphocyte Differential % / Count	☐	<2>	
DD-MMM-YYYY	Total White Blood Cell Count	☐		If < 3,000 / mm^3, is it

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

DD MMM YYYY			<4> /mm^3	due SLE? Yes No
DD-MMM-YYY DD MMM				
DD-MMM-YYY DD MMM				s it due SLE? No
DD-MMM-YYYY DD MMM YYYY	Urinary Casts (Heme-granular or red blood cell casts)	☐	<3>	If Positive, is it due SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Hematuria (>5 red blood cells / high power field)	☐	<3>	If Positive, is it due SLE? Yes Noi
DD-MMM-YYYY DD MMM YYYY	Proteinuria (>0.5 gm / 24 hours)	☐	<3>	If Positive, is it due SLE? Yes No
DD-MMM-YYYY DD MMM YYYY	Pyuria (>5 white blood cells / high power field)	☐	<3>	If Positive, is it due SLE? Yes No

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Note: If unit conversion is required, please refer to the AMA Manual of Style located at:

http://www.amamanualofstyle.com/page/si-conversion-calculator

Current Weight: kg

Has the patient developed an alcohol problem since the Enrollment visit? Yes No

PREGNANCY

Has the patient gott

Parity:

(G

(Spontaneou

Is the patient takin

Is the patient menc

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

If Yes, is the patient on hormone replacement therapy?

GENERAL MEDICAL STATUS

Please indicate whether the patient's status for any of the following items has changed since it was last reported.

NEOPLASMS: Benign, Malignant and Unspecified (including cysts and polyps)	
	Status
Family History of Cancer:	Current Past No Medical Condition Not Assessed
INFECTION	
	Status
Hepatitis B:	Current Past No Medical Condition Not Assessed

Hepatitis C:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
HIV Infection:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

AUTO-IMMUNE DISORDERS	
	Status
Type I Diabetes:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed
Sjorgren's Syndrome:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

BLOOD and LYMPHATIC SYSTEM DISORDERS	
	Status
Neutropenia:	○ Current ○ Past ○ No Medical Condition ○ Not Assessed

MEDICAL PROCEDURE/SURGERY	Has the Patient had Procedure/Surgery	Date
Dialysis:	○ Yes ○ No	DD-MMM-YYYY (DD MMM YYYY)
Post-Transplant (any transplant):	○ Yes ○ No	DD-MMM-YYYY (DD MMM YYYY)
Splenectomy:	○ Yes ○ No	DD-MMM-YYYY (DD MMM YYYY)

Form Name:

Surgical History Sequence:

Other, specify: Modified term: MedDRA lower level term code: MedDRA dictionary synonym:	○ Yes ○ No	DD-MMM-YYYY (DD MMM YYYY)

Done | Delete Entry

Create Next Other Surgery/Procedure

TOBACCO USE

Has the subject smoked since

If yes, average number of ciga

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Has the subject used smokeles

*1 cigar = 7 cigarettes

1 gram (or 0.03 oz.) of tobacc

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

VACCINATIONS

Please indicate whether the patient's status for any of the following vaccinations has changed since it was last

Has the patient

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

No

Please select all

Date of vaccination DD-MMM-YYYY

DD MMM YYYY

Done Delete Entry

Create Next Entry

MODIFIED SLE FLARE INDEX

Did the subject experience a flare since last vist? Yes No

If yes, please pr

If multiple flares

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Any increase in Pr

New cyclophospha
mycophenolate du

Inpatient hospitalization due to SLE? Yes No

New/Worse of the below conditions due to SLE requiring doubling Yes No of prednisone to >0.5 mg/kg/day or hospitalization? Yes No

If yes, indicate the new/worse condition and the criteria (questions 1 and 2) which was met

Condition	Are any of the following New or Worse? (If yes, please answer questions 1 and 2)	1. Was doubling of Prednisone to > 0.5mg/ kg/day required for this condition?	2. Was hospitalization required for this condition?
Seizures	Yes No	Yes No	Yes No
Psychosis	Yes No	Yes No	Yes No
Organic Brain Syndrome	Yes No	Yes No	Yes No
Visual Disturbance	Yes No	Yes No	Yes No
Cranial Nerve Disorder	Yes No	Yes No	Yes No
Lupus Headache	Yes No	Yes No	Yes No
CVA	Yes No	Yes No	Yes No
Other CNS-SLE	Yes No	Yes No	Yes No
Vasculitis	Yes No	Yes No	Yes No
Nephritis	Yes No	Yes No	Yes No
Myositis	Yes No	Yes No	Yes No
Hemolytic Anemia with Hb < 70g/L or decrease in Hb > 30g/L	Yes No	Yes No	Yes No

Platelets <60,000 /10^9/L	Yes No	Yes No	Yes No	

Done | Delete Entry

Create Next Entry

SLEDAI 2000

Date of Assessment: DD - MMM - YYYY

Check box if descriptor is present at the time of visit or in the preceding month.

