A randomized, double blind (sponsor open), comparative, multicenter study to evaluate the safety and efficacy of subcutaneous belimumab (GSK1550188) and intravenous rituximab coadministration in subjects with primary Sjögren*s syndrome.

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To evaluate the safety and efficacy of subcutaneousbelimumab (GSK1550188) and intravenous rituximab coadministrationin subjects with primary Sjögren*s syndrome.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Endocrine and glandular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46078

Source
ToetsingOnline

Brief title
201842

Condition

- Endocrine and glandular disorders NEC
- Eye disorders
- Autoimmune disorders

Synonym

1 - A randomized, double blind (sponsor open), comparative, multicenter study to eva ... 13-05-2025

Sicca syndrome, Sjögren□s syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: autoimmune disease, B-cells, belimumab rituximab, Sjögren□s syndrome

Outcome measures

Primary outcome

Objectives:

Safety and tolerability of anti-BLyS / anti-CD 20 coadministration

therapy and anti-BLyS and anti-CD 20 monotherapies

Endpoints:

Safety and tolerability; including incidence of SAEs and AESIs

Secondary outcome

Objectives:

Clinical efficacy of anti-BLyS / anti-CD 20 co-administration therapy and

anti-BLyS and anti-CD 20 monotherapies

Assessment of anti-BLyS / anti- CD 20 co-administration therapy and anti-BLyS

and anti-CD 20 monotherapies on tissue B-cells

Endpoints: - ESSDAI score over time

- Stimulated salivary flow over time

- Oral dryness numeric response scale over time

- B cell quantification within salivary gland biopsy at

Week 24

Study description

Background summary

Sjögren*s syndrome is manifest by sicca symptoms, constitutional findings, and potentially severe, life-threatening organ-specific extra-glandular manifestations. It is characterized by a combination of features including oral and ocular dryness, which can be disabling; ocular signs including objective evidence for involvement; salivary gland involvement including abnormal appearance of salivary glands; and presence of antibodies to Ro and/or La. Patients may also experience severe, variable and unpredictable fatigue, which is similar in character and severity to that of patients with systemic lupus erythematosus (SLE). Similarly, fibromyalgia and widespread chronic pain are found in 5% of pSS patients, again, comparable to SLE. Extra-glandular manifestations occur in 20 to 40% of patients and include rashes, peripheral neuropathy, Hashimoto*s thyroiditis, non-erosive arthritis, arthralgia, vasculitis, interstitial lung disease, B-cell lymphoma, pancreatitis, primary biliary cirrhosis, autoimmune hepatitis and renal disease.
BLyS (also known as BAFF) promotes B-cell maturation, proliferation and survival.
Transgenic mice that over-express this cytokine develop features of SLE, and go on to develop clinical characteristics of primary Sjögren*s syndrome [Mackay, 1999]. In recent years, several studies have focused on elucidating the role of BLyS in primary Sjögren*s syndrome. Serum BLyS levels were demonstrated to be increased, and to correlate

with,
levels of anti-Ro/SS-A antibodies and rheumatoid factor (RF) in patients with primary
Sjögren*s syndrome [Mariette, 2003] and elevated levels of BLyS have been detected in
saliva [Daridon, 2007; Lavie, 2008].
Belimumab, an anti-BLyS therapy, has been studied in patients with Sjögren*s syndrome.
In the open label, Phase II BELISS trial of belimumab in patients (n = 30) with primary
Sjögren*s syndrome, 60% of subjects (18/30) met the primary endpoint - improvement in
at least two of the following five parameters: dryness, fatigue, pain, systemic activity or
B-cell biomarkers - measured at 28 weeks [Mariette, 2013]. This study will allow the
opportunity to test the efficacy of belimumab in a placebo controlled, randomized trial
and will extend the observations of the BELISS study in assessing the effects on disease
activity in patients treated with belimumab for 12 months.
Rituximab, an anti-CD 20 therapy, has also been studied in patients with Sjögren*s
syndrome. In general, these studies - despite being heterogonous, especially with respect
to the patient populations recruited - have shown evidence of temporary beneficial effects
on symptoms of dryness and fatigue [Meijer, 2010; Devauchelle-Pensec, 2014; Dass,
2008]. Furthermore, additional studies have raised the possibility of rituximab positively
impacting systemic disease, salivary histology and biomarkers such as beta2 microglobulin [Carubbi, 2014]. As a result, rituximab has been recommended as a potential treatment [Ramos-Casals, 2012] in subjects with systemic disease.
Administration of anti-CD20 therapy has been shown to result in an increase in serum
BLyS [Cambridge, 2006; Lavie, 2007; Pers, 2007]. This increase is linked both to the
disappearance of BLyS-binding B cells in peripheral blood, as well as to a true homeostatic feedback characterized by increased BLyS mRNA expression in monocytes
after rituximab [Toubi, 2007; Lavie, 2007]. This increase in BLyS after rituximab could
favor the stimulation of new autoimmune B cells and, possibly explains the waning
clinical improvement over time seen in clinical studies of rituximab in patients with

