Benlysta for I.V. Infusion Benlysta Subcutaneous Injection Specified use-results survey

Statistical Analysis Plan

Title : Special Drug Use Observational Study of Benlysta for I.V. Infusion Benlysta for Subcutaneous Injection

Protocol No. :207735

Version : 13.0

Date : 2024.09.30

Author : PPD Real World Data Analytics, Biostatistics

Study Accountable Person/Non-Interventional Study Scientific Lead

: PPD , VEO Specialty Care

Approved by : PPD

Signature/Date

J-GPSP Officer

TABLE OF CONTENTS

1. Objectives of the survey

This Surveillance will be conducted to collect and evaluate information on the long-term safety and efficacy of Benlysta for I.V. Infusion and Benlysta for S.C. Injection (Hereinafter referred to as this drug) under the actual use conditions.

2. Software and Dictionaries

2.1. Statistical analysis and tabulation software

	Software and Version
OS	Microsoft Windows 10
Statistical analysis software	SAS Ver.9.4
Tabulation software	Microsoft Excel 2016

2.2. Dictionary

Item	Dictionary name
Name of disease (complication), name of adverse event, name of adverse reaction	MedDRA/J (* The version of MedDRA to be used shall be reviewed and determined by the team at each time of reporting.)
Name of drug, drug	GSKdrug (Data will be tabulated using the version used for coding by DM. * In principle, use the latest one.)

3. Definitions of Terms

Term	Definition
Start date of administration of this drug (registration form)	“Start date of administration of this drug ” in the registration form
Start date of this drug	First administration start date recorded in the “Administration status of this drug ” in the survey form
SELENA SLEDAI	Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index
PGA	Physician's global assessment
LLDAS	Lupus Low Disease Activity State
LOCF	Last observation carried forward
PML	Progressive Multifocal Leukoencephalopathy

4. Case and Data Handling

4.1. Sample size

✧ Number of patients: Number of patients meeting applicable conditions.

4.2. Analysis sets/sites

Item	Definition
Registered sites	Sites for all registered patients (patients eligible for registration). Sites with patients registered before the data lock date (excluding duplicate site codes).
Enrolled patients	Patients enrolled within the enrollment period specified in the protocol (from December 13, 2017 to the date of lifting of approval conditions) (registration-eligible patients). Subjects with an enrollment date before the data lock date.
Patients with locked CRF	All registered patients whose CRFs were collected and locked. Cases that have a recall date and a processing completion date and the processing completion date is before the data lock date.
Safety analysis population	Patients with locked CRFs who do not correspond to patients excluded from the safety analysis set (see 4.3.1)
Efficacy analysis population	Patients in the safety analysis set who are not excluded from the efficacy analysis set (see 4.3.2)
CRF collection target patients (Approval condition lifting)	Reports on registered patients whose CRFs were collected and patients eligible for CRF collection were identified (administration of this drug was started by October 31, 2018). The start date of administration of this drug (registration form) shall be the date of registration form.
Sites that can publish	PMW sites that are “11 _ Publication allowed (already concluded) ” or “ 13_ Publication allowed (no change required) ” and sites that are confirmed as “21 _ Being confirmed ” to be “ Publication allowed ”

Item	Definition
Subjects who completed the observation period (Interim analysis)	< Subjects falling under Population A > Disclosure-ready patients meeting any of the following conditions among patients treated with this drug before October 31, 2018 at study sites ・Completed up to Week 52: Separate Volume 1 (official approval) and Separate Volume 2 (official approval) ・Completed as discontinued: Volume 1 (official approval) in which the reason for discontinuation is described is official approval (excluding official approval of Volume 2 only) ・Completed as discontinued (logic assessment): Separate volume 1 (official approval) and Separate volume 2 is "Unnecessary " or" Unable to collect " < Subjects falling under Population B > This falls under "patients with depression-related events " among patients whose CRFs were additionally collected and are specified in a separate document.

4.3. Analysis Exclusion Criteria

4.3.1. Patients excluded from safety analysis

If there are overlapping reasons for exclusion and the reasons for exclusion should be prioritized, the reasons for exclusion from the safety analysis should be assigned in the following order:

Code	Safety Excluded from analysis	Priority Rank	Conditions for exclusion	Logic Judgment
S1	Outside the survey/registration period	1	・The date of completion of administration of this drug/the date of last observation is outside the survey period ・ Date of enrollment is outside the enrollment period	○
S2	Outside the contract period	2	・ The date of registration is outside the contract period.	○
S3	This drug naïve	3	・Patients with no description at all in the Dosage and Administration section of this drug or all descriptions of dosage are 0	○
S4	No visits after first dose (SC only)	4	・The reason for discontinuation/completion of administration in the [Status of continuation of administration of this drug at the end of the observation period] is "No	○

Code	Safety Excluded from analysis	Priority Rank	Conditions for exclusion	Logic Judgment
			visits after the first dose"	
S5	Adverse event data missing	5	・Cases for which [Presence/absence of adverse event] is "Unknown" or blank and there is no adverse event data	○
S6	Same case (co-examination/hospital transfer)	6	・A case judged to be the same case after consultation/transfer to another hospital	×
S7	Same case (duplicate description)	7	・Cases in which the same information is entered redundantly and judged to be the same case	×
S8	Others (safety)	8	・Exclusion items determined by the case review committee for reasons other than the above	×

4.3.2. Patients excluded from efficacy analysis

If there are overlapping reasons for exclusion and the reasons for exclusion should be prioritized, the reasons for exclusion from the efficacy analysis should be assigned in the following order:

Code	Efficacy Excluded from analysis	Priority Rank	Conditions for exclusion	Logic Judgment
E1	OFF LABEL USE	1:SLE 2: Children	・Indication other than "systemic lupus erythematosus" ・Cases used in pediatric patients	×
E2	Others (efficacy)	3	・Exclusion items determined by the case review committee for reasons other than the above	×

4.4. Handling of missing data

4.4.1. Data Imputation

4.4.2 will be followed for missing data, and no other data imputation will be performed.

4.4.2. SELENA SLEDAI, PGA

With the LOCF approach, if there is no data at the time of discontinuation/completion after Week 52 or Week 24 from the start of administration of this drug, the data will be imputed with the data up to Week 52 from the start of administration of this drug.

4.4.3. Missing continuous data

If there is a missing value in the tabulation of continuous data, it will be excluded from the tabulation. If continuous data are available at multiple time points, only the missing time points will be excluded. If continuous data are classified into categories, follow "4.4.4 Categorical Data."

4.4.4. Categorical data

- ✧ Data should be handled as "unknown" regardless of whether it is missing, unknown, or not recorded. (Excluding those defined in 4.6. Handling of presence/absence)
- ✧ Unless otherwise specified, missing values will be included in the denominator of percentages.
- ✧ Odds ratio excludes unknown category.

4.4.5. Date Variables

Imputation of date variables will be handled as follows.

< End date of administration of this drug >

- ✧ If the number of doses of this drug is once, imputation will use the start date of this drug administration.

< Adverse events >

- ✧ If the date of onset and date of outcome are missing, they will not be imputed and will be handled as unknown.

< Prior treatment drugs/Prior treatment (other than drugs)/Concomitant drugs >

- ✧ Only systemic steroids for SLE have a date but if the last record is ' Dosing Continued ', then it will be imputed with the last date from this drug Administration Status.

4.5. Treatment Disposition Date for Continued Treatment

The end date of administration in the case of continued administration will be imputed with the last date of administration in this drug administration status. However, if the administration status of this drug is blank, it will be handled as follows.

Date of completion of treatment = date of initiation of treatment + < number of days considered to be converted > -1

Deemed equivalent number of days

24 weeks → 168 days (when only CRF 1 is collected)

52 weeks → 364 days

*If the end date of administration calculated above is after the end date of the contract period, it will be

complemented with the end date of the contract.

4.6. Handling of presence/absence

Presence/absence shall be handled as follows.

Description of the column for presence/absence	Detailed item record	Handling of presence/absence
No	No	Should be "No."
	Yes	Should be "Yes."
Yes	No	Should be ‘ Unknown ’.
	Yes	Should be "Yes."
Unknown/not specified	No	Should be ‘ Unknown ’.
	Yes	Should be "Yes."

