# A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 104-Week Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE) (study 205646)

Published: 24-10-2017
Last updated: 12-04-2024

Primary:To evaluate the efficacy of belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE. Secondary:Other aspects of efficacy. Safety and tolerability. Questionnaires.

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Autoimmune disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON50250

**Source**
ToetsingOnline

**Brief title**
study 205646, BLISS-BELIEVE

### Condition

- Autoimmune disorders

**Synonym**
SLE; systemic lupus erythematosus

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** GlaxoSmithKline
**Source(s) of monetary or material Support:** GlaxoSmithKline BV

## Intervention

**Keyword:** belimumab, combination, rituximab, SLE

## Outcome measures

### Primary outcome

Proportion of participants with a state of disease control defined as a SLE Disease Activity Index (SLEDAI)-2K score *2, achieved without immunosuppressants and with corticosteroids at a prednisone equivalent dose of *5 mg/day at Week 52.

### Secondary outcome

Major: Clinical remission (SLEDAI-2K score=0) at Week 64.

Others (e.g.): Clinical or complete remission (SLEDAI-2K score=0) by visit and for *24 weeks. Disease control (SLEDAI-2K score *2) at week 104, by visit. Time to first (severe) flare. Adverse events. See protocol pages 10-12 for complete list.

# Study description

### Background summary

SLE is characterized by autoantibodies, including antibodies to double-stranded DNA (dsDNA), and by abnormal B cell activation and differentiation, indicating that therapies which deplete or modulate B cells could be beneficial in treating SLE. Belimumab and rituximab are monoclonal antibodies that achieve

their expected pharmacology through different but complementary mechanisms; therefore, based on their mechanisms of action, synergistic effects when used in combination in the treatment of SLE are possible compared to either treatment alone. Belimumab treatment increases peripheral memory B cells potentially by mobilization from tissues this may include the autoreactive B cell compartment. This mobilization would expose these cells to more efficient depletion by rituximab. Continuing belimumab after a single course of rituximab would then suppress the B-lymphocyte stimulator (BLyS) elevation observed after rituximab monotherapy, thus suppressing the signal which leads to rapid repopulation of B cells, including autoreactive B cells. This study will assess whether co-administration of belimumab and a single cycle of rituximab may optimize (registered) treatment with belimumab, resulting in improvements in clinical status with a favorable safety profile.

Protocol amendment 3: addition of a sub study (the effect of the study medication on B cells; 6 times approx. 10 mL blood).

**Study objective**

Primary:
To evaluate the efficacy of belimumab and a single cycle of rituximab administered in a combination regimen to adult participants with SLE.
Secondary:
Other aspects of efficacy. Safety and tolerability. Questionnaires.

**Study design**

Phase 3, 3-arm randomized double-blind placebo-controlled 104 week study.
Randomization (1:2:1) to:
D. Belimumab plus 1 course of rituximab placebo
E. Belimumab plus 1 course of rituximab
F. Belimumab plus standard therapy with immunosuppressants (open-label).
Belimumab will be administered weekly (200 mg subcutaneously) for 51 weeks (Arms A and B) or 104 weeks (Arm C).
Rituximab (or placebo) will be administered in week 4 and 6 (intravenously).
Premedication 30 min prior to infusions (incl. methylprednisolone 100 mg IV).
Standard therapy in Arm C will be administered for 104 weeks.
After the initial 12 weeks of study treatment, a protocol-specified corticosteroid taper will be initiated and conducted under the direction of the investigator for participants in all 3 arms. See protocol page 14 for details.
Participants in Arms A and B will enter into the 52-week observational phase of the study without belimumab and/or rituximab treatment after completing Week 52 (Weeks 53 through 104).
Blinded independent assessors will conduct the SLEDAI-2K at key time points.
An Independent Data Monitoring Committee (IDMC) will regularly review the safety data.

At least 200 subjects (400 to be screened).

### Intervention

Treatment with belimumab with or without rituximab.
Down titration (and potential discontinuation) of corticosteroids.