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

Weight				
8				ous or drug cause.
8	☐		Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized or catatonic behavior. Exclude uremia and drug causes.
8	☐		Organic Brain Syndrome	Altered mental function with impaired orientation, memory or other intellectual function with rapid onset and fluctuating clinical features. Include clouding of consciousness with reduced capacity to focus and inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	☐		Visual Disturbance	Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroids, or optic neuritis. Exclude hypertension, infection or drug causes.
8	☐		Cranial Nerve Disorder	New onset of sensory or motor neuropathy involving cranial nerves. Include vertigo due to lupus.
8	☐		Lupus Headache	Severe persistent headache: may be migrainous, but must be non-responsive to narcotic analgesia.
8	☐		CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis.
8	☐		Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	☐		Arthritis	> 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	☐		Myositis	Proximal muscle aching/weakness associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	Present	Not Done	Urinary Casts	Heme-granular or red blood cell casts.
4	Present	Not Done	Hematuria	>5 red blood cells/high power field. Exclude stone, infection or other cause.
4	Present	Not Done	Proteinuria	> 0.5 gm/24 hours.
4	Present	Not Done	Pyuria	> 5 white blood cells/high power field. Exclude infection.
2	☐		Rash	Inflammatory type rash.

2	☐		Alopecia	Abnormal, patchy or diffuse loss of hair.
2			Mucosal Ulcers	Oral or nasal ulcerations
2				or effusion, or
2				ne following: or
2	○ Present	○ Not Done	Low Complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
2	○ Present	○ Not Done	Increased DNA Binding	Increased DNA Binding by FARR assay above normal range for testing laboratory.
1	☐		Fever	>38 degrees C (38^{o} C). Exclude infectious cause.
1	○ Present	○ Not Done	Thrombocytopenia	<100,000 platelets/ x 10^{9}/L, exclude drug causes.
1	○ Present	○ Not Done	Leukopenia	<3,000 white blood cells/ x 10^{9}/L, exclude drug causes.
	TOTAL SCORE *(Sum of weights next to descriptors marked present)*			

* Not Done is only available for the following assessments: Urinary Casts, Hematuria, Proteinuria, Pyuria, Low Complement, Increased DNA Binding, Fever, Thrombocytopenia and Leukopenia.

Adapted from the original source: Dafna D Gladman, Dominique Ibanez and Murray B Urowitz, Systemic lupus erythematosus disease activity index 2000. *J Rheumatol 2002;29;288-291.*

SF-12

Please use Pre-Printed Forms Included in the Investigator Study Package to Complete the SF-12 Questionnaire

Date of Assessment

Language code:

1. In general, w

○ Excellent
○ Very Good
○ Good
○ Fair
○ Poor

2. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?

a. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf:

○ Yes, limited a lot
○ Yes, limited a little
○ No, not limited at all

b. Climbing several flights of stairs:

○ Yes, limited a lot
○ Yes, limited a little
○ No, not limited at all

3. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

a. Accomplished less than you would like:

○ All of the time

- Most of the time
- Some of the time
- A little of the time
- None of the time

PAGE NOT EFFECTIVE
FROM 18-JUL-2018

b. Were limite

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

a. Accomplished less than you would like:

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

b. Did work or other activities less carefully than usual:

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

5. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

- Not at all
- A little bit
- Moderately
- Quite a bit
- Extremely

6. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the past 4 weeks...

a. Have you felt calm and peaceful?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

b. Did you have a lot of energy?

- All of the time
- Most of the time
- Some of the time
- A little of

						the time
						None of the time
c. Have you	PAGE NOT EFFECTIVE FROM 18-JUL-2018					All of the time
						Most of the time
						Some of the time
						A little of the time
						None of the time

7. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?