The target shall be the adverse event field, and other items shall be judged based on the presence or absence of detailed description.

Checkboxes for drug category and drug name should be handled as described above.

4.7. Calculation of number of days and age

✧ Day

The number of days from the start date of this drug treatment will be calculated as follows in cases where the target day is before or after the start date of this drug treatment.

・In the case of the start date of this drug treatment ≤ the target date: the target date - the start date of this drug treatment +1

・If the start date of administration of this drug > target date: target date - start date of administration of this drug

*The number of days (Day) after the start of this drug administration is shown as 1 for the start day of this drug administration and -1 for the day before the start of this drug administration, with 0 not used.

✧ Age

Calculated using the start date of administration of this drug. However, if age data are separately obtained, the data will be preferentially adopted.

・this drug Start Date - Date of Birth (* Calculated with June 30 imputed.)

4.8. Drug Class

Drug Class	Definition
Immunosuppressants	To be defined in a separate document
Antimalarial drugs	
Steroids	
NSAIDs	
Biological preparations-Miscellaneous	
Cyclophosphamide IV	

4.9. Concomitant conditions

Concurrent medical conditions will be coded using MedDRA and tabulated according to the following categories.

Concomitant conditions	Definition
Hepatitis B	Same as the study plan
Renal impairment	HLGT (10029149): Nephropathy HLGT (10038430): Renal disorders (excl nephropathy)
Hepatic impairment	SMQ: PTs included in level 1 “Liver disorders (20000005) ”, excluding PTs included in level 3“ Liver related coagulation and bleeding disorders (20000015) ”
Allergy	HLGT (10001708): Allergic diseases
Other	Complications other than the above listed in the survey form

4.10. Responders

A responder is defined as a case where this drug treatment start date and post-treatment assessments are present and the following conditions are met:

Efficacy assessments	Responder definition
SELENA SLEDAI (Used for calculation of efficacy percentage)	≥ 4 decrease in score from baseline
PGA score	≥ 0.3 (10 mm) decrease from baseline
LLDAS (Lupus Low Disease Activity State)	1. SELENA-SLEDAI ≤ 4 and no major active organ involvement (renal, central nervous system, cardiopulmonary, vasculitis, pyrexia) on SELENA-SLEDAI, without hemolytic anemia or active gastrointestinal lesions reported as adverse events.
	2. No new signs or symptoms as compared to the last SELENA-SLEDAI assessment.
	3. PGA score ≤ 1 (33 mm)

Efficacy assessments	Responder definition
	4. Corticosteroid dose ≤ 7.5 mg/day at time of assessment
	5.Use of the same immunosuppressant as compared with prior medication. No unapproved drugs of rituximab, anifrolumab, ustekinumab, or baricitinib are used as concomitant medications. The use of anifrolumab with this drug initiated on 2021/9/27 or later is allowed.
LLDAS Adverse Events	Haemolytic anaemia: 10018916 (PT code) Active gastrointestinal lesions: to be defined in a separate document
Corticosteroid Reduction at Week 40~52	Average daily dose Proportion of patients who were able to reduce their average daily steroid dose by ≥ 25% and ≤ 7.5 mg/day from baseline at Week 40~52 (in patients with baseline average daily steroid dose > 7.5 mg/day). Subjects who discontinued or completed administration of this drug before Week 52 will be classified as non-responders.

4.11. SELENA SLEDAI Organ System Domain

Organ System [1]	Item	Score
Central Nervous System 1	Convulsion	8
	Psychosis	8
	Organic brain disorder	8
	Visual impairment	8
	Cranial nerve disorder	8
	Lupus headache	8
	Cerebrovascular disorder 1	8
Vascular 1	Vasculitis	8
Musculoskeletal	Arthritis	4
	Myositis	4
Renal System	Cylindruria	4
	Haematuria	4
	Proteinuria	4
	Pyuria	4
Mucocutaneous	Rash	2
	Hair loss	2
	Mucosal ulcer	2
Cardiovascular and Respiratory	Pleurisy	2
	Pericarditis	2

Organ System [1]	Item	Score
Immune system	Low complement Anti-dsDNA	2 2
General disorders 1	Pyrexia 1	1
Hematology 1	Platelets decreased White blood cell decreased	1 1

[1]: Cerebrovascular disorder is included from the central nervous system to the vascular system. Delete general disorders and include pyrexia in the vascular system.

4.12. Average daily steroid dose

The average daily steroid dose will be prednisolone-equivalent (prednisolone conversion table: to be defined in a separate document) and the average daily steroid dose during the 7 days prior to and including the day of evaluation will be used. The mean value during the 7 days before treatment including the dose on the first day of treatment will be used as the baseline. If there is no information on steroid administration during the observation period, it will be handled as "0 mg." Data obtained after the end date of administration of this drug will not be used for tabulation.
The prednisolone conversion table will be updated when new drugs are added and fixed with the data at the time of DBF.

4.13. Assessment window

4.13.1. Efficacy assessments and laboratory data

Visit * information, as defined below, will be used in the analysis. If a visit with an evaluation date (including unscheduled visit) closer to the specified date is adopted and the period from the specified date is the same, the latest visit will be adopted. If there are multiple visits to be adopted, the visit to be adopted shall be defined after discussion at the case review meeting.

The evaluation date (calculation) is calculated as follows.
Date of evaluation (calculation) = Target date (or date of discontinuation/completion of this drug treatment) - start date of this drug treatment +1

Evaluation time point	Scheduled date	Acceptable range (+- days)	Duration (days) to	Until
24 weeks after start of administration of this drug	169	28	141	197

52 weeks after start of administration of this drug	365	28	337	393

*Visit indicates the time of assessment

4.13.2. Systemic corticosteroids for SLE

Visit information, defined below, will be used in the analysis.

The evaluation date (calculation) is calculated as follows.

Date of evaluation (calculation) = Target date - Start date of this drug treatment +1

Evaluation time point	Date of Assessment (day)	Duration (days)	
		to	Until
Week 2	14	8	14
Week 4	28	22	28
Week 8	56	50	56
12 Week	84	78	84
Week 16	112	106	112
Week 20	140	134	140
Week 24	168	162	168
Week 28	196	190	196
Week 32	224	218	224
Week 36	252	246	252
Week 40	280	274	280
Week 44	308	302	308
Week 48	336	330	336
Week 52	364	358	364

4.14. Definition of Same Case

Identical cases are defined as follows. The details will be examined when they become known.

Hospital transfer: When a patient is transferred to another hospital and visits more than one medical institution and is found to be the same patient.

Co-examination: When the same or multiple physicians examined the same patient at multiple medical institutions in collaboration.

Duplicate case: Duplicate entries of the same information are found in the same patient.

4.15. Adverse events/adverse drug reactions

Term	Definition
Adverse Events	Event as entered into Argus.
Follow-up Events	Adverse events leading to death, serious infections, progressive multifocal leukoencephalopathy (PML), and malignancies in the follow-up investigation (only for patients for whom Separate Volume 3 is locked). Adverse events leading to death: Events whose outcome is “fatal ” Serious infections: According to 4.16. Safety Specifications Progressive multifocal leukoencephalopathy (PML): According to 4.16. Safety Specification Malignant tumor: According to 4.16. Safety Specification
Adverse reactions	Adverse events other than "“Causality as determined ” and“ Causality as reported ” are “Not related ” or“ Not related ”."
Serious Adverse Events (Adverse Drug Reactions)	Adverse events (adverse drug reactions) that are “serious.”
Adverse events occurring by Week 52 of the observation period	Adverse events that occurred by the day of first dose of this drug + 364. However, if the date of onset is unknown, the event will be considered to have occurred by Week 52 of the observation period.

4.16. Safety specification

Safety specifications will be made in accordance with the investigation plan.

4.17. Handling of fixed cases by volume

Data of fixed cases and each volume will be used as CRF data. (If Volume 1 is locked, the patient will be classified as a "locked patient," but data from CRFs from which subsequent volumes are not locked will not be used in analyses.)
For tabulation of "subjects who completed the observation period," refer to the definition of "subjects who completed the observation period (interim analysis)" in analysis sets/sites in 4.2.

4.18. Handling of treatment continuation/discontinuation/completion

Regardless of the description in the survey form, "patients who completed the observation period" will be handled as follows and tabulated.

