This document provides a short summary of this study for a general audience. You can find more information in the scientific summaries of the study. Links to those summaries are provided at the end of this document.

Study names

Short Title: A study to assess the effect and safety of belimumab when given in combination with rituximab in participants with systemic lupus erythematosus.

Full Scientific Title: A phase 3, multi-centre, randomised, 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.

Study Number: 205646

Who sponsored this study?

GlaxoSmithKline (GSK)
GSK Clinical Support Help Desk
Website: clinicalsupporthd.gsk.com/contact.html
Email: GSKClinicalSupportHD@gsk.com

General information about the clinical study

When was this study done?

This study started in March 2018 and ended in July 2021.

What was the main reason for this study?

The immune system, which includes a type of white blood cell called B cells, protects the body from germs such as bacteria and viruses. Systemic lupus erythematosus (SLE) is a long-term autoimmune disease in which B cells produce proteins called autoantibodies. Autoantibodies attack the body's own tissues and organs and can cause inflammation. This disease can affect almost any organ in the body and the symptoms vary across people with SLE. Common symptoms include skin rash and joint pain.

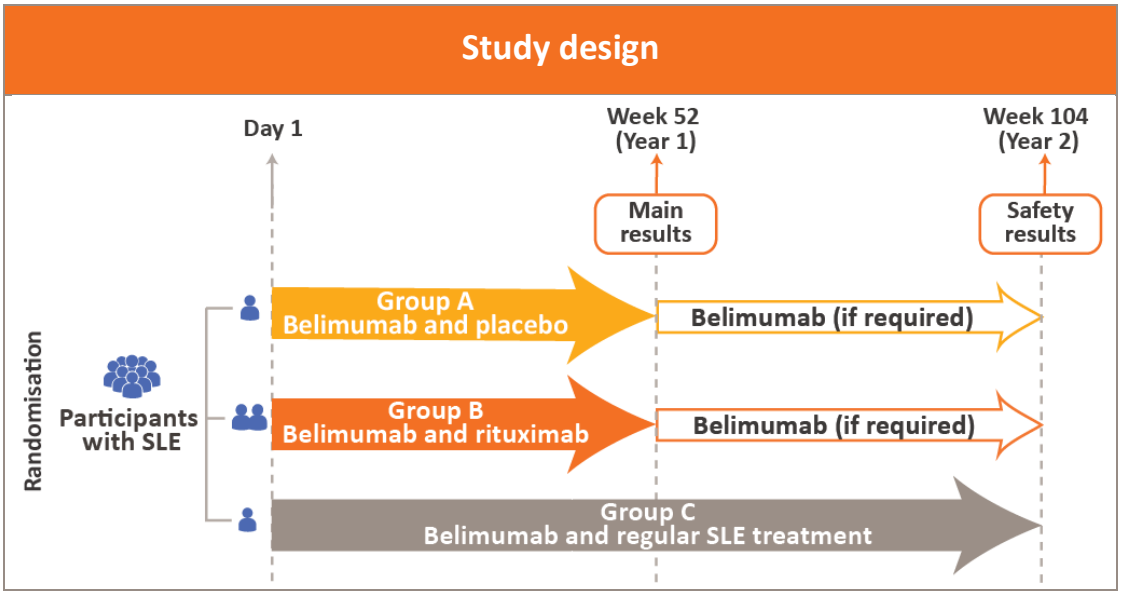
People with SLE who were receiving regular treatment took part in this study. Regular SLE treatment could include the use of corticosteroids that reduces inflammation and immunosuppressants that slows down the immune system.

Which medicines were studied?

Belimumab and rituximab are the two medicines that were studied. The researchers mainly wanted to see if belimumab when given in combination with rituximab worked better than belimumab given alone in participants with SLE. They also assessed the safety of these medicines.

On Day 1, participants were included in one of the following three treatment groups – **Group A**, **B**, or **C** respectively by chance (randomisation), as shown in the figure below.

The number of participants included in Group B was twice the number of participants included in Group A or Group C.



- Belimumab was given as an injection under the skin of the thigh or the abdomen once a week.
- Rituximab or placebo (no active medicine) was given as an injection directly through a vein at Week 4 and Week 6.