- All of the time
- Most of the time
- Some of the time
- A little of the time
- None of the time

FACIT FATIGUE SCALE v4.0

Please use Pre-Printed Forms Included in the Investigator Study Package to Complete the FACIT-Fatigue Scale v4.0

Date of Assess

Language code

PAGE NOT EFFECTIVE FROM 18-JUL-2018

		0	1	2	3	a **Very much** 4
HI7	I feel fatigued	◯	◯	◯	◯	◯
HI12	I feel weak all over	◯	◯	◯	◯	◯
An1	I feel listless (''washed out'')	◯	◯	◯	◯	◯
An2	I feel tired	◯	◯	◯	◯	◯
An3	I have trouble starting things because I am tired	◯	◯	◯	◯	◯
An4	I have trouble finishing things because I am tired	◯	◯	◯	◯	◯
An5	I have energy	◯	◯	◯	◯	◯
An7	I am able to do my usual activities	◯	◯	◯	◯	◯
An8	I need to sleep during the day	◯	◯	◯	◯	◯
An12	I am too tired to eat	◯	◯	◯	◯	◯
An14	I need help doing my usual activities	◯	◯	◯	◯	◯
An15	I am frustrated by being too tired to do the things I want to do	◯	◯	◯	◯	◯
An16	I have to limit my social activity because I am tired	◯	◯	◯	◯	◯

Please indicate the current status of the form: ○ Complete ◉ Incomplete

☐ **Sign Form** Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for Follow-Up

<1> - Follow-Up Visit ID
6 Month
12 Month
18 Month
24 Month
30 Month
36 Month
42 Month
48 Month
54 Month
60 Month

<2> - IgA Result , IgM Result , IgG Result , C3 Result , C4 Result , CH50 Result , Lymphocyte Differential Result
Low
Normal
High

<3> - ANA Status Result , Anti-ds DNA Result , Thrombocytopenia Result , Urinary Casts Result , Hematuria Result , Proteinuria Result , Pyuria Result
Positive
Negative

<4> - Total White Blood Cell Count Result
< 2,000
2,000 - 2,999
3,000 - 3,999
>= 4,000

<5> - Neutrophil Differential Result
< 1,000
1,000 - 1,999
>= 2,000

<6> - Vaccination Status
BCG
Pneumococcal
Influenza
Human papillomavirus (HPV)
Hepatitis A
Hepatitis B
Varicella zoster
Other vaccination

<7> - SF-12 Language Code - Follow-Up , Facit-Fatigue Language Code
Afrikaans
Arabic
Australian languages
Bengali
Bantu languages
Bosnian
Bulgarian
Catalan; Valencian
Cebuano
Chinese
Czech
Danish
Dutch; Flemish

English
Estonian
Finnish
French
Georgian
German
Greek, modern (1453-)
Alemanic; Swiss German; A
Gujarati
Hebrew
Hiligaynon
Hindi
Croatian
Hungarian
Icelandic
Indonesian
Italian
Japanese
Kannada
Central Khmer
Korean
Latvian
Lithuanian
Macedonian
Malayalam
Marathi
Malay
Mandar
Ndebele, South
Ndebele, North
Norwegian
Pedi; Sepedi; Northern Sotho
Panjabi; Punjabi
Philippine languages
Polish
Portuguese
Romanian
Russian
Slovak
Slovenian
Sotho, Southern (Sesotho)
Spanish
Serbian
Swati
Swedish
Tamil
Telugu
Tagalog
Thai
Turkish
Ukrainian
Urdu
Vietnamese
Xhosa
Zulu

Serious Adverse Event **Patient ID:** **Created:** 27-May-2022 07:48:53 **Last Updated:** 27-May-2022 07:48:53

Legend: Clear Selection Show Warnings Show History

[+] Errors

SERIOUS ADVERSE EVENT of SPECIAL INTEREST (SAE-SI)

Information regarding the collection of Adverse Events can be found in the Study Protocol, Section 7 and Appendices 1 and 2. Please review these guidelines for a list of the Events of Special Interest that are to be reported through this registry. Other Adverse Events (including Serious Adverse Events) not collected as AESIs in this registry should be reported in accordance with the laws and regulations for marketed products in the country where the event occurred.

Event: (Diagnosis only if known, otherwise Sign/Symptom) Please include only one event term per SAE form. If multiple events, complete a new form for each.

Modified term:

MedDRA lower level term code:

MedDRA dictionary synonym:

SAE Sequence Number:

SAE Start Date and Time: DD-MMM-YYYY HH24:MI
DD MMM YYYY HH MI

Outcome: Please complete End of Study Form if Outcome = Fatal <1>

SAE Stop Date and Time:
(Date of Death, if Outcome = Fatal)
DD MMM YYYY HH MI

Maximum Intensity: Record maximum intensity throughout duration of event. <2>

Action Taken with current SLE therapy as a Result of SAE: <3>

Did the patient withdraw from the study as a result of this SAE? (If YES, please complete the End of Study form) Yes No

Is there a reasonable possibility that the SAE may have been caused by current SLE therapy? Use best judgment at initial entry. May be amended when additional information becomes available. Yes No

If Yes, please specify which therapy:
(Select all that apply)