Treatment Disposition for this drug	Administration end date	Handling
Treatment continued	< Week 52	Treated as patients who

	-28 (days)	discontinued/completed treatment Reason for discontinuation/completion should be “Unknown ”
	≥ 52 weeks -28 (days)	Treatment continued (No change)
Discontinuation/completion of treatment	< Week 52	Discontinuation/Completion of Treatment (No Change)
	≥ 52 weeks	They will be handled as patients continuing treatment, and the described reasons for discontinuation/completion of treatment will not be used.

4.19. Handling of tabulations for articles

Regarding "Depression, suicidal ideation, suicide attempt", the analysis plan to collect additional CRFs and perform an exploratory analysis of risk factors is attached in Appendix 6 for patients other than patients whose CRFs were collected (Registered patients whose CRFs were collected and patients eligible for CRF collection were identified (administration of this drug started by October 31, 2018)) who developed these events.

In this analysis plan, the specifications for tabulation for literature are also described in common with the stability report, etc., but the details of the analysis plan for the additional analysis based on the collection of additional CRFs will be followed. If the specifications of the stability report and output form are different, the description in the English version of the mock prepared for the paper shall take priority.

Analysis sets:

Since "Supplemental Form (CRFs whose collection started in October 2023 or later: However, patients subject to continuous collection are not considered as additions.)" are collected only from patients with events related to "Depression, suicidal ideation, suicide attempt," they cannot be combined with existing survey data (survey data based on survey form data collected before September 2023) to determine the incidence, etc. and will be used for risk factor analysis. Therefore, it is specified as "excluded from safety analysis (others [safety])" in the periodic safety update report and reexamination application documents submitted to PMDA after June 2024.

Adverse events in the tabulation for literature in the final report: Adverse events excluding those from the follow-up site survey will be tabulated according to 4.15: Adverse events observed by Week 52 of the observation period.

5. STATISTICAL CONSIDERATIONS

5.1. Summary statistics

Refers to sample size, mean, standard deviation, minimum, 25% point, median, 75% point, and maximum.

5.2. Change, percent change, percentage

The change, percent change, and percent change from baseline will be calculated using the following formula. Baseline for average daily steroid dose includes the start date of treatment.

- ✧ Change = measured value at each observation time point - measured value at baseline
- ✧ Percent change (%) = (Change/measured value at baseline) x 100
- ✧ Percentage (%) = (Number of patients/Number of patients analyzed) × 100

5.3. Display of Results

The tabulation results shall be presented as follows.

Classification	Display digit
Percent change, percentage	Round off to 1 decimal place.
Number of subjects	Display as whole number.
Mean, standard deviation, 25% point, median, 75% point, confidence interval	Round off the second digit below the number of digits to be displayed and display to the first digit below the number of digits to be displayed.
Min, Max	Round off to the same number of digits to be displayed.
Odds ratio, confidence interval for odds ratio, correlation coefficient	Round off to three decimal places.

5.4. Exploratory analysis of influencing factors

CCI

[redacted]

5.5. Incidence rate based on person-year method

- ✧ Incidence rate per X patient-years = number of events ×X/patient-years of observation.

Unless otherwise specified, X=100.

- ✧ Person-years of observation (Total Patient-Years) is defined as the sum of duration of treatment with this drug calculated for each analysis population (duration of treatment with this drug = date of completion of treatment with this drug - date of initial treatment with this drug + 1).

6. Primary analysis items

6.1. Patient composition

6.1.1. Patient composition (Figure 1.01)

Analyzed: -

Analysis details: The following numbers of patients, numbers of patients excluded, and reasons for exclusion will be shown using a flow chart.

If there are multiple reasons for exclusion in the same patient, they will be summarized in the item of higher priority.

The number of study sites will be tabulated for each study site, regardless of clinical department.

< All subjects >

・Registered sites

・Enrolled patients

・CRF uncollected

・CRF collection facility

・Patients whose CRFs were collected

・CRF unfixed patients

・CRF locked facility

・Patients with locked CRF

・Patients excluded from safety analysis

・Number of sites

・Safety analysis population

・Patients excluded from efficacy analysis

・Efficacy analysis population

For patients whose CRFs were collected, patients whose CRFs were locked, and patients in the safety analysis set, the number of patients will also be calculated for each CRF volume.

6.1.2. Patient composition (Figure 1.012)

Analyzed: -

Analysis details: The following numbers of patients, numbers of patients excluded, and reasons for exclusion will be shown using a flow chart.

If there are multiple reasons for exclusion in the same patient, they will be summarized in the item of higher priority.

The number of study sites will be tabulated for each study site, regardless of clinical department. [Analysis for lifting of approval conditions]

< All subjects >

・Registered sites
・Enrolled patients
・Institutions where survey forms are collected
・CRF collection target patients
・CRF uncollected
・CRF collection facility
・Patients whose CRFs were collected
・CRF unfixed patients
・CRF locked facility
・Patients with locked CRF
・Patients excluded from safety analysis
・Number of sites
・Safety analysis population
・Patients excluded from efficacy analysis
・Efficacy analysis population

For patients whose CRFs were collected, patients whose CRFs were locked, and patients in the safety analysis set, the number of patients will also be calculated for each CRF volume.

6.2. Patient demographics and baseline characteristics

6.2.1. Composition ratio of patients and summary statistics (Table 1.02x, 1.021x, 1.022x, 1.024x, 1.026x)

Analyzed:	Safety analysis set, efficacy analysis set
Analysis details:	The number of patients and composition ratio (%) and/or summary statistics will be calculated for each analysis set by patient background factor. Unless otherwise specified, the denominator for the composition ratio (%) will be the total of each analysis set. For patient demographics, baseline values (summary statistics), and laboratory test values (summary statistics), the same analyses will be performed for each initial route of administration (IV, SC) (safety analysis set).
Patient characteristics	< Category > ・Gender (Male, Female) ・Age 1 [years] (<15, 15 ≤ to <65, 65 ≤, unknown) ・Age 2 [years] (<45, 45 ≤ to <65, 65 ≤ to <75, 75 ≤, unknown) ・Reason for use of this drug 1(Treatment of patients with systemic lupus erythematosus (SLE) who have inadequately responded to conventional treatments and other) If there are SLE and other reasons for use, SLE will be tabulated with priority. SLE cases (Severe lupus nephritis, severe central nervous system lupus)

If multiple symptoms are selected, they will be counted multiple times.

・Reason for use of this drug 2(Treatment of patients with systemic lupus erythematosus (SLE) who have inadequately responded to conventional treatments and other)

If multiple symptoms are selected, they will be counted multiple times.

・Autoantibodies associated with SLE (Antinuclear antibody, anti-dsDNA antibody, anti-Sm antibody, lupus anticoagulant, anti-cardiolipin antibody, and other autoantibodies related to SLE)

antinuclear antibody (Positive, Negative), anti-dsDNA antibody (Positive, Negative), anti-Sm antibody (Positive, Negative), lupus anticoagulant (Positive, Negative), anti-cardiolipin antibody (Positive, Negative), and other autoantibodies related to SLE (Positive, Negative)

・Duration of SLE (<5, 5 ≤ to <10, 10 ≤ to <15, 15 ≤ to <20, 20 ≤, unknown)

・Weight [kg] (<30, 30 ≤ to <40, 40 ≤ to <50, 50 ≤ to <60, 60 ≤, unknown)

・Status of vaccination (24 weeks before the start of administration of this drug) (absent, present, unknown)

Breakdown of vaccination (Use of pneumococcal vaccine, influenza vaccine, HPV vaccine, hepatitis A vaccine, hepatitis B vaccine, varicella zoster vaccine, or other vaccines)

・Past history (Tuberculosis, hepatitis B)

If multiple symptoms are selected, they will be counted multiple times.

