BENLYSTA for Intravenous Injection/ Subcutaneous Injection Special Drug Use Investigation

Protocol

GlaxoSmithKline K.K.

Revised : 27 June, 2025 (Vers. 4.2)

<Table of Contents>

1. Objectives

The objective of this study is to collect and assess the information about long-term safety and effectiveness of Benlysta for intravenous injection and Benlysta for subcutaneous injection (hereinafter referred to as "Benlysta") in daily clinical practice.

[Conditions for Approval]

By conducting a drug use investigation (DUI) in all patients until data are accumulated from a certain number of patients after Benlysta being marketed, collect the data on safety and effectiveness of Benlysta in an early stage and thereby take the necessary measures for proper use of Benlysta.

2. Safety Specification

In this study, the safety concerns and priority study matters are as follows, occurrence of adverse drug reactions (ADRs), etc. will be monitored.

- Serious hypersensitivity
- Serious infections (including tuberculosis (TB), pneumonia, pneumocystis jiroveci pneumonia (PCP), sepsis, and opportunistic infection (OI))
- Reactivation of hepatitis B (HB) virus
- Progressive multifocal leukoencephalopathy (PML)
- Interstitial pneumonitis (IP)
- Malignant tumour (MT)
- Depression, suicidal ideation, suicide attempt

3. Target Population

The study will include all patients to whom Benlysta is administered (except patients aged <15 years who start Benlysta administration since approval for paediatric dosage*). In addition, among patients who start the administration after launch, those to whom Benlysta has already administered before the conclusion of the contract and those who has already started administration at diagnosis, because of hospital transfer, etc. will be included as well.

* : Because the study for paediatric patients is separately conducted following approval for paediatric dosage

The [INDICATIONS] of PRECAUTIONS CONCERNING INDICATIONS of Benlysta are as follows (For details, see the latest Package Insert).

＜Revised: October 2019 (Version 4), excerpts from the Package Insert＞

【INDICATIONS】

Patients with systemic lupus erythematosus (SLE) who inadequately respond to existing treatments

PRECAUTIONS CONCERNING INDICATIONS

1. Administer Benlysta to patients additionally if they have disease activity even if they are treated for SLE appropriately with steroids and immunosuppressants etc. in the past.
2. Use Benlysta in SLE patients who are confirmed positive for autoantibodies, such as anti-nuclear antibody and anti–double stranded DNA (anti-dsDNA) antibody.

3. In clinical studies, the effectiveness and safety of Benlysta have not been investigated in SLE patients with severe lupus nephritis or severe central nervous system (CNS) lupus (See "CLINICAL STUDIES" section).
4. In clinical studies, the effectiveness and safety of Benlysta have not been investigated in combination with other biologics or intravenous cyclophosphamide (See "CLINICAL STUDIES" section).
5. Be well informed about the contents of “CLINICAL STUDIES” section and have good understanding of the effectiveness and safety of Benlysta and select appropriate patients (See “CLINICAL STUDIES” section).

4. Target Sample Size and Rationale

1) Target number of patients : 600 (as a safety analysis set)
2) Rationale : Benlysta may increase sensitivity to infections due to the mechanism of action. In clinical studies, there were some reports of patients who had a fatal course. Focusing on serious infections, the incidence rates of the serious adverse event (AE) “Infections and Infestations” (SOC) were 5.3% (25/470 patients) and 4.1% (23/556 patients) in the phase III international joint studies [Study BEL113750 (intravenous administration) and Study BEL112341 (subcutaneous administration)], respectively.

Under the assumption that the incidence rate of the serious infections is 5.3% as a threshold on the basis of the results of the phase III international joint studies, 553 patients are required to monitor the incidence rate in the post-marketing surveillance with estimation accuracy that enables a power for the 5.3% threshold to be ≥80% in case where the real risk exists 1.5 times or more of the threshold. It is considered possible to evaluate occurrence of the serious infections in the special DUI (SDUI) having 600 patients as a target sample size.

