BEconneCTD-ILD

GSK221672

A Phase 3, randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of belimumab administered subcutaneously in adults with interstitial lung disease (ILD) associated with connective tissue disease (CTD)

This document is based on protocol amendment 1 dated 20 Jan 2025.

Medical Monitor Contact Information

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Inclusion Criteria

Participants are eligible to be included only if all of the following criteria apply:

- Participant is 18 years of age inclusive, or older at the time of signing the informed consent. **INC#1**
- Documented diagnosis of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), idiopathic inflammatory myopathy (IIM; including polymyositis, dermatomyositis, antisynthetase syndrome), Sjogren's syndrome (pSS), or mixed connective tissue disease (MCTD) in accordance with internationally recognized classification criteria (see Protocol Section 10.9 [Appendix 9]). NOTE: patients with overlap syndrome (including SSc overlap) are permitted if their primary diagnosis is RA, SLE, IIM, pSS or MCTD. **INC#2**
- Diagnosis of ILD on HRCT with disease extent of ≥10% of the whole lung (WL-ILD), as confirmed by central reader at screening. NOTE: the 10% extent of ILD includes the combined assessment of reticulation/fibrosis and ground glass opacity) **INC#3**

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Scan the code or visit [**studywebsite.com**].

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Inclusion Criteria (cont)

- Evidence of ILD progression in the previous 24 months defined as at least one of the following criteria **INC#4**
  - ≥10% relative decline in FVC, OR
  - ≥5 to <10% relative decline in FVC combined with worsening of respiratory symptoms, OR
  - ≥5 to <10% relative decline in FVC combined with radiological evidence of ILD (combined assessment of reticulation/fibrosis and ground glass opacity) progression as assessed by the investigator comparing the screening scan and a previous scan done within 24 months prior to screening, OR
  - Relative decline in DLCO (corrected for hemoglobin) ≥10% combined with radiological evidence of ILD (combined assessment of reticulation/fibrosis and ground glass opacity) progression as assessed by the investigator comparing the screening scan and a previous scan done within 24 months prior to screening.
- Must be currently receiving stable standard therapy to manage ILD and/or underlying CTD, or to have failed or failed to tolerate first line standard therapy. Standard therapy can include the following, alone or in combination, in accordance with current treatment guidelines and local labels: **INC# 5**
  - Oral corticosteroids (≤20 mg/day oral prednisolone or equivalent) at a stable dose for at least 30 days prior to Day 1.
  - MMF ≤3000 mg/day or mycophenolate sodium ≤2160 mg/day, at a stable dose for at least 180 days prior to Day 1
  - MTX ≤25 mg/week, at a stable dose for at least 90 days prior to Day 1.
  - AZA ≤2.5 mg/kg/day, at a stable dose for at least 90 days prior to Day 1.
  - Tacrolimus ≤2.5 mg daily (a higher dose of 5 mg daily is allowed if the locally approved or recommended dose is higher than 2.5 mg daily), at a stable dose for at least 90 days prior to Day 1.
  - Cyclosporin ≤4 mg/kg daily, at a stable dose for at least 90 days prior to Day 1.
  - Hydroxychloroquine ≤400 mg/day, at a stable dose for at least 90 days prior to Day 1.
  - Leflunomide ≤20 mg/day at a stable dose for at least 90 days prior to Day 1.

Inclusion Criteria (cont)

- Participant is capable and willing to self-administer the study medication or has a caregiver who is capable and willing to administer the study medication throughout the study **INC#6**.
- Female participants **INC#7**: A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a WONCBP as defined in Protocol Section 10.4 (Appendix 4: Contraceptive and Barrier Guidance).

    OR
  - Is a WOCBP and using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Protocol Section 10.4 (Appendix 4: Contraceptive and Barrier Guidance) during the study intervention period and for at least 4 months after the last dose of study intervention. The investigator should evaluate potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

A WOCBP must have a negative highly sensitive pregnancy test (urine or serum, as required by local regulations) within 24 hours before the first dose of study intervention. See Protocol Section 8.3.5.

If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Additional requirements for pregnancy testing during and after study intervention are located in Protocol Section 8.3.5.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol **INC#8**.