・Mean daily dose of steroid at the start of treatment [mg/day] (0, 0< to ≤ 7.5, 7.5<, unknown)

・Mean daily dose of steroid at the start of treatment 2 [mg/day] (0, 0< to ≤ 5, 5< to ≤ 10, 10<, unknown)

・Pregnancy (No, Yes)

・Prior treatment for SLE (Steroids, immunosuppressants, antimalarials, NSAIDs, other biologics, cyclophosphamide intravenous injection) (No, Yes)

・Prior medications for SLE (Steroids, immunosuppressants, antimalarials, NSAIDs, other biologics, cyclophosphamide intravenous injection)

・Presence or absence of concomitant medication (No, Yes)

・Concomitant medication for SLE (Steroids, immunosuppressants, antimalarials, NSAIDs, other biologics, cyclophosphamide intravenous injection) (No, Yes)

・Details of concomitant medications for SLE (Steroids, immunosuppressants, antimalarials, NSAIDs, other biologics, cyclophosphamide intravenous injection)

・Presence or absence of concomitant therapy (No, Yes)

・Complications (No, Yes)

・Presence or absence of complication (renal impairment) (No, Yes)

・Presence or absence of complication (hepatic impairment) (No, Yes)

・Complication (allergy) (No, Yes)

・Status of administration of this drug at the end of the observation period (Continuation of administration, discontinuation/completion of administration)

< Summary statistics >

	・Age [years]
	・Age [years] (children: < 15 years)
	・Age [years] (elderly: ≥ 65 years)
	・Mean daily dose of steroid at the start of treatment [mg/day]
	・Duration of SLE [year]
	・Weight [kg]
Baseline	< Category >
	・SELENA SLEDAI score (≤ 9, 10 ≤, unknown)
	・Each item of SELENA SLEDAI
	・PGA score (0 ≤ to ≤ 1, 1< to ≤ 2.5, 2.5< to ≤ 3, unknown)
	< Summary statistics >
	・SELENA SLEDAI score
	・PGA score
	・Lupus Impact Tracker
Laboratory Evaluations	< Category >
	・Anti-dsDNA antibody [IU/mL] (Negative, Positive (≥ 30 IU/mL), Unknown)
	・Complement Levels: Low C3 and/or Low C4 Other than the above Unknown
	・C3 (baseline) [mg/dL] (<90, 90 ≤, unknown)
	・C4 (baseline) [mg/dL] (<10, 10 ≤, unknown)
	< Summary statistics >
	・Anti-dsDNA [IU/mL]
	・C3[mg/dL]
	・C4[mg/dL]
	・CH50[U/mL]
	・Protein-creatinine ratio [g/g・Cr]
Screening test	< Category >
	・Tuberculosis Screening Prior to Initiation of this drug Presence or absence of chest imaging, tuberculin test, and interferon-γ release assay (No, Yes) Chest imaging/presence or absence of tuberculosis (If absent or present, by active tuberculosis or old tuberculosis), including findings of old tuberculosis PPD skin test/positive status (Negative, Positive) Interferon-gamma release assay/positive status (Negative, Positive)
	・Hepatitis B screening prior to initiating this drug Presence or absence of HBs antigen, HBs antibody, HBc antibody, and HBV-DNA quantification (No, Yes)

HBs antigen/positive status (Negative, Positive)

HBs Ab/positive status (Negative, Positive)

HBc Ab/positive status (Negative, Positive)

・Patients with special surveillance item (reactivation of hepatitis B virus)

HBs antigen, HBs antibody, HBc antibody, and HBV-DNA assay in patients with priority investigation item (reactivation of hepatitis B virus) (Yes)

< Summary statistics >

・HBV-DNA, quantitative [Log IU/mL]

Proper use status

< Category >

・ Prior medications for SLE (Steroids, immunosuppressants, antimalarials, NSAIDs, other biologics, cyclophosphamide intravenous injection)

Prior treatment for SLE (No, Yes)

SELENA SLEDAI score by presence/absence of prior treatment for SLE (0 ≤ to <4, 4 ≤ to <10, 10 ≤ to <12, 12 ≤, not judged)

Prior medications for SLE (Steroids, immunosuppressants, antimalarials, NSAIDs, other biologics, cyclophosphamide intravenous injection)

・Autoantibodies associated with SLE

Antinuclear antibody or anti-dsDNA antibody (Positive (antinuclear antibody [positive] and/or anti-dsDNA [positive]), negative, or not done)

SLE-related autoantibodies (antinuclear or anti-dsDNA [negative or not performed]): other autoantibodies (positive) (overlapping) (Anti-Smith, lupus anticoagulant, anticardiolipin, and other autoantibodies associated with SLE), negative for all or not performed

6.2.2. Number of patients by complication symptom (Table 1.03x)

Analyzed: Safety analysis set, efficacy analysis set

Analysis details: The number of patients with complications (number of patients with complications) and the proportion of patients with complications will be calculated for each SOC and PT by category of complications.

As for the order of output, data will be output in the descending order of the number of subjects for safety SOC, in the descending order of international consensus for SOC, in the descending order of the number of subjects for PT, and in the order of PT code.

The denominator of the proportions of patients with each complication will be the respective number of patients analyzed. For the safety analysis set, the number of patients with adverse reactions and the incidence of adverse reactions will be calculated, and for the efficacy analysis set, the number of patients with response and the incidence of response will be calculated.

The SELENA SLEDAI score will be used for the number of responders and response rate.

The denominator for the incidence of adverse reactions and response rate is the number of patients for each SOC and PT.

Complication Category

・Hepatitis B (Table 1.031)

・Renal impairment (Table 1.032)

・Hepatic impairment (Table 1.033)

・Allergies (Table 1.034)

・Other (Table 1.035)

6.2.3. Number of patients by prior medication (anti-SLE drug) (Table 1.04x, 1.041x)

Analyzed: Safety analysis set, efficacy analysis set

Analysis details: The number of target patients (number of patients using the drug) and use rate will be calculated by drug class, drug code (GSKdrug), and generic name, and output in the descending order of the number of patients in the safety analysis set and in the order of drug codes.

For the safety analysis set, the number of patients with adverse reactions and the incidence of adverse reactions (Table 1.041), adverse events (Table 1.042), and serious infections (Table 1.043) will be calculated, and for the efficacy analysis set, the number of responders and the response rate will be calculated.

For adverse drug reactions (Table 1.041) by prior treatment (anti-SLE drugs), similar analyses will be performed for each initial route of administration (IV, SC) (safety analysis set).

The SELENA SLEDAI score will be used for the number of responders and response rate.

The denominator of the usage rate is the number of patients in each analysis set.

The denominator for the incidence of adverse reactions and response rate is the number of patients per drug.

6.2.4. Number of patients by concomitant drug (anti-SLE drug) (Tables 1.05 and 1.051)

Analyzed: Safety analysis set, efficacy analysis set

Analysis details: The number of target patients (number of patients using concomitant drugs) and use rate will be calculated by drug class, drug code (GSKdrug), and generic name, and output in the descending order of the number of patients in the safety analysis set and in the order of drug codes.

The number of patients with adverse reactions and the incidence of adverse reactions will be calculated for the safety analysis set, and the number of patients with response and the incidence of response will be calculated for the efficacy analysis set.

The same should be done for concomitant medications (anti-SLE drugs) used until Week 24 (described in Separate Volume 1).

The SELENA SLEDAI score will be used for the number of responders and response rate.

The denominator of the usage rate is the number of patients in each analysis set.

The denominator for the incidence of adverse reactions and response rate is the number of patients per drug.

6.2.5. Composition ratio of this drug administration status (Table 1.06x, 1.062x)

Analyzed: Safety analysis set, efficacy analysis set

Analysis details: The number and composition ratio (%) and/or summary statistics will be calculated for each analysis set of route of administration, total number of doses, duration of treatment, total dose, and mean dose per administration.

For the status of administration of this drug (summary statistics), similar analyses will be performed by initial route of administration (IV, SC) (safety analysis set).

Unless otherwise specified, the denominator for the composition ratio (%) will be the total of each analysis set.

For total number of doses (IV), total dose (IV) [mg/kg], and average dose per administration (IV) [mg/kg], the denominator will be the number of subjects dosed by route (IV).

For total number of doses (SC), total dose (SC) [mg], and average dose per administration (SC) [mg], the denominator will be the number of subjects dosed by route of administration (SC).