The incidence rate of ADRs occurring in one patient was 0.2% in the phase III international joint studies. The power to detect an ADR whose incidence rate of 0.2% is 69.9% in at least one patient out of 600 patients.

5. Planned Number of Medical Institutions by Department

All medical institutions where Benlysta is prescribed (except medical institutions that prescribe Benlysta only for patients aged <15 years since approval for paediatric dosage)

6. Study Period

1. Study conduct

Study period : launch date of Benlysta to three months after termination of the observation period in patients eligible for case report form (CRF) collection (period of the follow-up investigation, if conducted) or lifting date of approval conditions, whichever comes later

Observation period :

The observation period per patient will be 52 weeks from the start of Benlysta administration.

For patients who continue administration at the end of the observation period, conduct the two-year follow-up investigation as much as possible, and monitor occurrence of AEs leading to death, serious infections, PML, and MT.

If a patient has withdrawn from /terminated administration of Benlysta, it will be until the withdrawal/termination.

Scheduled enrolment period : launch date of Benlysta to six months after lifting of approval conditions

Patients are eligible for CRF collection when starting Benlysta administration by 31 October, 2018, and CRFs will be collected as required when patients start the administration since 1 November, 2018. Additionally, patients are eligible for enrolment when starting the administration by the acknowledgment of the report at a committee meeting, where the all-case investigation-related conditions for approval are lifted (except patients aged <15 years who start Benlysta administration since approval for paediatric dosage), and enrolment will continue.

2. Study end

Completion of final analysis : July 2025

Completion of final report writing : December 2025

7. Study Methods

1. Requirements for supply

For supply, confirm that medical institutions and physicians meet the following requirements.

1) Requirements for medical institutions

Medical institutions sufficiently capable of taking emergency measures, including infections, such as pneumonia, sepsis, and TB

2) Requirements for physicians

Physicians who correspond to any of the following;

1. Certified as a rheumatologist and an attending rheumatologist, experienced in the treatment of SLE
2. Specialised in rheumatic disease, certified as an intractable disease designated physician and cooperated intractable disease designated physician, experienced in the treatment of SLE
3. Sufficiently experienced in the treatment of SLE, providing the treatment of SLE in proper cooperation with physicians who correspond to the above-mentioned
4. Providing the treatment of SLE under direct supervision of physicians who correspond to 1 and 2

The person in charge of the study (medical representative or monitoring outsourcee) will visit medical institutions before supply, explain to the planned physicians for prescribing Benlysta, etc. that Benlysta is obligated to conduct an all-case investigation, obtain the Confirmation Letter from them (head physicians) as confirmation.

2. Request and contract for the study

1) The person in charge of the study will explain the objectives, target population, study items, study methods, etc. to the planned physicians for the study, etc. at medical institutions by/to which Benlysta is adopted/supplied, and will request them to cooperate with the study.

2) If cooperation to the study has been obtained, the Written Contract should be concluded with the heads (e.g. directors, etc.) of the medical institutions before the start of the study.

3. Enrolment of target population

The study will be conducted using an all-case investigation method.

1) The investigator will record the patient information, etc. about patients eligible for enrolment in the Enrolment Form, and will fax it to the Enrolment Centre or submit it to the person in charge of the study immediately after the start of administration. The personally identifiable information, such as the name, address, date of birth, initials of patients, should not be recorded in the Enrolment Form.
<Enrolment Centre>
CCI
[redacted]

2) After approval of Benlysta, the Written Contract should be concluded before the start of administration in principle, however, patients to whom Benlysta has unavoidably been administered before the conclusion of the contract will be also enrolled as a retrospective patient.