Exclusion Criteria

Participants are excluded if any of the following criteria apply:

Medical conditions

- Diagnosis of ILD other than CTD-ILD. **EXC#1**
- Primary diagnosis of Systemic Sclerosis (SSc). **EXC#2**

Exclusion Criteria (cont)

- Participants with rapidly progressive disease (absolute drop of 10% or more of FVC between screening and baseline visit and/or recent pulmonary hospitalization). **EXC#3**
- FVC ≤45% of predicted, or a DLco (corrected for hemoglobin) ≤40% of predicted at screening. **EXC#4**
- History or presence of diffuse alveolar hemorrhage (DAH) or other confounding pulmonary disease, signs, or symptoms **EXC#5**
- Pulmonary arterial hypertension requiring therapy, as determined by the investigator at, or prior to first day of dosing (Day 1). **EXC#6**
- Dependence on continuous oxygen supplementation **EXC#7**
- History or presence of cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, hematologic, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study intervention or interfering with the interpretation of data. **EXC#8**
- Obstructive pulmonary disease (pre-bronchodilator FEV1/FVC <0.7). **EXC#9**
- Significant emphysema on screening or historical HRCT (extent of emphysema exceeds extent of ILD). **EXC#10**
- Confirmed PML or unexplained new-onset or deteriorating neurologic signs and symptoms. **EXC#11**
- Significant allergies to human or murine proteins, humanized monoclonal antibodies, or contrast agents. **EXC#12**
- Clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe post-treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear IgA dermatosis, toxic epidermal necrolysis, and exfoliative dermatitis). **EXC#13**
- Participants with PHQ-9 score ≥10, that in the opinion of a mental healthcare professional pose a serious suicide risk, or have any history of suicidal behavior in the last 6 months and/or any suicidal ideation in the last 2 months, or who in the investigator's judgment, poses a significant suicide risk.

  NOTE: For participants with a PHQ-9 score ≥10, at the screening visit or at the Day 1 visit before the first administration of the study drug, it is required that they be referred for an assessment by a mental healthcare professional (e.g. locally licensed psychiatrist, psychologist, or master's level therapist) before the investigator makes a final decision regarding suitability for enrollment. **EXC#14**

Exclusion Criteria (cont)

- Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years **EXC#15**
- Breast cancer within the past 10 years **EXC#16**
- Major surgery (including joint surgery) within 3 months prior to screening or planned during the duration of the study. **EXC#17**
- An active infection, or a history of infections as follows **EXC#18**:
  - History of opportunistic infections that have not resolved by 6 months prior to the first day of dosing (Day 1) or recurrent infection as determined by the investigator. This does not include infections that may occur in immunocompetent individuals, such as fungal nail infections or vaginal candidiasis, unless it is of an unusual severity or frequency.
  - A serious infection requiring treatment with IV antibiotics and/or hospitalization, if the last dose of antibiotics or the hospital discharge date was within 60 days of the first day of dosing (Day 1).
  - An acute or chronic infection requiring treatment with oral antibiotics or antiviral medications, if the last dose was received within 30 days of the first day of dosing (Day 1). Prophylactic anti-infective treatment is allowed.
  - Any active or unresolved bacterial, viral, or fungal infection present on the first day of dosing (Day 1), whether requiring treatment or not. This does not include fungal nail infections.
  - Active or past osteomyelitis, unless fully resolved in the opinion of the investigator.
- Symptomatic herpes zoster within 3 months prior to Day 1 **EXC#19**
- Diagnosis of active TB confirmed by 1) evidence of active TB disease from chest imaging (posterior anterior and lateral x-rays or chest CT), 2) medical history and examination, and 3) positive microscopy smear or culture for mycobacteria /positive TB PCR i.e., Xpert. A positive TST or a positive (not indeterminate) interferon-gamma release assay (IGRA) TB test such as QuantiFERON-TB Gold Plus test is indicative, but not required for diagnosis of active TB. A positive TST is defined as a skin induration ≥5 mm at 48 to 72 hours (regardless of Bacillus Calmette-Guerin or other vaccination history).