Items:

・Primary route of administration (IV, SC SC is separated from AI and PFS and unknown)

・Route of administration (IV, SC, change *) *: Number of subjects for IV and SC excluding changes

・Duration of treatment (days) (<28, 28 ≤ to <168, 168 ≤ to <364, 364 ≤, unknown)

・Total number of infusions (IV) (<6, 6 ≤ to <11, 11 ≤ to <15, 15 ≤, unknown)

・Total number of SC injections (<13, 13 ≤ to <25, 25 ≤ to <37, 37 ≤ to <52, 52 ≤, unknown)

・Total dose (IV) [mg/kg] (≤ 50, 50< to ≤ 100, 100 < to ≤ 140, 140<, unknown)

・Total dose (SC) [mg] (≤ 2400, 2400< to ≤ 4800, 4800< to ≤ 7200, 7200< to ≤ 10200, 10200<)

・Mean single dose (IV) [mg/kg] (<10, 10, 10<, unknown)

・Mean dose per administration (SC) [mg] (<200, 200, 200<, unknown)

6.2.6. Duration of this drug treatment by reason for treatment discontinuation/completion 1.07 (Figure 1.02, 1.021)

Analyzed: Safety analysis population

Analysis details: According to "4.18 Handling of treatment continuation/discontinuation/completion," the data will be output by the number of patients with treatment discontinuation/completion, the reason for treatment discontinuation/completion, and the duration (weeks) of treatment with this drug until discontinuation/completion for the patients who discontinued/completed the treatment with this drug.

Reasons for discontinuation/completion will be regarded as overlapping.

A Kaplan-Meier plot (discontinuation rate) of time to discontinuation of this drug will be generated.

In addition, a Kaplan-Meier plot of the extension period of this drug (continuation rate) will be provided.

Duration (weeks) of administration of this drug until discontinuation/completion of administration:

・<2, 2 ≤ to <4, 4 ≤ to <8, 8 ≤ to <12, 12 ≤ to <16, 16 ≤ to <20, 20 ≤ to <24, 24 ≤ to <28, 28 ≤ to <36, 36 ≤ to <44, 44 ≤ to <52, 52 ≤, unknown

6.3. SAFETY EVALUATION

6.3.1. List of occurrence of ADRs by patient background (Table 2.01)

Analyzed: Safety analysis population

Analysis details: The number of target patients, the number of patients with adverse reactions, and the incidence of adverse reactions will be calculated for each patient background item.

The denominator of the incidence of adverse reactions is the number of patients included in each background item.

Patient characteristics: The following will be added to the section of "Patient composition ratio."

・SELENA SLEDAI (baseline): ≤ 9, 10 ≤, unknown

・PGA score (baseline): (0 ≤ to ≤ 1, 1< to ≤ 2.5, 2.5< to ≤ 3, unknown)

・Anti-dsDNA antibody (baseline) [IU/mL]: <30, 30 ≤

・Complement Levels:

Low C3 and/or Low C4

Other than the above

Unknown

・C3 (baseline) [mg/dL]: (<90, 90 ≤, unknown)

・C4 (baseline) [mg/dL]: (<10, 10 ≤, unknown)

6.3.2. Time to onset of adverse reaction/event (Tables 2.021~2.024, 2.061~2.065, Figure 2.01~2.05)

Analyzed:	Safety analysis population, safety analysis population (patients for whom follow-up survey forms were collected)
Analysis details:	The proportion of each SOC and PT will be tabulated by category of number of days to onset of adverse reaction/adverse event for each PT (weeks). In addition, the incidence of adverse reactions/adverse events and the cumulative incidence of adverse reactions/adverse events will be tabulated for all subjects and serious adverse reactions/adverse events. The proportion will be presented by number of days as the sum of cases excluding overlapping adverse reactions/adverse events. The cumulative percentage of cases by number of days will be presented. However, each case counts only in days for its first occurrence (first reaction/AE). “Unknown ” in the same case shall be counted preferentially. As for the order of output, data will be output in the descending order of the number of subjects by SOC in the total column, in the descending order of the number of subjects by PT, and in the order of PT codes. Also, For the incidence of adverse events/serious adverse events (number of events/number of patients), a bar graph will be prepared for each category of time to onset (weeks). Similar bars will be produced for Hypersensitivity, Hypersensitivity "Infections (Including tuberculosis, pneumonia, pneumocystis pneumonia, sepsis, and opportunistic infection)," Hypersensitivity "Depression, suicidal ideation, suicide attempt" and Malignancy. However, "Depression, suicidal ideation, suicide attempt" and "malignant tumors" are handled as adverse events only. The number of days with onset is calculated as follows. Date of onset - date of start of treatment +1 (7 days is counted as 1 week) *SOC and PT are summarized by SOC and PT, respectively, of initial onset. *This should be done in the same way for events collected as follow-up (Table 2.061-2.065).
Time (weeks) to onset of adverse reaction/adverse event category:	・<2, 2 ≤ to <4, 4 ≤ to <8, 8 ≤ to <12, 12 ≤ to <16, 16 ≤ to <20, 20 ≤ to <24, 24 ≤ to <28, 28 ≤ to <36, 36 ≤ to <44, 44 ≤ to <52, 52 ≤, unknown
Category of time (weeks) to onset of event to be collected in the follow-up:	・<52, 52 ≤ to <60, 60 ≤ to <68, 68 ≤ to <76, 76 ≤ to <84, 84 ≤ to <92, 92 ≤ to <100, 100 ≤ to <108, 108 ≤ to <116, 116 ≤ to <124, 124 ≤ to <132, 132 ≤ to <140, 140 ≤ to <148, 148 ≤ to <156, 156 ≤, unknown

6.3.3. Incidences of adverse drug reactions/adverse events by sex (Table 2.031x, 2.041x, 2.071x, 2.081x)

Analyzed:	Safety analysis population, safety analysis population (patients for whom follow-up survey forms were collected)
Analysis details:	For adverse drug reactions/adverse events, the proportions will be calculated for each SOC and PT by safety evaluation items and by patients with specific backgrounds and by seriousness (serious/overall). As for the order of output, data will be output in the descending order of the number of subjects by SOC in the total/overall column, in the descending order of the number of subjects by PT, and in the order of PT codes. Adverse events in the safety specifications will be tabulated as necessary. Reasons for use of this drug (Presence or absence of severe lupus nephritis, presence or absence of severe central nervous system lupus) will also be tabulated. *This should be done similarly for events collected as follow up (Table 2.071x). Adverse events will be tabulated by discontinued patients and by prior therapeutic drug. (Table 2.04115~24) Tabulation Tables 2.03101~08 and 2.04101~08 for adverse events and adverse reactions will be summarized into one table to prepare tabulation tables. (Table 2.08101~08, Table 2.08115~24)
Safety Specification:	“Safety Specification ”
Patients with Specific Backgrounds	Age [years], Pregnancy, Renal impairment, Hepatic impairment

6.3.4. Onset status of related AEs by route of administration (Table 9.1, 9.2.1, 9.2.2)

Analyzed:	Safety analysis population
Analysis details:	For adverse drug reactions, the proportion of each SOC/PT will be tabulated by seriousness (serious/all) by the following items. As for the order of output, data will be output in the descending order of the number of subjects by SOC in the total/overall column, in the descending order of the number of subjects by PT, and in the order of PT codes.
Items:	Route of administration, switching route of administration for intravenous infusion, switching route of administration for subcutaneous injection

6.3.5. Serious sex of adverse reaction/event (Tables 2.032 and 2.042)

Analyzed:	Safety analysis population
Analysis details:	For adverse drug reactions/adverse events, the number of patients with adverse drug reactions/adverse events and the incidence of adverse drug reactions/adverse events will be tabulated by seriousness (serious, non-serious, and overall) and outcome. *In tabulation by outcome, if multiple events occur in the same patient, they will be included

in the following order of priority for tabulation.

① Serious > non-serious, (2) Death > sequelae > not recovered > recovering > recovered > unknown

6.3.6. Outcome of adverse drug reactions/adverse events by serious sex (by event) (Table 2.033x, 2.043x, 2.073x, 2.08306)

Analyzed: Safety analysis population, safety analysis population (patients for whom follow-up survey forms were collected)

Analysis details: Regarding adverse drug reactions/adverse events, the number of patients with adverse drug reactions/adverse events and the incidence of adverse drug reactions/adverse events will be tabulated by safety variables and by patient with specific background, by seriousness (non-serious, serious, and overall), and by outcome.

*In tabulation by outcome, if multiple events occurred in the same patient with the same SOC and PT, they will be included in the following order of priority for tabulation.