Sjögren*s syndrome.
Anti-BLyS and anti-CD20 therapeutics operate through different but complementary mechanisms: anti-BLyS (e.g., belimumab) therapeutics rapidly increase peripheral memory B cells (possibly by mobilization/redistribution of tissue B cells), decrease
naive, activated and plasma B cell subsets, and increase stringency on B cell selection
during reconstitution; while anti-CD20 (e.g., rituximab) therapeutics eliminate peripheral
B cells through complement dependent cytotoxicity (CDC) and antibody-dependent cellmediated
cytotoxicity (ADCC). Paired together, these two mechanisms may achieve synergistic effects through improved depletion of memory and germinal center tissue B
cells and increased stringency during B cell reconstitution with additive effects through
more efficient targeting of circulating plasma cells.
Pre-clinical evidence supporting the hypothesis that dual B-cell targeted immunotherapy
maybe more efficacious than monotherapy, has been generated in a human-CD20 expressing mouse model. This model demonstrated limited tissue depletion with anti-
CD20 antibody mono-therapy but increased efficacy of anti-CD20 therapy when B cells
were mobilized into the peripheral blood through concomitant inhibition of adhesion
[Gong, 2005]. The combined effect of administration of mouse BLyS receptor (BR3)-Fc
and anti-hCD20 in this model leads to more effective tissue B cell depletion. Similar
observations have been made in SLE models [Lin, 2015] where dual targeting resulted in
greater efficacy with increased tissue B cell depletion, greater reduction in a range of
auto-antibody levels and significant decreases in total IgG1, IgG2b, IgG3, IgM and IgA
when compared to BLyS inhibition and CD20 B-cell depletion alone. Total plasma cells
in the long lived bone marrow niche, thought to be less sensitive to immunotherapy, were
not affected relative to monotherapy with the exception of IgG1+ plasma cells.
Assessment of the translatability of the IgG reductions to humans are difficult to make
due to species differences in B-cell biology and different treatments; however the mouse
data raises the hypothetical risk that immunoglobulin levels may reduce more with

combination treatment.
There also exists limited clinical evidence that dual B-cell targeted immunotherapy with
both BLyS blockade and B cell depletion may be more efficacious than monotherapy.
One subject in the BELISS trial [Mariette, 2013; De Vita, 2014] had severe refractory
Sjögren*s syndrome including parotid B-cell MALT lymphoma and cryoglobulinemic vasculitis. Previous treatment (prior to BELISS) with rituximab, steroids, cyclophosphamide, azathioprine, plasmapheresis, hyperbaric therapy and surgery had
failed. Administration of belimumab to this patient in the BELISS study was also ineffective. However, 49 days after her last infusion with belimumab, the subject was
again treated with rituximab. She experienced complete and sustained remission of her
lymphoma, regression of her previously non-healing cutaneous ulcer and complete normalization of her serologic biomarkers. Although this is a limited, single-case study, it
raises the possibility of profound effects achievable through concomitant exposure to
anti-BLyS and anti-CD20 therapeutics.

Study objective

To evaluate the safety and efficacy of subcutaneous belimumab (GSK1550188) and intravenous rituximab coadministration in subjects with primary Sjögren*s syndrome.

Study design

A randomized, double blind (sponsor open), comparative, multicenter study.