Group A and Group B:

Participants who were taking immunosuppressants before starting the study, were asked to stop taking these medicines by Week 4. During Year 1, neither the participants in these treatment groups nor the study doctors knew who was receiving which

medicine (rituximab or placebo) with belimumab. This is called a double-blind study. After Year 1, these participants could continue to take belimumab in Year 2, if required, based on study doctor's decision.

Group C:

Participants who were taking immunosuppressants before starting the study, could continue taking these medicines throughout the study. The participants in Group C and the main study doctors knew that the participants were receiving belimumab and regular SLE treatment. Additionally, independent study doctors, who did not know which treatment group the participant was in, assessed their SLE symptoms.

Between Week 12 and Week 26, the doses of corticosteroids were reduced for all participants.

Which participants took part in this study?

Studies have a list of requirements for participants who can enrol (inclusion criteria) and those who can't (exclusion criteria). For this study, the main inclusion and exclusion criteria are listed below.

Men and women were included in the study if they:

- Were at least 18 years old.
- Had SLE with symptoms of at least moderate severity.
- Tested positive for the presence of autoantibodies at two different time points before Day 1.
- Were receiving the same regular SLE treatment for at least one month before Day 1.

Men and women were excluded from the study if they had:

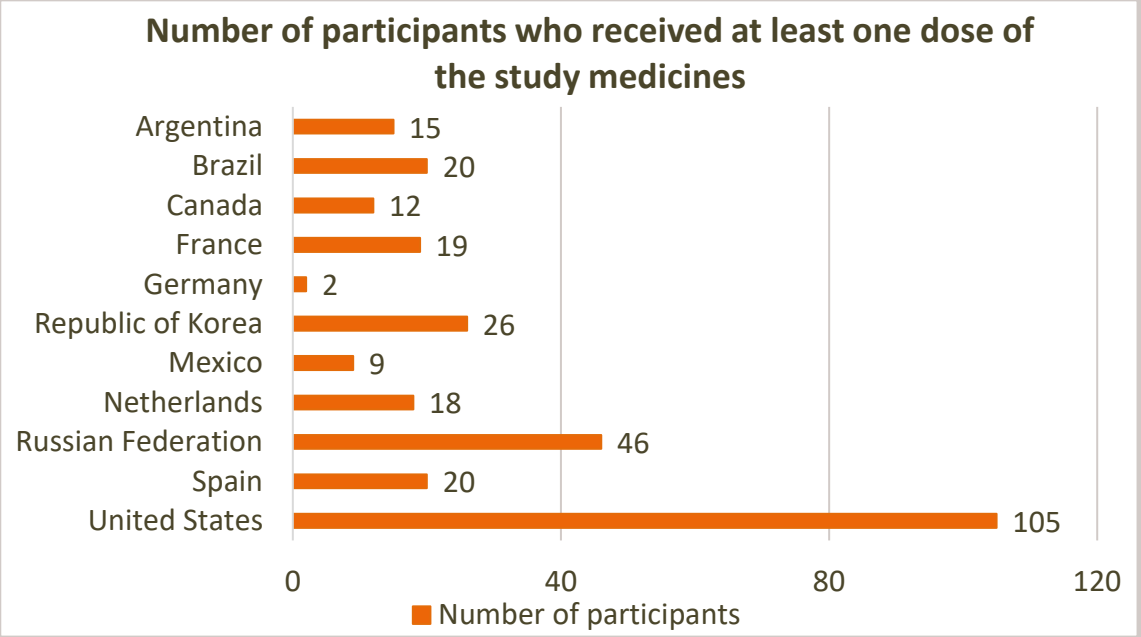
- Taken belimumab, rituximab, or any other treatment(s) that affected B cells within one year before Day 1.
- A major organ transplant or bone marrow transplant.
- Been treated for severe kidney disease caused by SLE or inflammation of the kidneys within three months before Day 1.
- Been treated for nervous system disorders caused by SLE within two months before Day 1.
- A history of suicidal behavior within six months or had suicidal thoughts within two months before starting the study.