① Serious > non-serious, (2) Death > sequelae > not recovered > recovering > recovered > unknown

Adverse events in the safety specifications will be tabulated as necessary.

Reasons for use of this drug (Severe lupus nephritis, severe central nervous system lupus) will also be tabulated.

*This should be done similarly for events collected as follow up (Table 2.073x).

Tabulation Tables 2.03306 and 2.04306 for adverse events and adverse reactions will be summarized into one table to prepare tabulation tables. (Table 2.08306)

Tables 2.03301, 2.03303, and 2.03308 will be prepared by narrowing the observation period to Week 52 as Tables 2.0330102, 2.0330302, and 2.0330802.

Safety Specification: "Safety Specification "

Patients with Specific Backgrounds: Age [years], Pregnancy, Renal impairment, Hepatic impairment

6.3.7. Occurrence of serious hypersensitivity by number of doses (from the first to first 6 doses) (Table 2.05)

Analyzed: Safety analysis population

Analysis details: For serious hypersensitivity, the proportion of cases by SOC/PT will be tabulated by number of doses. As for the order of output, data will be output in the descending order of the number of subjects by SOC in the total/overall column, in the descending order of the number of subjects by PT, and in the order of PT codes.

By number of doses: Events that occurred on each day of administration and the next day were tabulated.

6.3.8. Incidence of adverse drug reactions/adverse events (Table 2.09xx, 2.11)

Analyzed: Safety analysis population

Analysis details: For adverse drug reactions/adverse events by seriousness (serious/all), the incidence of PT based on the person-year method and the proportion of PT by number of patients will be tabulated. As for the order of output, data should be output in the descending order of the number of PTs in the overall column of adverse events and in the order of PT codes (if the number of PTs is the same).

Safety specifications will be prepared in the same manner.

The person-year method shall be prepared in accordance with the "5.5. Incidence rate calculated using person-year method."

Safety Specification: "Safety Specification "

6.4. EFFICACY EVALUATION

6.4.1. Response rate by patient characteristic (Tables 3.01 and 10.1)

Analyzed: Efficacy analysis population

Analysis details: The number of target patients, number of effective/ineffective patients, and response rate will be calculated for each patient background item, initial administration route, and administration route.

The SELENA SLEDAI score will be used for the number of responders, number of non-responders, and response rate.

The denominator of the response rate is the number of patients included in each baseline characteristic.

Patient characteristics: Same items as "Patient composition ratio," initial route of administration, route of administration

6.4.2. Changes in responder rates (LOCF) (Tables 3.021, 3.0211, 3.0212, 3.022, 10.2)

Analyzed: Efficacy analysis population

Analysis details: The number of responders/non-responders and the responder rate will be calculated in chronological order for each efficacy endpoint (SELENA SLEDAI score, PGA score, LLDAS, reduction of steroid dose at Week 40~52). 95% confidence intervals will be calculated for assessment at discontinuation/completion (LOCF). Data will also be summarized by the presence or absence of severe lupus nephritis, presence or absence of severe central nervous system lupus, and route of administration as reasons for this drug use.

For data at discontinuation/completion (LOCF), the same analysis will be performed by patient characteristic.

For steroid dose reduction at Week 40~52, subjects whose baseline average daily steroid dose is > 7.5 mg/day will be included.

Chronological order: Week 24, Week 52, at discontinuation/completion (LOCF), and Week 40~52 (steroid dose reduction at Week

40~52)

Patient characteristics:
- SELENA SLEDAI (baseline): ≤ 9, ≤ 10
- Anti-dsDNA antibody (baseline) [IU/mL]: <30, 30 ≤
- Complement Levels:
  Low C3 and/or Low C4
  Other than the above
- C3 (baseline) [mg/dL] (<90, 90 ≤)
- C4 (baseline) [mg/dL] (<10, 10 ≤)
- Use of steroids at the start of treatment: No, Yes
- Baseline steroid [mg/day]: ≤ 7.5, 7.5<
- Immunosuppressant use: No, Yes

6.4.3. Changes over time in efficacy endpoints (LOCF) (Tables 3.03, 3.0301, 3.0302)

Analyzed: Efficacy analysis population

Analysis details: Summary statistics of (SELENA SLEDAI, PGA, Lupus Impact Tracker) will be calculated for each efficacy endpoint in chronological order.
Data will also be summarized by the presence or absence of severe lupus nephritis and by the presence or absence of severe central nervous system lupus as the reason for this drug use.

Calculation items: Score, change, percent change

Chronological order: Baseline, Week 24, and Week 52, and at discontinuation/completion (LOCF)

6.4.4. Change in the proportion of responders per system organ class in SELENA SLEDAI score (LOCF) (Tables 3.04, 3.0401, 3.0402)

Analyzed: Efficacy analysis population

Analysis details: SELENA SLEDAI score The proportion of patients with a decrease in SELENA SLEDAI score from baseline will be calculated over time for each organ system index.
Data will also be summarized by the presence or absence of severe lupus nephritis and by the presence or absence of severe central nervous system lupus as the reason for this drug use.

CONDITION: Patients with baseline SELENA SLEDAI score > 0 will be included.

Chronological order: Week 24, Week 52, or at discontinuation/completion (LOCF)

6.4.5. Proportion of patients with worsening of SELENA SLEDAI score by organ system over time (LOCF) (Tables 3.05, 3.0501, 3.0502)

Analyzed: Efficacy analysis population

Analysis details: SELENA SLEDA score The proportion of subjects with worsening of SELENA SLEDAI score from baseline will be calculated over time for each organ system index.

Data will also be summarized by the presence or absence of severe lupus nephritis and by the presence or absence of severe central nervous system lupus as the reason for this drug use.

CONDITION: Patients with baseline SELENA SLEDAI score ≥ 0 will be included.

Chronological order: Week 24, Week 52, or at discontinuation/completion (LOCF)

6.4.6. Changes in Lupus Impact Tracker scores (LOCF) (Table 3.06)

Analyzed: Efficacy analysis population

Analysis details: For Lupus Impact Tracker scores, summary statistics will be calculated for each item in chronological order.

Calculation items: Score, change, percent change

Chronological order: Baseline, Week 24, and Week 52, and at discontinuation/completion (LOCF)

6.4.7. Changes over time in laboratory tests (Anti-dsDNA, C3, C4, CH50, protein/creatinine ratio) (Table 3.07)

Analyzed: Efficacy analysis population

Analysis details: For anti-dsDNA antibody, C3, C4, CH50, and protein/creatinine ratio, summary statistics will be calculated chronologically for each item.

Chronological order: Baseline, Week 24, and Week 52, and at discontinuation/completion (LOCF)

6.4.8. Number of days with steroid dose reduction to ≤ 7.5 mg/day and/or ≥ 50% reduction from baseline (Table 3.11)

Analyzed: Efficacy analysis population

Analysis details: Summary statistics will be calculated over time for the number of days with steroid dose reduction to ≤ 7.5 mg/day and/or at least a 50% reduction from baseline.

CONDITION: Patients with baseline average daily steroid dose >7.5 mg/day will be included.

Chronological order: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

6.4.9. Changes in mean daily steroid dose (Observed) (Table 3.12x)

Analyzed: Efficacy analysis population

Analysis details: For average daily steroid dose, summary statistics will be calculated over time.

Calculation items: Mean daily steroid dose, change, and percent change

Chronological order: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

6.4.10. Change from baseline in average daily steroid dose (Table 3.13)

Analyzed: Efficacy analysis population

Analysis details: The proportion of patients leading to the following calculation items will be calculated in chronological order.

Calculation items: 1. Mean daily steroid dose decreased

2. Mean daily steroid dose increased
3. Decrease from baseline average daily steroid dose >7.5 mg/day to ≤ 7.5 mg/day
4. Increase from baseline average daily steroid dose ≤ 7.5 mg/day

Chronological order: Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52

6.4.11. Cumulative steroid dose (Table 3.14)

Analyzed: Efficacy analysis population

Analysis details: For cumulative steroid dose, summary statistics will be calculated.