### Study burden and risks

Risk: Adverse events of belimumab with or without rituximab. Decrease of disease control.
Burden:
Visits every 4 weeks (year 1), every 8 weeks (year 8).
Belimumab SC injection (ca 1 mL) during 1 (Arms A, B) or 2 (Arm C) years. 2 IV infusions with rituximab (or placebo) (250 mL) and IV pre-medication met methylprednisolone (2,5 mL) (arm A, B).
Physical examination: every visit.
SLEDAI-2K score: every visit.
Blood draws: every visit (30-150 mL, 1.200 mL blood in total).
Pregnancy test: every visit.
Alcohol en drugs screen: at screening.
ECG: at screening.
Diary (data on administration belimumab): 1-2 years (as long as belimumab is administered).
Questionnaires: C-SSRS every visit, FACIT-fatigue, Lupus QoL, WPAI, global assessment 9 times in total.
Optional: genetics blood sample (6 ml), 6 blood samples of approx. 10 mL for optional research on B cells.

## Contacts

**Public**
GlaxoSmithKline

Van Asch van Wijckstraat 55H
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NL
**Scientific**
GlaxoSmithKline

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Amersfoort 3811 LP
NL

# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

* Males and females >< = 18 years of age.
* SLE according to the ACR criteria (at least 4/11 criteria).
* Screening SLEDAI-2K score *6 (total score).
* Unequivocally positive autoantibody test results. See protocol page 49 for details.
* Stable SLE treatment regimen consisting of any of the following medications (alone or in combination) for a period of at least 30 days prior to Day 1: corticosteroids, immunosuppressants, anti-malarials, NSAIDs. See protocol page 49-50 for details.
* Female participant of childbearing potential who agrees to follow the contraceptive guidance in appendix 3 of the protocol during the treatment period and for at least 16 weeks after the last dose of belimumab or at least 12 months after the last dose of rituximab (or placebo).

## Exclusion criteria

* Symptomatic herpes zoster within 3 months prior to screening.
* Evidence of active or latent tuberculosis. See protocol page 50 for details
* Clinical evidence of significant unstable or uncontrolled acute or chronic diseases not due to SLE. See protocol page 51 for details.
* Acute or chronic infection requiring management. See protocol page 51 for details.
* Severe lupus kidney disease. See protocol page 52 for details.
* Live vaccine within 1 month prior to screening, or plans to receive such vaccines during the screening period or during the study.
* Use in the past year of belimumab, rituximab, abatacept, any B-cell targeted therapy, biologic investigational agent other than B cell targeted therapy. See

protocol page 52 for details.
* 3 or more courses of systemic corticosteroids within the past year.
* Use in the 90 days prior to study day 1: anti-TNF therapy, anakinra, IV immunoglobulins, >100 mg prednisone per day, plasmapheresis.
* Use in the 60 days prior to study day 1: non-biologic investigational drug, IV cyclophosphamide, any steroid injection.
* Positive HIV, hepatitis B or C test.
* Pregnancy or breastfeeding.

# Study design

## Design

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|---|---|
| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |
| Control: | Placebo |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 16-05-2018 |
| Enrollment: | 10 |
| Type: | Actual |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | Benlysta |
| Generic name: | belimumab |
| Registration: | Yes - NL outside intended use |
| Product type: | Medicine |
| Brand name: | MabThera |

| | |
|---|---|
| Generic name: | rituximab |
| Registration: | Yes - NL outside intended use |

## Ethics review

| | |
|---|---|
| Approved WMO Date: | 24-10-2017 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 16-02-2018 |
| Application type: | First submission |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 28-02-2018 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 26-03-2018 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 06-04-2018 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 11-04-2018 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 11-12-2018 |

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| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 02-01-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 24-01-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 29-01-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 12-02-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 19-02-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 17-06-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 24-06-2019 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

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| Approved WMO Date: | 19-02-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 25-02-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 01-05-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 11-05-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 19-05-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 26-06-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 07-07-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 27-11-2020 |
| Application type: | Amendment |

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|---|---|
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 16-12-2020 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 29-01-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |
| Approved WMO Date: | 02-02-2021 |
| Application type: | Amendment |
| Review commission: | MEC-U: Medical Research Ethics Committees United (Nieuwegein) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2016-003050-32-NL |
| CCMO | NL63490.100.17 |
| Other | www.gskclinicalstudyregister.com 205646 |

# Study results