Exclusion Criteria (cont)

OR

Untreated latent TB infection confirmed by: 1) no evidence of active TB based on chest imaging, medical history and physical examination and laboratory evaluation of sputum; and 2) a positive TST, defined as a skin induration ≥5 mm at 48 to 72 hours (regardless of Bacillus Calmette-Guerin or other vaccination history); or a positive (not indeterminate) interferon-gamma release assay (IGRA) TB test such as QuantiFERON-TB Gold Plus test. Those with IGRA positive tests or positive TST who can document ongoing LTBI treatment for at least 4 weeks may be enrolled. Those with IGRA positive tests with documentation of the following may also be enrolled:

- Successful completion of treatment for active TB
- Completion of treatment for LTBI (with treatment as per local practice, for example: 3 months of isoniazid and rifampin or 4 months of rifampin or 3 months weekly isoniazid and rifapentine, or 9 months of isoniazid)
- For those participants requiring Isoniazid (INH) therapy for latent TB, AST and ALT must be assessed following 3 weeks of INH treatment in screening. Participants will fail screening if ALT >2 × ULN is identified; these participants may be re-screened if ALT elevation resolves to ALT <2 × ULN during ongoing INH therapy following discussion with the medical monitor.

Those enrolled with positive IGRA or TST will be monitored during the study for new pulmonary symptoms (worsening cough, worse in intensity and productive) as well as fevers, night sweats or weight loss. Those reporting any of the above must be immediately evaluated by a physician for physical examination, imaging by chest x-ray or CT chest scan, laboratory evaluation of sputum (microscopy smear and culture for mycobacteria), and referral to TB specialist. **EXC#20**

NOTE: The choice to perform a TST or IGRA test (centrally or locally) will be made by the investigator according to local licensing and standard of care. The QuantiFERON-TB Gold Plus test can only be used in countries where it is licensed, and the use of this test is dependent on previous treatments. This test may not be suitable if previous treatments produced significant immunosuppression.

Exclusion Criteria (cont)

Prior/Concomitant therapy

- Previous or planned major organ transplant (e.g., heart, lung, kidney, liver) or bone marrow transplant (e.g., autologous stem cell transplant). **EXC#21**
- Plasmapheresis or extracorporeal photopheresis, or use of plasma filtering devices within 6 months prior to Day 1. **EXC#22**
- Any prior treatment with anti-BlyS agents, including belimumab **EXC#23**
- Treatment with systemic biologic agents, including the following biologic DMARDs anti IL6 therapies such as tocilizumab, sarilumab, anti CTLA4 such as abatacept or anti-TNF therapies (e.g., adalimumab, etanercept, infliximab, certolizumab) or other biologic DMARDs such as denosumab or anakinra, within 8 weeks (4 weeks for etanercept) or 5 half-lives (whichever is longer) prior to Day 1 and intravenous immunoglobulin (including anti-thymocyte globulin) or monoclonal antibodies, including marketed drugs, within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1. **EXC#24**
- Treatment with rituximab or any other B-cell depleting therapies such as ofatumumab, ocrelizumab or inebilizumab within 6 months prior to Day 1. **EXC#25**
- Treatment with:
  - Janus kinase (JAK) inhibitors (tofacitinib, baricitinib, upadacitinib, filgotinib, peficitinib, others; either experimental or approved, within 4 weeks or 5 half-lives (whichever is longer) prior to Day 1
  - Other non-biologic systemic immunosuppressive medication including targeted synthetic DMARDs within 3 months prior to Day 1
  - Exception are the permitted medications listed under INC#5, when they are being continued during the study. **EXC#26**
- Treatment with cyclophosphamide (oral or intravenous) within 6 months prior to Day 1. **EXC#27**
- Use of anti-fibrotic agents including pirfenidone or tyrosine kinase inhibitors (e.g., nintedanib, nilotinib, imatinib, dasatinib) within 4 weeks prior to Day 1. **EXC#28**
- Cytotoxic drugs such as, chlorambucil, nitrogen mustard, or other alkylating agents within 6 months of Day 1. **EXC#29**

Exclusion Criteria (cont)

- Treatment with IM or IV corticosteroids within 4 weeks prior to Day 1. **EXC#30**
- Live or live-attenuated vaccine(s) within 30 days prior to Day 1 or plans to receive such vaccines during the study. **EXC#31**
- Participants who are expected to be non-compliant with restrictions on medications and vaccinations prior to the study, during the study or during the 8-week safety follow-up of the study. See Protocol Section 6.9.4 for details of prohibited medications/treatments and in Protocol Section 6.9.1 for details of permitted medications/treatments. **EXC#32**