6.4.12. Time-course plots for the proportion of responders in SELENA SLEDAI score, PGA score, and LLDAS (Figure 3.0x)

Analyzed:	Efficacy analysis population
Analysis details:	For each efficacy endpoint (SELENA SLEDAI score, PGA score, LLDAS), responder rates will be calculated over time and bar charts will be prepared. The denominator for the responder rate is the number of patients. Additionally, for the Lupus Impact Tracker, a bar chart of mean + standard deviation will be produced over time.
Chronological order:	Week 24, Week 52, and at discontinuation/completion (LOCF) (SELENA SLEDAI score, PGA score, LLDAS)

6.4.13. Time Course Plot of Lupus Impact Tracker Score (Figure 3.04)

Analyzed:	Efficacy analysis population
Analysis details:	For the Lupus Impact Tracker scores, bar charts of mean + standard deviation will be prepared over time for each item.
Chronological order:	Baseline, Week 24, and Week 52, and at discontinuation/completion (LOCF)

6.4.14. Time course of percent improvement in steroid group (Figure 3.05)

Analyzed:	Efficacy analysis population
Analysis details:	For the improvement rate of steroid treatment, Kaplan-Meier plots will be calculated with the time point when the dose of steroid becomes 7.5 mg/day or less or the dose of steroid from baseline becomes 50% or less as an event.
CONDITION:	Patients with baseline average daily steroid dose >7.5 mg/day will be included.

6.4.15. Changes in laboratory values (Anti-dsDNA, C3, C4, CH50, protein/creatinine ratio) (mean + SD) (Figure 3.06x)

Analyzed:	Efficacy analysis population
Analysis details:	For anti-dsDNA antibody, C3, C4, CH50, and protein/creatinine ratio, time-course plots of mean + standard deviation will be prepared for each item.
Chronological order:	Baseline, Week 24, and Week 52, and at discontinuation/completion (LOCF)

6.4.16. Changes in the proportion of patients receiving immunosuppressants (Table 3.15)

Analyzed:	Efficacy analysis population
Analysis details:	The number of target patients (number of patients using the drug) and the usage rate will be calculated by immunosuppressant and immunosuppressant (biologic drug) for each drug code (GSKdrug) and generic name. The denominator of the usage rate is the number of patients in each analysis set.
Chronological order:	Prior treatment, Separate volume 1, Separate volume 2

6.5. List/fixed form

- ✧ List for consideration of inclusion/exclusion (List1)
- ✧ Listing of adverse events (Listing 2)
- ✧ Survey case report forms/list of patients (List 3)
- ✧ List of serious adverse reactions (Listing 4)
- ✧ List of adverse events by safety specification item (all patients) (Listing 5.1x)
- ✧ List of adverse events by safety specification (serious cases) (List 5.2x)
- ✧ Listing of adverse reactions by safety specification item (all patients) (Listing 5.3x)
- ✧ Listing of adverse reactions by safety specification (serious cases) (Listing 5.4x)
- ✧ Summary list of deaths (Listing 6)
- ✧ Listing of adverse events in patients excluded from the safety analysis (Listing 7)
- ✧ List of MedDRA codes of safety specifications (List 8)
- ✧ List of events to be collected in follow-up (Listing 9)
- ✧ List of administration status of this drug (patients with multiple changes in administration routes) (List 21)
- ✧ List of subjects who did not undergo screening (Listing 22)
- ✧ Incidences of adverse reactions and infections in the additional pharmacovigilance plan (Attached Form 12)
- ✧ Incidences of adverse reactions and infections in the additional pharmacovigilance plan (Attached Form 12) (52 W)
- ✧ Incidences of adverse events in the additional pharmacovigilance plan (Attached Form 12 AE.)
- ✧ Case summaries from post-marketing surveillance, etc. (Attached Form 16)

6.6. Exploratory Analyses

CCI

CCI
[redacted]

CCI

[redacted]

CCI

[redacted]

6.7. Additional tabulation for MA

[Addition of forms]

The following tables and figures will be prepared by category of the average daily dose of steroid at the start of treatment [mg/day] (0, 0< to ≤ 5 mg, 5< to ≤ 10 mg, 10 mg<, unknown).

Original table number	Additional Table No.	Title
Table 3.01	Table 5.011	Response rate by steroid dose category and patient background
Table 1.022	Table 5.012	Summary statistics of patient characteristics by steroid dose category
Table 3.021	Table 5.02	Changes in responder rates by steroid dose category (LOCF)
Table 3.03	Table 5.03	Changes in efficacy endpoints by steroid dose category (LOCF)
Table 3.07	Table 5.04	Changes in laboratory tests (Anti-dsDNA, C3, C4, CH50, protein/creatinine ratio) by steroid dose category
Table 3.12	Table 5.05	Changes in mean daily steroid dose by steroid dose category
Table 3.13	Table 5.06	Change from baseline in mean daily steroid dose by steroid dose category
Graphic 3.01	Graphic 5.01	Changes in the proportion of responders in SELENA SLEDAI score by steroid dose category
Figure 3.06x	Figure 5.02x	Changes in laboratory tests (Anti-dsDNA, C3, C4, CH50, protein/creatinine ratio) by steroid dose category (mean + SD)

7. Appendix

Additional analysis plan (V2.0): For risk factor analysis using additional collection survey form for literature

Benlsyta_207735_Additional_SAP_V4.0_20240705.docx

E_Benlysta_207735_Additional_Mock_V4.0_20240705.xlsx

E_Benlysta_207735_Additional_TOC_V4.0_20240705.xlsx

8. Document Change History

Date	Version	Author	Description
07-Sep-2018	1.0	PPD PPD	Original Version
08-Feb-2019	2.0	PPD PPD	2.2: Correction of “ethical drug data file ” to“ GSKdrug ” 3.: Addition of LLDAS and LOCF 4.3.1: Deleted “start date of administration of this drug or ” in the condition for exclusion of S1 and S2 (allowed for all-case surveillance). Terminology for identical cases in S6 and S7 was changed to make it easier to understand. 4.3.2: Addition of imputation method for SELENA SLEDAI, PGA, and Lupus Impact Tracker 4.4.5: Corrected to the effect that the date of this drug promotion status will be used for imputation in the case of "continuation of administration" of steroids. Correction of 4.5: Week 52 from “365 days ” to“ 364 days ” 4.8: Addition of therapeutic class definitions 4.9: Addition of the definition of complication classification 4.10: Added Responders (definition of efficacy) 4.11: Added SELENA SLEDAI organ domain categories and score 4.12: Addition of average daily steroid dose 4.13.1: The title was divided into sections as "Efficacy assessments and laboratory data." The sentence, "For the visit at the start of treatment with this drug, the visit information described in the CRF will be used for analysis" was deleted, because unscheduled data can be obtained also on the start day of treatment. 4.13.2: Addition of steroid for SLE 4.14: Corrected the description of the same case. 5.2: It was added that baseline should include the start date of treatment in

Date	Version	Author	Description
			the calculation of steroids.
08-Feb-2019	2.0	PPD PPD	6.2.1: The title was changed to "Case Composition Ratio and Summary Statistics" (As a result of considering the items that were not categorized in the overseas studies, it was decided to present them in a separate table.). Addition of overlapping tabulation of reasons for administration of this drug Disease duration and body weight category Medical history, the average daily dose of steroid was added at the start of treatment. Addition of summary statistics item Addition of baseline category, laboratory test items, screening items, and periodic use status 6.2.2: Clarification that the SELENA SLEDAI score is used for efficacy 6.2.3, 6.2.4: Corrected to GSKdrug, and description adjustment Clarification that the SELENA SLEDAI score is used for efficacy 6.2.5: The route of administration and the total number of doses were added to the details of analyses. The initial administration route and administration route were added to the items, and the items other than administration period were divided into IV and SC. 6.3.3: Clarified that it is by safety specification 6.3.4, 6.3.5: The tabulation of transcription of serious sex of adverse reactions/adverse events was added. 6.3.6: Addition of "Occurrence status of serious hypersensitivity by number of doses (from the first to 6 doses)" in accordance with the overseas situation 6.4: Addition of efficacy analysis item 6.5: Clarification of Listing3 added In addition, typographical errors and formatting were corrected.
06-Sep-2019	3.0	PPD PPD	4.3.1: Details were added because subjects who completed the study before the contract period were not excluded. 4.4.4: Handling of "unknown" and details were added 4.4. 5; Modified to impute at the end date of administration of this drug. 4.5: Corrected the description of the end date of administration of this drug. 4.10, 6.4.2: Changed "responder" to "responder." Unified PGA to "score"