- BENLYSTA
- Anti-Malarials
- Azathioprine
- Corticosteroid
- Mycophenolate Mofetil
- Methotrexate
- Oral Cyclophosphamide
- IV Cyclophosphamide
- Calcineurin Inhibitor
- Rituximab
- TNF Alpha-Blockers
- Abatacept
- Tocilizumab
- Leflunomide
- Sirolimus
- Other

Was the SAE caused by activities related to study participation other than current SLE therapy (e.g., procedures, blood draws, washout, etc.)? Yes No

Seriousness: <4>

Specify:

Where any relevant concomitant medications taken? (Include details of any medication that may help explain the SAE, may have caused the SAE or was used to treat the SAE.) Yes No

Concomitant Medications

Form Name:

AE Sequence:

ConMeds Unique ID Number:

Medication Name:
(Trade name preferred)

(Synonym)

(Modified Term)

(Collection code)

Dose: Units: <5>

Frequency: Route: <6>

Start Date: DD-MMM-YYYY DD MMM YYYY Stop Date: DD-MMM-YYYY DD MMM YYYY Ongoing

Primary Indication:
(Please enter a medical diagnosis, not a description)

Drug Type: Concomitant Treatment Cause of SAE

Done Delete Entry

Create Next Concomitant Medications

Were there any diagnostic tests performed that may be relevant to this SAE? (If YES, please list all diagnostic tests below) Yes No

Diagnostic Test

Form Name:

AE Sequence:

Diagnostic Test Unique ID Number:

Diagnostic Test Name:

Diagnostic Test Result:

Diagnostic Test Date: DD-MMM-YYYY DD MMM YYYY Diagnostic Test Units:

Normal Low Range: Normal High Range:

Relevant Diagnostics Results not noted above:

Done Delete Entry

Create Next Diagnostic Test

Were there any medical conditions that may be relevant to this SAE? (If YES, please list all medical conditions below) Yes No

Medical Condition Repeat Group

Form Name:

AE Sequence:

Medical Condition Unique ID Number:

Specific Condition Name:
(Please enter a medical diagnosis, not a description)

Start Date: DD-MMM-YYYY DD MMM YYYY Stop Date: DD-MMM-YYYY DD MMM YYYY Ongoing

Done Delete Entry

Create Next Medical Condition

If current SLE therapy was stopped temporarily, did the reported event(s) recur after the therapy was restarted? Yes No

SLE Therapy Repeat Group

Form Name:

AE Sequence:

SLE Therapy Unique ID Number:

Please enter all SLE therapies including any current or prior therapy with Benlysta: <7>
(Create a new record for each therapy)

Dose: Frequency:

Start Date: DD-MMM-YYYY DD MMM YYYY

Stop Date: DD-MMM-YYYY DD MMM YYYY

Ongoing

Done Delete Entry

Create Next SLE Therapy

General Narrative Comments: Provide a brief narrative description of the SAE, possible other causes of the event (e.g. lack of efficacy, withdrawal of a drug, the disease under study or other medical conditions) and details of the treatment.

Please indicate the current status of the form: Complete Incomplete

Sign Form Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for Serious Adverse Event

<1> - AE Outcome
Resolved / Recovered
Resolved / Recovered w/ Sequelae
Resolving / Recovering
Not Resolved / Not Recovered
Fatal

<2> - Maximum Intensity of Event
Mild
Moderate
Severe
Not Applicable

<3> - Action taken with Study Treatment
SLE Therapy Withdrawn
Dose Reduced
Dose Increased
Dose Not Changed
Dose Interrupted / Delayed
Not Applicable

<4> - AE Seriousness
Results in Death
Life-Threatening
Requires Hospitalization or Prolongation of Existing Hospitalization
Results in Disability / Incapacity
Congenital Anomaly / Birth Defect
Possible Drug-Induced Liver Injury
Other

<5> - ConMed Units
Percent
100 International Units/ml
Actuation
Ampoule
Application