Overall, 292 participants received at least one dose of the study medicines. The study included 24 men (8%) and 268 women (92%). The average age was 41 years. The youngest participant was 18 years old and the oldest participant was 72 years old.

For more detailed information about the participants included in this study, see the scientific results summaries (links to those summaries are provided at the end of this document).

Where was this study done?

Study sites were in 11 countries.



What were the main results of the study?

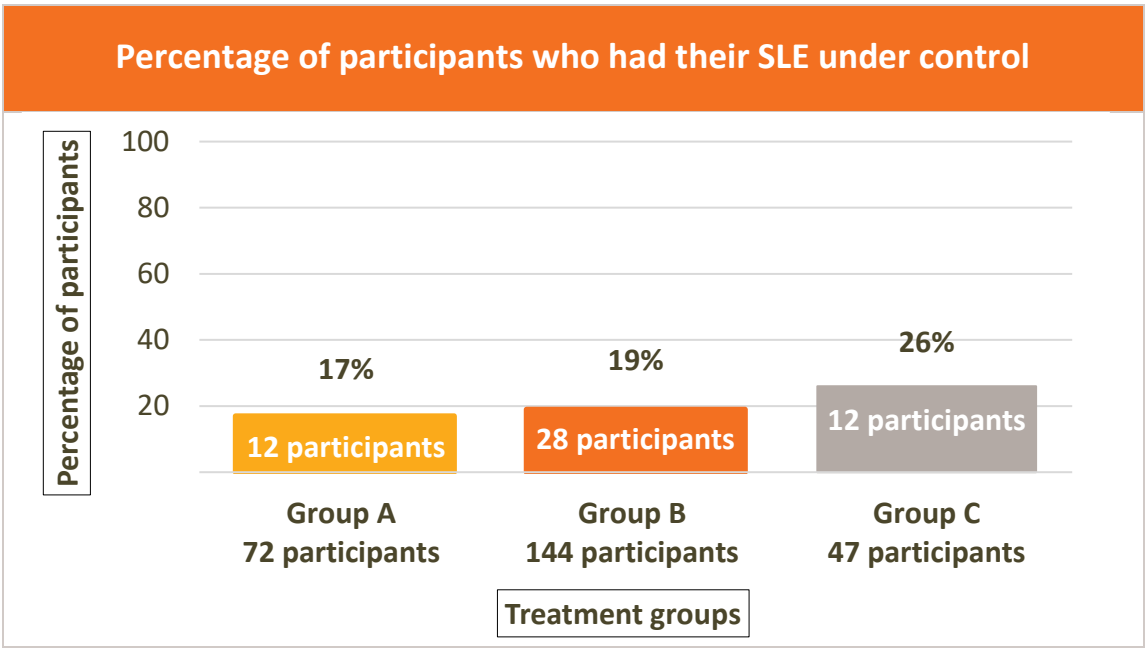
An independent study doctor, who did not know whether the participant was in Group A, B, or C, recorded the participants' SLE symptoms using a scoring scale. For this study, participants were considered to have their SLE under control if they:

- Had an SLE symptom score of two or lower.
- Were not taking immunosuppressants.
- Needed either no corticosteroids or only needed low-dose corticosteroids daily.
- Completed one year in the study.

The main focus of this study was to compare the percentage of participants between Group A and Group B, who had their SLE under control at the end of Year 1.

The SLE symptoms score for 29 participants from Group C are not included in the results, as the independent study doctors assessing symptoms may have known that these participants were in Group C.

The results for the remaining 263 participants are shown in the figure below.



More information about the study results is available in the scientific results summaries (links to those summaries are provided at the end of this document).

What were the side effects?

Unwanted medical events (adverse events) can happen to people when they receive a medicine. Study doctors record these events. A summary of these events can be found in the scientific results summaries (links to those summaries are provided at the end of this document).

If the study doctor thinks that the event was caused by the study medicine, they record this as a possible side effect (adverse reaction).

In this summary, side effects refer to those events that the study doctor thinks may have been caused by belimumab and/or rituximab. The side effects in this summary may be different to those in the Informed Consent or other documents related to belimumab and/or rituximab.