Prior/Concurrent clinical study experience

- Current enrolment or past participation in any other investigational study involving an investigational intervention (e.g., drug, vaccine, invasive device) within 3 months or 5 half-lives of the investigational drug (whichever is longer) before randomization or any other type of medical research within 3 months before randomization. **EXC#33**

Diagnostic assessments

- Positive HIV antibody test. **EXC#34**
- Serologic evidence of Hepatitis B infection based on the results of testing for HBsAg, Anti-HBc and Anti-HBs as follows: **EXC#35**
  - Patients positive for HBsAg are excluded.
  - Patients negative for HBsAg but positive for Anti-HBc, regardless of Anti-HBs antibody status, will require clarification of their status by testing for HBV DNA.
    - → if HBV DNA is detectable, patients will be excluded from participation.
    - → if HBV DNA is not detectable, patients will be eligible to enroll.

  NOTE: For those subjects included, additional ongoing assessment is required. Safety assessment for Hepatitis B during the trial will be as follows:
  - ALT, AST, HBsAg and HBV DNA will be tested approximately once a month for the first 6 months after initiation of study treatment, and approximately once every 3 months thereafter.
  - If HBsAg is positive or HBV DNA is detectable, study drug must be discontinued and the participant should be referred for a review by a liver specialist or hepatologist and consideration of hepatitis B treatment initiation.

Exclusion Criteria (cont)

- If there is ALT/AST elevation greater than 2.5×ULN but repeat HBV DNA levels are nondetectable and HBsAg is negative, then investigate other causes for ALT/AST elevation. The suspected reason for ALT and/or AST elevation should be documented.
- In case of Hepatitis B reactivation, follow local guidelines for treatment of Hepatitis B.

- Positive Hepatitis C antibody test result at screening or within 3 months prior to starting study intervention. NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled, only if a confirmatory negative hepatitis C RNA test is obtained. **EXC#36**
- Positive Hepatitis C RNA test result at screening or within 3 months prior to first dose of study intervention. NOTE: Test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing. **EXC#37**
- History of a primary immunodeficiency, or hypogammaglobulinaemia (IgG <400 mg/dL), or IgA deficiency (IgA <10 mg/dL). **EXC#38**
- Have a Grade 3 or greater neutropenia, defined as absolute neutrophil count <1000/mm3 (<1.0x10^9/L) based on the CTCAE v5.0. **EXC#39**
- Have any other clinically significant abnormal laboratory value, that in the opinion of the investigator, is capable of significantly altering the absorption, metabolism, or elimination of drugs; constitutes a risk when taking the study intervention or interferes with the interpretation of data. **EXC#40**

Other exclusion criteria

- Exposure to ionizing radiation in excess of 10 mSv above background over the three-year period before screening as a result of occupational exposure or previous participation in research studies. **EXC#41**
- Current drug or alcohol abuse or dependence, or a history of drug or alcohol abuse or dependence within a year prior to Day 1. **EXC#42**
- Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the investigator, contraindicates participation in the study. **EXC#43**
- Use of any medicinal products intended to treat medical conditions that are not approved by the governing health authority in the participant's country or region. **EXC#44**

Exclusion Criteria (cont)

Liver safety exclusion criteria

- Alanine transaminase (ALT) >2× upper limit of normal (ULN) **EXC#45**
- Total bilirubin >1.5×ULN (isolated total bilirubin >1.5×ULN is acceptable if total bilirubin is fractionated and direct bilirubin <35%) **EXC#46**
- Cirrhosis or current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, or persistent jaundice. **EXC#47**

  NOTE: Stable non-cirrhotic chronic liver disease (including Gilbert's syndrome, asymptomatic gallstones, and chronic stable hepatitis B or C) is acceptable if the participant otherwise meets entry criteria

Cardiac safety exclusion criteria

- QTc >450 msec or QTc >480 msec for patients with bundle branch block **EXC#48**

  NOTE: The QTc is the QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is either machine-read or manually over-read.

  The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study and used throughout the study for the individual participant. In other words, several different formulas cannot be used to calculate the QTc for an individual participant and then the lowest QTc value used to include or discontinue the participant from the trial.