4. Data collection and case report form (CRF) completion
   1) The investigator will confirm the study items, such as the characteristics of patients eligible for CRF collection.
   2) During the observation period, the investigator will monitor the information about safety and effectiveness, etc. If an enrolled patient does not visit the hospital during the observation period, the investigator will monitor the information about AEs and others by telephone, etc. as far as possible.
   3) The CRF consists of three CRFs to maximum, and the observation period per CRF will be defined as below.
      • CRF 1 : Week 1 to 24 after the start of administration
      • CRF 2 : Week 25 to 52 after the start of administration
      • Follow-up Investigation CRF : Year 1 to 3 after the start of administration
   4) The investigator will record the obtained information on the CRF. At the end of the observation period of enrolled patients for each CRF (or at withdrawal/termination, if a patient has withdrawn from /terminated administration of Benlysta), submit the completed CRF to the person in charge of the study. The personally identifiable information, such as the name, address, date of birth, initials of patients, should not be recorded in the CRF.
5. Confirmation of all-case investigation implementation
   Annually and after the end of the study period, the investigator will confirm whether or not enrolled patients are all receiving Benlysta, affix his/her signature or name/seal to the "Confirmation Letter of All-Case Investigation" and submit it to the person in charge of the study.

8. Study Items

The investigator will collect the information about the following items, etc. as far as possible and record it on the CRF.

1. Information about a medical institution
   Name of a medical institution, department, investigator
2. Patient characteristics (at the start of administration of Benlysta)
   Identification number, gender, year of birth or age, start date of administration of Benlysta, reason for use of Benlysta (including the presence or absence of severe lupus nephritis, severe CNS lupus), autoantibody associated with SLE (type, presence or absence of "positive"), disease duration of SLE, body weight, presence or absence of vaccination (24 weeks before the start of administration), type of vaccine and date of vaccination, past history

(TB, HB), presence or absence of comorbidities (HB, renal impairment, hepatic impairment, allergy, others) and name of comorbidities

<Definition of severe lupus nephritis, severe CNS lupus>

- Severe lupus nephritis
  Lupus nephritis with a proteinuria level of >6 gm/24 hours or equivalent according to a spot urine protein/creatinine ratio or a serum creatinine level of >2.5 mg/dl
- Severe CNS lupus
  CNS lupus with seizure, psychosis, organic brain syndrome, cerebrovascular accident, encephalitis or CNS vasculitis

To protect the confidentiality regarding identification of an individual patient, the identification number should be a unique number assigned to an individual patient by the investigator, etc.

In this study, any disease, symptom, and allergy history which is present before the start of administration of Benlysta except SLE will be handled as a “comorbidity”.

The disease activity and diseased organ systems will be defined by SELENA SLEDAI score at the start date of administration (specified in "11. Course of clinical symptoms" section).

3. Screening test regarding TB before the start of administration
   Presence or absence, and results of chest image test, tuberculin reaction, interferon-gamma release assay
   (The chest image test includes the presence or absence of findings of old TB.)

<Related descriptions in the Package Insert (For details, see the latest Package Insert)>

<Revised: October 2019 (Version 4), excerpts from the Package Insert>

2. IMPORTANT PRECAUTIONS (for intravenous use)*

(3) Confirm the presence or absence of infection tuberculosis by performing interferon-gamma release assays and timely chest computed tomography, etc. in addition to sufficient interviews and chest X-ray tests for tuberculosis prior to administration of Benlysta. Consult with experienced physicians in diagnosing tuberculosis if patients have a history of tuberculosis and suspected infection tuberculosis. For any of the following patients, administer appropriate antituberculosis drugs prior to administration of Benlysta, in principle.
1)Patients with an estimated shadow to consistent with old tuberculosis on chest image test
2)Patients with a history of tuberculosis treatment (including extrapulmonary tuberculosis)
3)Patients who are strongly suspected of having been previously infected by tests such as interferon-gamma release assays
4)Patients with a history of close contact with tuberculosis patients
In addition, extra caution should be exercised regarding occurrence of tuberculosis, for example, perform regularly appropriate tests, such as chest X-ray tests during administration of Benlysta, and instruct patients to contact their attending physicians immediately if suspected symptoms of tuberculosis occur (persistent cough, pyrexia, etc.). Do not administer Benlysta if active tuberculosis has been confirmed.

*: Described in “2. IMPORTANT PRECAUTIONS (4)” in the Package Insert for subcutaneous use.