Area under curve
Bottle
Capsule
Caplet
Cubic Centimeter (CC)
Cells
Cup
Finger tip unit
Gram
Grams per Kilogram
Grams per Liters
Grams per Meter-Squared
Grams per Meter-Squared per 12 hours
Grams per Meter-Squared per Day
Grams per Milliliter
Gamma per Kilogram per Minute
Drops
Gum
Inhalation
International Units
International Units per Kilogram
International Units per Kilogram per Hour
International units per milliliter
Kilocalories
Liter
Liters per Minute
Lozenge
Minimum Alveolar Concentration
Mega Becquerels (MBq)
Microgram (mcg)
Micrograms per Gram
Micrograms per Hour
Micrograms per Kilogram
Micrograms per Kilogram per Minute
Micrograms per Minute
Micrograms per Milliliter
Millicurie
Microliter
Milliequivalent
Milliequivalents per 24 hours
Milligram
Milligrams Percent
Milligram per Day
Milligram per Hour
Milligram per Kilogram
Milligram per Kilogram per Hour
Milligram per Kilogram per Minute
Milligram per Meter-Squared
Milligrams per Meter-Square per Day
Milligrams per Milliliter
Milligram per Week
Million international units
Milliliter
Milliliters per Hour
Milliliters per Kilogram
Milliliters per Minute
Millimole
Millimoles per Kilogram
Millimoles per milliliter
Megaunits (Million Units)
Nebule
Nanogram
Nanogram per Kilogram per Minute
Ounce
Pack
Patch
Pill
Powder
Puff
Pulveris
Ring
Sachet
Spray

Suppository
Tablet
Tablespoon
Trouche
Teaspoon
Units
Units per Gram
Units per Hour
Units per Kilogram
Units per Kilogram per Minute
Units per minute
Microgram (ug)
Micromoles
Micromoles per 24 hours
Unknown
Vial

<6> - ConMed Route

Buccal
Conjunctival
Dental
Epidural
Endotracheal
Gastrostomy Tube
Intra-Arterial
Intra-Articular
Intra-Bursa
Intradermal
Inhalation
Intralesional
Intramuscular
Intranasal
Intracardiac
Injection
Intrapleural
Intravesical
Intraocular
Intraosteal
Intraperitoneal
Intrathecal
Intrauterine
Intravenous
Jejunostomy Feeding Tube (JEJ or PEJ)
Nasogastric
Nasal
Right Eye
Ophthalmic
Left Eye
Otic
Other
Both Eyes
Parenteral
Oral
Rectal
Subcutaneous
Sublingual
Transdermal
Transmucosal
Topical
Unknown
Urethral
Vaginal

<7> - SLE Therapy Name

BENLYSTA
Anti-Malarials
Azathioprine
Corticosteroid
Mycophenolate Mofetil
Methotrexate
Oral Cyclophosphamide
IV Cyclophosphamide

Calcineurin Inhibitor
Rituximab
TNF Alpha-Blockers
Abatacept
Tocilizumab
Leflunomide
Sirolimus
Other

Non-Serious AE **Patient ID:** **Created:** 27-May-2022 07:48:57 **Last Updated:** 27-May-2022 07:48:57

Legend: Clear Selection Show Warnings Show History

[+] Errors

NON-SERIOUS ADVERSE EVENT of SPECIAL INTEREST (AESI)

Information regarding the collection of Adverse Events can be found in the Study Protocol, Section 7 and Appendices 1 and 2. Please review these guidelines for a list of the Events of Special Interest that are to be reported through this registry. Other Adverse Events (including Serious Adverse Events) not collected as AESIs in this registry should be reported in accordance with the laws and regulations for marketed products in the country where the event occurred.

Event: (Diagnosis only if known, otherwise Sign/Symptom) Please include only one event term per AE form. If multiple events, complete a new form for each.

Modified term:

MedDRA lower level term code:

MedDRA dictionary synonym:

AE Sequence Number:

Start Date: DD-MMM-YYYY (DD MMM YYYY)

Outcome: <1>

Stop Date: DD-MMM-YYYY (DD MMM YYYY)

Frequency: Single Episode Intermittent

Maximum Intensity:
Record maximum intensity throughout duration of event. <2>

Action Taken with current SLE therapy as a Result of AE: <3>

Did the patient withdraw from the study as a result of this AE? (If YES, please complete the End of Study form) Yes No

Is there a reasonable possibility that the AE may have been caused by current SLE therapy?
Use best judgment at initial entry. May be amended when additional information becomes available. Yes No

If Yes, please specify which therapy:
(Select all that apply)

- BENLYSTA
- Anti-Malarials
- Azathioprine
- Corticosteroid
- Mycophenolate Mofetil
- Methotrexate
- Oral Cyclophosphamide
- IV Cyclophosphamide
- Calcineurin Inhibitor
- Rituximab
- TNF Alpha-Blockers
- Abatacept
- Tocilizumab
- Leflunomide
- Sirolimus
- Other

Where any relevant concomitant medications taken? Yes No
(Include details of any medication that may help explain the AE, may have caused the AE or was used to treat the AE.)