In blinded studies, the doctor does not know which study medicine the participant is taking.

The side effects in this summary have been reported during the two-year study period.

Serious side effects

In this study, serious side effects were reported as fatal serious side effects and non-fatal serious side effects.

One participant (less than 1%) in Group B had a serious side effect of pneumonia that resulted in the death of the participant (fatal serious side effect). The study doctor thought that this side effect may have been caused by belimumab and rituximab. No fatal serious side effects were reported by participants in the other two treatment groups.

The table below shows the number of participants (percent) with non-fatal serious side effects that the study doctor thought may have been caused by belimumab and/or rituximab.

Number of participants (percent) with non-fatal serious side effects			
Caused by	**Group A 72 participants**	**Group B 144 participants**	**Group C 76 participants**
Belimumab	1 (1%)	2 (1%)	2 (3%)
Rituximab	0	1 (less than 1%)	Not applicable*
Belimumab and rituximab	2 (3%)	5 (3%)	Not applicable*

*Study doctors knew that the participants in Group C were not receiving rituximab.

No specific non-fatal serious side effect was reported by 2% or more of participants each in any treatment group.

Non-serious side effects

The table below shows the number of participants (percent) with non-serious side effects that the study doctor thought may have been caused by belimumab and/or rituximab.

Number of participants (percent) with non-serious side effects			
Caused by	**Group A 72 participants**	**Group B 144 participants**	**Group C 76 participants**
Belimumab	19 (26%)	34 (24%)	27 (36%)
Rituximab	3 (4%)	19 (13%)	Not applicable*
Belimumab and rituximab	8 (11%)	25 (17%)	Not applicable*

*Study doctors knew that the participants in Group C were not receiving rituximab.

No specific non-serious side effects caused by rituximab or belimumab and rituximab were reported by 5% or more of participants in any treatment group. The table below shows the number of participants (percent) with non-serious side effects caused by belimumab that were reported by 5% or more of participants in any treatment group.

Number of participants (percent) with non-serious side effects caused by belimumab			
Caused by	**Group A 72 participants**	**Group B 144 participants**	**Group C 76 participants**
Headache	3 (4%)	7 (5%)	4 (5%)
Very low levels of neutrophils (a type of white blood cell)	0	2 (1%)	4 (5%)
Inflammation of the lining of the tubes which carry air to and from the lungs	0	0	4 (5%)

How has this study helped participants and researchers?

In this study, the percentage of participants with their SLE under control was slightly higher in Group B compared with Group A. This difference was not big enough for the researchers to be sure that addition of rituximab to belimumab was better than belimumab alone. The side effects reported were as expected in people with SLE taking belimumab and/or rituximab. A higher number of participants in Group B had serious infections compared with the other two treatment groups. However, the study doctors did not think most of these were caused by belimumab and/or rituximab.

Are there plans for further studies?

Other studies of belimumab in participants with SLE have been completed. Some studies are ongoing or planned.

Where can I find more information about this study?

Clinical studies have unique study numbers that are included in publications and other information about the study. The unique study numbers associated with this study are shown below with internet links to scientific summaries.

The scientific summaries include more details about the requirements for study enrolment, the study visit schedule, results from other endpoints, and more detailed information about adverse events.

Organisation and Website	Study Number
European Medicines Agency (www.clinicaltrialsregister.eu)	2016-003050-32[1]
United States National Institutes of Health (NIH) (www.clinicaltrials.gov)	NCT03312907[2]

Your doctor can help you understand more about this study and the results. Speak to your doctor about the treatment options available in your country. You should not make changes to your care based on the results of this or any single study. Keep taking your current treatment unless instructed by your doctor.

We would like to thank the participants who contributed to this study. The results of this study will help answer scientific questions about treating people with SLE.

The content for this document was finalised by GSK on 24 February 2022. The information in this summary does not include additional information available after this date.

[1] https://www.clinicaltrialsregister.eu/ctr-search/search?query=2016-003050-32

[2] https://clinicaltrials.gov/ct2/show/NCT03312907