4. Screening test regarding HB before the start of administration

Presence or absence, and results of testing for HBs antigen, HBs antibody, HBc antibody, HBV-DNA quantification

<Related descriptions in the Package Insert (For details, see the latest Package Insert)>

<Revised: October 2019 (Version 4), excerpts from the Package Insert>

2. IMPORTANT PRECAUTIONS (for intravenous use)*

(6) Confirm the presence or absence of HB virus infection prior to administration of Benlysta as hepatitis associated with reactivation of HB virus may occur in patients who are HB virus carriers or have been previously infected with HB virus (HBs antigen negative, and HBc antibody or HBs antibody positive).
If Benlysta is administered to patients who are HB virus carriers or have been previously infected with HB, caution should be exercised regarding occurrence of signs and symptoms of reactivation of HB virus, for example, monitor hepatic function test values and hepatitis virus markers.

*: Described in "2. IMPORTANT PRECAUTIONS (7)" in the Package Insert for subcutaneous use.

5. Pre-treatment drugs intended for SLE
Presence or absence of drugs intended for SLE and name of drugs, from 4 weeks before the start of administration to the day before the start
Biological preparations and cyclophosphamide (intravenous injection) except Benlysta will be monitored from 24 weeks before the start of administration to the day before the start.
6. Administration status of Benlysta
Administration route of Benlysta during the observation period (Regarding subcutaneous injection, record any of the autoinjector or syringe.), single dose, duration of administration, administration interval during each period, dosing frequency during each period, reason for revision of the Dosage and Administration and drug withdrawal
7. Concomitant drugs (SLE drugs)
Presence or absence of concomitant drugs (SLE drugs), name of drugs, during the observation period
For systemic steroids, the information about the presence or absence of concomitant use, name of drugs, administration route, daily dose (dose, unit), duration of administration, reason for revision of the Dosage and Administration will be collected. For cyclophosphamide, the information about the presence or absence of concomitant use and administration route will be collected.
8. Concomitant drugs (except SLE drugs)
Presence or absence of concomitant drugs intended for SLE (except SLE drugs), name of drugs, reason for administration, during the observation period
9. Concomitant therapies intended for SLE (except drugs)
Presence or absence of concomitant therapies intended for SLE (except drugs), name of therapies, during the observation period
10. Vaccination
Presence or absence of vaccination, type of vaccine, date of vaccination, during the observation period
11. Course of clinical symptoms
The information about the following items will be collected.

1) Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA SLEDAI)

Record the presence or absence of assessment, assessment date, results of assessment at the start date of administration*, Week 24 and 52 after the start of administration, or withdrawal/termination (See Appendix 1).

* : If no information is available about the results of assessment at the start date of administration, record the information closest to the start date in the results of SLE diagnosis to the start date.

2) Physician's Global Assessment (PGA)

Record the presence or absence of assessment, assessment date, results of assessment at the start date of administration, Week 24 and 52 after the start of administration, or withdrawal/termination.

The PGA is a 0-10 cm visual analogue scale (VAS). The investigator will assess the patient's global disease activity, and draw a vertical line between 0 CCI and 3 CCI (See Appendix 2).

0 : CCI

1 : CCI

2 : CCI

3 : CCI

3) Assessment of Daily Living by Lupus Impact Tracker

Record the presence or absence of assessment, assessment date, results of assessment at the start date of administration, Week 24 and 52 after the start of administration, or withdrawal/termination.

The investigator will interview patients about their conditions in the previous one month using Lupus Impact Tracker, the impact on daily living will be assessed using a 5-point scale of 0 CCI to 4 CCI

CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

* 0 : CCI 1 : CCI 2 : CCI
3 : CCI 4 : CCI

12. Laboratory tests

1) Monitoring for TB (if a patient has TB as a past history)

Presence or absence, test date, results of chest image test and interferon-gamma release assay (The chest image test includes the presence or absence of findings of activity.)