Form Name:

AE Sequence:

ConMeds Unique ID Number:

Medication Name:
(Trade name preferred)

(Synonym)

(Modified Term)

(Collection code)

Dose: Units: <4>

Frequency: Route: <5>

Was medication taken prior to study? Yes No

Primary Indication:
(Please enter a medical diagnosis, not a description)

Start Date: DD-MMM-YYYY (DD MMM YYYY) Stop Date: DD-MMM-YYYY (DD MMM YYYY) Ongoing

Done Delete Entry

Create Next Concomitant Medications

Where there any medical conditions that may be relevant to this AE? Yes No
(If Yes, please list all medical conditions below)

Form Name:

AE Sequence:

Medical Condition Unique ID Number:

Specific Condition Name:
(Please enter a medical diagnosis, not a description)

Start Date: DD-MMM-YYYY (DD MMM YYYY) Stop Date: DD-MMM-YYYY (DD MMM YYYY) Ongoing

Done Delete Entry

Create Next Medical Condition

Were there any diagnostic tests performed that may be relevant to this AE? Yes No
(If YES, please list all diagnostic tests below)

Form Name:

AE Sequence:

Diagnostic Test Unique ID Number:

Diagnostic Test Name:

Diagnostic Test Date: DD-MMM-YYYY (DD MMM YYYY) Diagnostic Test Result:

Done Delete Entry

Create Next Diagnostic Test

If current SLE therapy was stopped temporarily, did the reported event(s) recur after the therapy was restarted? Yes No

General Narrative Comments:
Provide a brief narrative description of the AE, possible other causes of the event (e.g. lack of efficacy, withdrawal of a drug, the disease under study or other medical conditions) and details of the treatment.

Please indicate the current status of the form: Complete Incomplete

Sign Form Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for Non-Serious AE

<1> - AE Outcome
Resolved/Recovered
Resolved/Recovered w/ Sequelae
Resolving/Recovering
Not Resolving/Not Recovering

<2> - Maximum Intensity of Event
Mild
Moderate
Severe
Not Applicable

<3> - Action taken with Study Treatment
SLE Therapy Withdrawn
Dose Reduced
Dose Increased
Dose Not Changed
Dose Interrupted/Delayed
Not Applicable

<4> - ConMed Units
Percent
100 International Units/ml
Actuation
Ampoule
Application
Area under curve
Bottle
Capsule
Caplet
Cubic Centimeter (CC)
Cells
Cup
Finger tip unit
Gram
Grams per Kilogram
Grams per Liters
Grams per Meter-Squared
Grams per Meter-Squared per 12 hours
Grams per Meter-Squared per Day
Grams per Milliliter
Gamma per Kilogram per Minute
Drops
Gum
Inhalation
International Units
International Units per Kilogram
International Units per Kilogram per Hour
International Units per milliliter
Kilocalories
Liter
Liters per Minute
Lozenge
Minimum Alveolar Concentration
Mega Becquerels (MBq)
Microgram (mcg)
Micrograms per Gram
Micrograms per Hour
Micrograms per Kilogram
Micrograms per Kilogram per Minute
Micrograms per Minute
Micrograms per Milliliter
Millicurie
Microliter
Milliequivalent
Milliequivalents per 24 hours
Milligram
Milligrams Percent

Milligram per Day
Milligram per Hour
Milligram per Kilogram
Milligram per Kilogram per Hour
Milligram per Kilogram per Minute
Milligram per Meter-Squared
Milligrams per Meter-Square per Day
Milligrams per Milliliter
Milligram per Week
Million international units
Milliliter
Milliliters per Hour
Milliliters per Kilogram
Milliliters per Minute
Millimole
Millimoles per Kilogram
Millimoles per milliliter
Megaunits (Million Units)
Nebule
Nanogram
Nanogram per Kilogram per Minute
Ounce
Pack
Patch
Pill
Powder
Puff
Pulveris
Ring
Sachet
Spray
Suppository
Tablet
Tablespoon
Trouche
Teaspoon
Units
Units per Gram
Units per Hour
Units per Kilogram
Units per Kilogram per Minute
Units per minute
Microgram (ug)
Micromoles
Micromoles per 24 hours
Unknown
Vial

<5> - ConMed Route

Buccal
Conjunctival
Dental
Epidural
Endotracheal
Gastrostomy Tube
Intra-Arterial
Intra-Articular
Intra-Bursa
Intradermal
Inhalation
Intralesional
Intramuscular
Intranasal
Intracardiac
Injection
Intrapleural
Intravesical
Intraocular
Intraosteal
Intraperitoneal
Intrathecal
Intrauterine
Intravenous

Jejunostomy Feeding Tube (JEJ or PEJ)
Nasogastric
Nasal
Right Eye
Ophthalmic
Left Eye
Otic
Other
Both Eyes
Parenteral
Oral
Rectal
Subcutaneous
Sublingual
Transdermal
Transmucosal
Topical
Unknown
Urethral
Vaginal