Date	Version	Author	Description
			for all, and added "reduction in steroid dose at Week 40~ 52." 4.13.1: Deletion of assessment window at discontinuation/completion 4.17: Specified the handling of fixed cases by booklet 6: Changed from “Table ” to“ Figure ” 6.2.1, 6.3.1, 6.4.2: Addition of items and modification of terms/definitions 6.2.5: Denominator to match dosage form specified 6.3.4: Handling of multiple events was corrected along with Mock. 6.3.5: Addition that adverse events will be tabulated as necessary 6.4.7, 6.4.15: Tabulation of changes in laboratory values/addition of graphs 6.4.10: 1 item deleted and moved to Responder Definition 6.5: Deletion of "List of factors other than this drug that are suspected to be related" and addition of reexamination application material "Attached Form 12" 6.6.5: Addition of “Outcomes of serious ADRs by sex for which significant differences were found ” 6.6.6: Addition of “Outcomes of serious ADRs by sex for which significant differences were found (by event) ” Overall: Term for steroids was unified to "average daily dose" and adjusted. In addition, typographical errors were corrected, and the format and terms were unified.
02-Mar-2020	4.0	PPD PPD	4.3.1: Related text was deleted because dates of start/end of treatment are not subject to exclusion, regardless of the contract period. 6.1.1: The number of sites registered in the survey (Table 1.01) was deleted because it is unnecessary. 6.1.2: Addition of fixed number of volumes (Table 1.08) 6.2.1, 6.3.1, 6.3.4, 6.3.5: Corrected descriptions of items according to the mock. 6.6.1: Addition of efficacy analysis set, fixation of items 6.6.2, 6.6.3: Addition of efficacy analysis set, modification of terms 6.6.4, 6.6.5, 6.6.6: Changed to output for the items with $p<0.05$ in the multivariate analysis. General term correction: “Anti-dsDNA ” →“ Anti-dsDNA antibody ”
25-Dec-2020	5.0	PPD PPD	4.12: It was clearly stated that the tabulation of steroid was performed during the period of administration of this drug.

Date	Version	Author	Description
			4.15: Clarification added re AEs noted in follow up 4.18: Criteria for continuation/completion/discontinuation of treatment were added. 5.3 and 5.4: Since no test is performed and no p-value is calculated, related parts are deleted/changed. 5.4: Specification of the judgment criteria for influencing factors, and specification of handling of multivariate analysis 6.1: Added that "the number of subjects will be calculated for each separate volume" (deleted from 6.1.1) 6.2.1: Added Status of continuation of administration of this drug, added “Mean daily dose of steroid at the start of administration (2) ” in association with the addition of 6.7, deleted ‘ unknown ’ from the items of the structure (e.g., laboratory test) for which no record is generated if there is no measurement, and added the items related to ‘ priority investigation items. ’ Former 6.2.6: The continuation status was added to 6.2.1 and the reason was added chronologically in 6.3.7. 6.2.6: Added “Period of administration of this drug by reason for discontinuation/completion of administration ” in line with the standard analysis plan. 6.3.2: Addition of tabulation of adverse events 6.3.2, 6.3.3, 6.3.5: Tabulation of adverse reactions/adverse events described in follow-up investigation was added. 6.3.3, 6.3.5, 6.4.2.6.4.3, 6.4.4, 6.4.5: Tabulation by presence/absence of severe lupus nephritis and by presence/absence of severe central nervous system lupus as reasons for this drug use was added. 6.5: The list of serious adverse events was changed to the list of serious adverse reactions. The list by safety specification item was changed to adverse events and to all cases and serious cases. The list of patients excluded from the safety revision was deleted. Appendix Form 16 was deleted because it is essential only for the application for reexamination under the partnership. (Appendix Form 12 will be kept because it will be used for the stability report.) 6.7: Addition of forms to be used when making presentations at academic conferences/preparing papers from MA 6.6: Modification of the exploratory analysis algorithm CCI [redacted]

Date	Version	Author	Description
			CCI [redacted] 6.7: Added as a summary table to be used for presentation at academic conferences and submission of papers (It may be also used for reports as needed.) In addition, errors in writing were corrected, and the format and terms were unified.
03-Dec-2021	6.0	PPD PPD	3.Definition of terms: Addition of PML 4.2: Added the definitions of "institutions which may publish information" and "patients who completed the observation period (interim analysis)." 4.3.2: Added pediatrics to ‘ Off label use ’ and corrected the order of priority 4.10: The text to permit the post-approval use of “anifrolumab ” was added to the definition of LLDAS. 4.15: Corrected follow-up events 4.17: Added that "Patients who completed the observation period (interim analysis)" should be referred to. 6.3.2: Category correction 6.3.2, 6.3.3, 6.3.5: Tabulation of follow-up investigation was unified to “events. ” 6.5: The list of adverse reactions by safety specification (all patients), the list of adverse reactions by safety specification (serious cases), and the incidences of adverse events under the additional pharmacovigilance plan were added. In addition, errors in writing were corrected, and the format and terms were unified.
01-Jul-2022	7.0	PPD PPD	4.10: Change of LLDAS definition 6.2.1, 6.3.1, 6.4.2, 6.6.1: Changed the definition of Complement Levels. Added for 6.2.3:2022JCR Graph added for 6.2.6:2022JCR 6.3.3, 6.3.5: Patients with specific backgrounds, added for 2022JCR and for interim papers 6.5: Addition of listing related to follow-up investigation In addition, errors in writing were corrected, and the format and terms were unified.

Date	Version	Author	Description
23-Dec-2022	8.0	PPD PPD	4.2: Addition of patients for whom the surveillance form should be collected (lifting of approval conditions) 5.5: Addition of incidence rate based on person-years method for an interim article 5.6.2: Addition of the figure of patient composition for the lifting of approval conditions 5.7.4: Addition of concomitant drugs used by Week 24 (described in Separate Volume 1) for the interim report 5.7.6: The duration of treatment was changed from (days) to (weeks), and a Kaplan-Meier plot for continuation rate was added. 5.8.2: The category of period was changed from (days) to (weeks), and the graph was added. 5.9.16: Added for the interim report 5.11. 1, 5.11.3: For the interim report, the analysis as adverse events, serious adverse events, infections, and serious infections was added.
23-Jan-2023	8.1	PPD PPD	Cover page: Department signature change 5.7.1, 5.7.3, 5.7.5, 5.11.1: Added tabulation for patient background variables for SC and IV (including baseline) in response to the comment from the author of the interim article that was not reflected at the time of the revision of Version 8.0 (It was changed to V8.1 because it was a revision associated with V8.0.). 5.11.1: The item was corrected due to inconsistency with Mock.
05-Mar-2024	9.0	PPD PPD	Cover page: Change of approver 4.18: Change of the definition of “discontinuation/completion of administration ” in the logic judgment 4.19: Addition of handling of tabulation for literature 7. Appendix: Analysis plan for additional analysis for literature is attached.
26-Apr-2024	10.0	PPD PPD	Cover page: Change of approver 4.2: Modification of the definition of subjects who completed the observation period (interim analysis) 7. Appendix: Replaced with the Statistical Analysis Plan for Additional Analyses for the Publication (V2.0)
17-May-2024	11.0	PPD PPD	7. Changed to Appendix: Analysis Plan for Additional Analyses for Scientific Manuscripts (Version 3.0), and deleted file pasting because no file is attached when converted to PDF.
05-Jul-2024	12.0	PPD PPD	7. Appendix: Changed to the Analysis Plan for Additional Analyses for Publications (V4.0)

Date	Version	Author	Description
30-Sep-2024	13.0	PPD PPD	4.18: Handling change for fixed cases of Volume 1 only 4.19: Addition of handling of the survey form of “depression-related events” collected additionally, and addition of handling of AEs for the final article Addition of forms to respond to inquiries at the time of reporting the lifting of approval conditions 4.15: Added the definition of the 52 week observation period. 6.3.4: Onset status of related AEs by administration route 6.3.6: Addition of a report that narrowed the observation period to 52 weeks to compare with overseas clinical studies 6.4.1: Addition of initial administration route and efficacy percentage by administration route 6.4.2: Addition of responders by administration route 6.5: A list was added.