2) Monitoring for HB (if a patient is a HB virus carrier or has a past HB infection)

Presence or absence, test date, results of HBV-DNA quantification test and hepatic function test (aspartate aminotransferase (AST), alanine aminotransferase (ALT))

3) The information about the following items will be collected.
Presence or absence of assessment, assessment date, results of assessment at the start date of administration*, Week 24 and 52 after the start of administration, or withdrawal/termination
* : If no information is available about the results of assessment at the start date of administration, record the information closest to the start date in the results of SLE diagnosis to the start date.
   i) Immunological test
   Anti-double-stranded DNA (anti-dsDNA) antibody, C3, C4, CH50
   ii) Renal function test
   Protein/creatinine ratio

13. Continuation status of Benlysta administration at the end of the observation period
Continuation status of Benlysta administration at the end of the observation period, the reason if a patient has withdrawn from/terminated administration
14. Possibility of study continuation
Possibility of implementing the two-year follow-up investigation after the end of the observation period (until 3 years after the start of administration) (if a patient continues Benlysta administration at the end of the observation period)
15. Pregnancy
(For female patients) whether or not Benlysta is administered to a pregnant woman, whether or not a patient is pregnant during the observation period and estimated delivery date
In addition, the follow-up investigation should be conducted for a mother and her foetus as far as possible regarding the course of delivery, spontaneous abortion, elective abortion, and AEs, etc.
16. Adverse events (AEs)
Presence or absence of AEs after the start of administration, diagnosis or symptoms, occurrence date, outcome of AEs, outcome date, seriousness, reason for assessing as serious, relationship to Benlysta, factors suspected of being related to AEs except Benlysta
If the events corresponding to the priority study matters occur, the detailed investigation will be conducted about the course of occurrence, therapeutic regimen, etc.
   1) To grasp the priority study matters and ADRs, the investigator will collect the information about all AEs (e.g., a disease, symptom, abnormal laboratory value) occurring after the start of administration, regardless of whether or not Benlysta is related to an AE. Considering whether or not the possibility of a reasonable relationship to Benlysta is present, etc., the relationship to Benlysta will be assessed on any of “related” or “not related”.
   2) The AEs assessed as “related” to Benlysta will be handled as an “ADR” suspected of being caused by Benlysta.
17. Two-year follow-up investigation after the end of the observation period (if Yes in "14. Possibility of study continuation")
Assessment date, presence or absence of AEs leading to death, serious infections, PML, and MT, diagnosis or symptoms, occurrence date, outcome of AEs, outcome date, seriousness, reason for assessing as serious, relationship to Benlysta, factors suspected of being related to AEs except Benlysta

9. Analysis Items and Methods

1. Analysis items
   1) Patient disposition-related matters
      i) Number of enrolled patients and number of patients whose CRF is collected and fixed
      ii) Number of patients included in the safety analysis set and number of patients included in the effectiveness analysis set, number of patients excluded from analysis and the reason for exclusion
   2) Safety-related matters
      i) Occurrence of ADRs/infections (type, severity, and incidence rate of ADRs, etc.)
      ii) Factors that potentially affect safety (occurrence of ADRs and infections by patient characteristics, etc.)
      iii) Occurrence of ADRs of events defined as a priority study matter
   3) Effectiveness-related matters
      i) Changes in SELENA SLEDAI score, Lupus Impact Tracker score, PGA score, steroid dose, each laboratory test item, and achievement of Lupus Low Disease Activity State (LLDAS)
2. Analysis methods

Concerning the items associated with safety and effectiveness, etc., the odds ratio and 95% confidence interval will be calculated for the factors that potentially affect them. These will be graphically presented using a forest plot, etc., as appropriate. For comparison of the scores, etc., the mean values and quartile points, etc. for values at the time of measurement and changes from baseline will be calculated.

10. Organizational Structure

See Attachment 1.