Sle Medications **Patient ID:** **Created:** 27-May-2022 07:49:01 **Last Updated:** 27-May-2022 07:49:01

Legend: Clear Selection Show Warnings Show History

[+] Errors

SLE MEDICATIONS

Please complete one form per medication taken

Drug name: <1>

Route: Intravenous Subcutaneous

Other, specify:

(Modified Term)

(Collection code)

(Synonym)

Start Date: DD-MMM-YYYY (DD MMM YYYY)

Reason for starting medication: <2>

Other, specify:

Stop Date: DD-MMM-YYYY (DD MMM YYYY) Ongoing

Reason for stopping medication: <3>

Other, Specify:

Done Delete Entry

Create Next Entry

Please indicate the current status of the form: Complete Incomplete

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Username

Password

Selection Options for Sle Medications

<1> - SLE Drug Name

BENLYSTA
Anti-Malarials (e.g. hydroxychloroquine, chloroquine, quinacrine)
Azathioprine (6-mercaptopurine)
Mycophenolate Mofetil
Methotrexate
Oral Cyclophosphamide
IV Cyclophosphamide
Calcineurin Inhibitor (e.g. tacrolimus, cyclosporine)
Rituximab
TNF Alpha-Blockers
Abatacept
Tocilizumab
Leflunomide
Sirolimus
Other

<2> - Reason for starting medication

Historical therapy
Additional therapy needed
Replacement therapy due to new access
Replacement therapy due to adverse event
Replacement therapy due to lack of response
Replacement therapy due to tolerability
Replacement therapy due to lack of access

Replacement therapy due to patient refusal
Other

<3> - Reason for stopping medication
No longer needed
Adverse event
Tolerability
Patient refusal
Lack of access to drug
Lack of response
Other

PSRHQ **Patient ID:** **Created:** 27-May-2022 07:49:04 **Last Updated:** 27-May-2022 07:49:04

Legend: Clear Selection Show Warnings Show History

[+] Errors

POSSIBLE SUICIDALITY-RELATED HISTORY QUESTIONNAIRE

Date of assessment: DD MMM YYYY

Has the patient had any SLE-related neuropsychiatric events prior to study start? ◯ Yes ◯ No

If Yes, check all that apply and provide the most recent date of occurrence:

	EVENT	DATE
☐	Acute Confusional State	DD-MMM-YYYY (DD MMM YYYY)
☐	Acute Inflammatory Demyelinating Polyradiculoneuropathy (Guillain-Barre Syndrome)	DD-MMM-YYYY (DD MMM YYYY)
☐	Anxiety Disorder	DD-MMM-YYYY (DD MMM YYYY)
☐	Aseptic Meningitis	DD-MMM-YYYY (DD MMM YYYY)
☐	Autonomic Disorder	DD-MMM-YYYY (DD MMM YYYY)
☐	Cerebrovascular Disease	DD-MMM-YYYY (DD MMM YYYY)
☐	Cognitive Dysfunction	DD-MMM-YYYY (DD MMM YYYY)
☐	Demyelinating Syndrome	DD-MMM-YYYY (DD MMM YYYY)
☐	Headache	DD-MMM-YYYY (DD MMM YYYY)
☐	Mononeuropathy Single	DD-MMM-YYYY (DD MMM YYYY)
☐	Mononeuropathy Multiplex	DD-MMM-YYYY (DD MMM YYYY)
☐	Mood Disorders	DD-MMM-YYYY (DD MMM YYYY)
☐	Movement Disorder (Chorea)	DD-MMM-YYYY (DD MMM YYYY)
☐	Myasthenia Gravis	DD-MMM-YYYY (DD MMM YYYY)
☐	Myelopathy	DD-MMM-YYYY (DD MMM YYYY)
☐	Neuropathy, Cranial	DD-MMM-YYYY (DD MMM YYYY)

☐	Plexopathy	DD-MMM-YYYY DD MMM YYYY
☐	Polyneuropathy	DD-MMM-YYYY DD MMM YYYY
☐	Psychosis	DD-MMM-YYYY DD MMM YYYY
☐	Seizures and Seizure Disorders	DD-MMM-YYYY DD MMM YYYY

Please indicate the current status of the form: ○ Complete ◉ Incomplete

☐ **Sign Form** Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for PSRHQ

PSRQ **Patient ID:** **Created:** 27-May-2022 07:49:07 **Last Updated:** 27-May-2022 07:49:07