11. Name, Address of the Outsourcees, and the Scope of the Outsourced Operations

CCI

[redacted]

CCI [redacted]

12. Scheduled Timing to Be a Milestone for Assessing the Status and Results in the Study or Reporting to the Pharmaceuticals and Medical Devices Agency (PMDA) and Rationale

- At the time of Periodic Safety Reports : consideration will be comprehensively given to the safety and effectiveness information.
- At the time of re-examination application : the final report will be prepared/submitted, based on the results of tabular analysis obtained from the fixed data of all collected CRFs.

13. Additional Measures that Have a Potential to Be Taken Depending to the Study Results and the Decision Criteria for the Start

The Risk Management Plan, including the following, will be reviewed at the timings to be a milestone.

- Regarding the safety specification, including the priority study matters, if the proportion of occurrence, peak occurrence period and risk factors become visible as an ADR caused by Benlysta, the necessity for revising the Package Insert and study materials will be considered as appropriate.
- Including whether or not a new concern in the safety specification is present, the necessity for changes in the content of plan in the study will be considered.
- The necessity for creation of the Risk Minimization Plan for a new concern in the safety specification will be considered.

14. Publication of the Study Results

The information regarding the results of the study will be provided to clinical sites as an interim report and a final report as appropriate for the purpose of “proper use” and “safety assurance”, considering a proper timing and the number of patients whose CRF is collected, etc., by means of presentation at academic conferences and papers.

In addition, the summaries of the plan and results in the study will be disclosed in GSK Clinical Study Register.

15. Other Requirements

1. Protocol revision

   The progress in the study, the number of patients excluded from analysis, occurrence of unexpected/serious ADRs, large increase in occurrence of specific ADRs and validity of the study items, etc. will be timely grasped during the study period, and the Protocol will be reviewed and revised if required.

   If the content of the Protocol in the study has been changed, the Change Notification should be submitted to the PMDA in advance, except for minor changes.

2. Measures to be taken in detecting issues or concerns

If issues, etc. have been detected from the results of assessment/analysis during the study period or after completion of the study, consideration will be given on whether or not the SDUI or Post-marketing Clinical Study should be newly conducted, as appropriate.

16. Attachments

Appendix 1

SELENA SLEDAI INSTRUMENT SCORE (From [Petri, N Engl J Med 2005])

Wt	Descriptor	Definition
8	Seizure	Recent onset (last 10 days). Exclude metabolic, infectious or drug cause, or seizure due to past irreversible CNS damage.
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, or increased or decreased psychomotor activity. Exclude metabolic, infectious or drug causes.
8	Visual disturbance	Retinal and eye changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, optic neuritis, scleritis or episcleritis. 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 nonresponsive to narcotic analgesia.
8	CVA	New onset of cerebrovascular accident(s). Exclude arteriosclerosis or hypertensive causes.
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis.
4	Arthritis	More than 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion).
4	Myositis	Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis.
4	Urinary casts	Heme-granular or red blood cell casts.
4	Hematuria	>5 red blood cells/ high power field. Exclude stone, infection or other cause.
4	Proteinuria	New onset or recent increase of more than 0.5 gm/24 hours.
4	Pyuria	>5 white blood cells/ high power field. Exclude infection.
2	Rash	Ongoing inflammatory lupus rash.
2	Alopecia	Ongoing abnormal, patchy or diffuse loss of hair due to active lupus.
2	Mucosal ulcers	Ongoing oral or nasal ulcerations due to active lupus.
2	Pleurisy	Classic and severe pleuritic chest pain or pleural rub or effusion or new pleural thickening due to lupus.
2	Pericarditis	Classic and severe pericardial pain or rub or effusion, or electrocardiogram confirmation.
2	Low complement	Decrease in CH50, C3 or C4 below the lower limit of normal for testing laboratory.
2	Increased DNA binding	>25% binding by Farr assay or above normal range for testing laboratory.
1	Fever	>38°C, Exclude infectious cause.
1	Thrombocytopenia	<100,000 platelets/mm^3.
1	Leukopenia	<3,000 white blood cells/mm^3. Exclude drug causes.

Appendix 2

Physician's Global Assessment (PGA) Visual Analogue Scale (From [Petri, N Engl J Med 2005])