Legend: Clear Selection Show Warnings Show History

[+] Errors

POSSIBLE SUICIDALITY-RELATED QUESTIONNAIRE

Date of assessment: DD - MMM - YYYY Assessment Not Done

Is the patient currently using illicit drugs? Yes No

If Yes, check all that apply:

Amphetamines Benzodiazepines Cannabinoids Cocaine

Opiates Other Specify:

Is the patient currently using alcohol? Yes No

If Yes, Average Unit(s) of Alcohol/Week:

Has the patient experienced any recent stress? Yes No

If Yes, check all that apply:

Family Problems Relationships Employment/Unemployment Finances

Other Factors Specify:

Any family history of suicidality? Yes No

If Yes, check ideation and/or behavior next to all that apply:

Father:	Ideation	Behavior
Mother:	Ideation	Behavior
Sibling	Ideation	Behavior
Other:	Ideation	Behavior

Any family history of psychiatric disorders? Yes No

If Yes, specify disorder next to all that apply:

Father:

Mother:

Sibling:

Other:

Please indicate the current status of the form: Complete Incomplete

Sign Form Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for PSRQ

Hospital Log **Patient ID:** **Created:** 27-May-2022 07:49:11 **Last Updated:** 27-May-2022 07:49:11

Legend: Clear Selection Show Warnings Show History

[+] Errors

HOSPITALIZATION LOG

Date of Admission	Date of Discharge	Directly Related to SLE?	Which category best represents the *Primary Diagnosis* on discharge?
DD MMM YYYY	DD MMM YYYY	Yes No	<1>

If other, specify:

Modified term:

MedDRA lower level term code:

MedDRA dictionary synonym:

Done Delete Entry

Create Next Hospitalization Record

Please indicate the current status of the form: Complete Incomplete

Sign Form Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for Hospital Log

<1> - Primary Diagnosis on Discharge
Blood & Lymphatic System Disorders
Cardiovascular Disorders
Endocrine Disorders
Gastrointestinal Disorders
Hepatobillary Disorders
Hypersensitivity/Infusion Reaction
Infections & Infestations
Musculoskeletal & Connective Tissue Disorders (including fractures)
Neoplasms
Nervous System Disorders
Pregnancy, Peuperium & Perinatal Conditions
Psychiatric Disorders
Renal & Urinary Disorders
Reproductive System & Breast Disorders
Respiratory, Thoracic & Mediastinal Disorders
Other

End of Study **Patient ID:** **Created:** 27-May-2022 07:49:14 **Last Updated:** 27-May-2022 07:49:14

Legend: Clear Selection Show Warnings Show History

[+] Errors

END OF STUDY

Date of patient completion or withdrawal: DD MMM YYYY

Was the patient withdrawn from the study? Yes No

If yes, please select the primary reason for withdrawal:

- Adverse Event
  - Adverse Event of Special Interest -- please provide details on the AE/SAE of Special Interest Form
  - Other Adverse Event (not of special interest)
  - Death
- Lost to Follow-Up
- Withdrew Consent Please specify:
- Investigator Discretion Please specify:
- Study Closed/Terminated

Please indicate the current status of the form: Complete Incomplete

Sign Form Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for End of Study

FU Visit Tracker **Patient ID:** **Created:** 27-May-2022 07:49:21 **Last Updated:** 27-May-2022 07:49:21

Legend: Clear Selection Show Warnings Show History

[+] Errors

FU Visit Tracker

Follow up (FU) visit	Projected/Expected FU Visit date based on enrollment visit date	FU Visit Date (If visit is completed)	Onsite or Remote Visit Completed	Visit Not Done	If Visit Not Done, were attempts to contact the patient made and documented
FU 1/ Month 6		DD - MMM - YYYY	Onsite Remote		Yes No
FU 2/ Month 12		DD - MMM - YYYY	Onsite Remote		Yes No
FU 3/ Month 18		DD - MMM - YYYY	Onsite Remote		Yes No
FU 4/ Month 24		DD - MMM - YYYY	Onsite Remote		Yes No
FU 5/ Month 30		DD - MMM - YYYY	Onsite Remote		Yes No
FU 6/ Month 36		DD - MMM - YYYY	Onsite Remote		Yes No
FU 7/ Month 42		DD - MMM - YYYY	Onsite Remote		Yes No
FU 8/ Month 48		DD - MMM - YYYY	Onsite Remote		Yes No
FU 9/ Month 54		DD - MMM - YYYY	Onsite Remote		Yes No
FU 10/ Month 60		DD - MMM - YYYY	Onsite Remote		Yes No

Please indicate the current status of the form: Complete Incomplete

Sign Form Check here to digitally sign to approve this form. *You must enter a username and password to sign the form.*

Username

Password

Selection Options for FU Visit Tracker