A total of 20 clinic visits (pre-screening, week 1 visit to week 68 visit and one individualized follow up by telephone one individualized follow up site visit)

Pre- screening Visit /Visit 0 (it should occur approximately within 35 days before screening visit)
Baseline/ randomisation
week 1 visit (7 +/- 1 days)
week 4 visit (28 +/- 7 days)
week 8 visit (56 +/- 7 days)
week 10 visit (70 +/- 7 days)

week 12 visit (84 +/- 7 days)
week 16 visit (112 +/- 7 days)
week 20 visit (140 +/- 7 days)
week 24 visit (168 +/- 7 days)
week 28 visit (196+/- 7 days)
week 32 visit (224 +/- 7 days)
week 36 visit (252 +/- 7 days)
week 40 visit (280 +/- 7 days)
week 44 visit (308 +/- 7 days)
week 48 visit (336 +/- 7 days)
week 52 visit (364 +/- 7 days)
week 68 visit (general follow up period)
Individualized follow up period
IFU Final Visit

The study duration per patients is approximately two years

Intervention

Approximately 70 subjects will be recruited into the study initially. At Day 0, subjects
will be randomized 1:2:2:2 to one of the four treatment arms below.
1. Placebo Arm: Approximately 10 subjects will receive belimumab placebo weekly subcutaneous injections to Week 52 and rituximab placebo infusions at Weeks 8 and 10.
2. Belimumab Monotherapy Arm: Approximately 20 subjects will receive 200 mg weekly subcutaneous injections of belimumab to Week 52 and placebo rituximab infusions at Weeks 8 and 10.
3. Co-administrationTherapy Arm: Approximately 20 subjects will receive belimumab 200 mg SC weekly for 24 weeks followed by weekly placebo belimumab injections to Week 52 with rituximab 1,000 mg intravenously at Weeks 8 and 10.
4. Rituximab Monotherapy Arm: Approximately 20 subjects will receive 1,000 mg IV rituximab infusions at Weeks 8 and 10 and weekly subcutaneous injections of placebo belimumab to Week 52.

Study burden and risks

The patients will follow at least 20 visits over a period of 68 weeks.

Patients will undergo the following tests / examinations: physical examination , vital signs (blood pressure, respiration) , ECG, blood collection for different purposes , urinalysis, pregnancy test , salivary gland biopsy, injection of research product
infusion of research product , quit symptomatic treatment of complaints in the last 24 hours before administration research product , saliva test, tear

production test , simple neurlogic research , decrease several questionnaires experience serious illness / symptoms (ESSPRI , PGA) , Schirmer's test , dryness mouth and eyes , fatigue , suicidal feelings, end interview (recorded only if patient consent before).

Belimumab very common side effects (> 1/10) : Nausea, diarrhea , infections, such as respiratory infections and cystitis.

Belimumab common side effects (this refers to) max 1/10 : fever or increase , stuffy or runny nose , sore throat,
cough (bronchitis) , difficulty in sleeping, pain in the feet or hands,
depression , headaches (migraines) , urinary tract infection and
reduced number of white blood cells

Rituximab : very common (this is > 1/10) Infections such as pneumonia (caused by bacteria) , painful urination (urinary tract infections), allergic reactions during infusion , but may occur after the infusion to 24 hours, changes in blood pressure , nausea, rash, fever, itchy , stuffy or runny nose , sneezing, shivering , rapid heartbeat and fatigue, headache , decreased resistance to infections (see changes in laboratory tests carried out by your study doctor) ; this also relates to a reduced amount of certain proteins in the blood (immunoglobulins)
which help in the protection against an infection .

Rituximab : Common side effects (may affect up to 1 in 10 people): Respiratory tract infections (eg, bronchitis .) , Sinus or maxillary sinus inflammation (with pressure or throbbing pain behind nose , cheeks and eyes) , abdominal pain , vomiting and diarrhea , respiratory problems , athlete's foot , elevated cholesterol, numbness, tingling , pricking , or burning of the skin, migraines , dizziness, hair loss, anxiety , depression, indigestion , diarrhea, heartburn , irritation and / or ulceration of the throat and mouth , stomach pain and pain the spine , muscles and / or joints

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age *18 years, at the time of signing the informed consent.;2. Documented Primary Sjögren*s Syndrome by American European Consensus Group
criteria including:
- either SS-A or SS-B positive.
3. Baseline unstimulated salivary flow >0.0 mL/min or evidence of glandular reserve function (stimulated baseline salivary flow >0.05 mL/min).
4. Symptomatic oral dryness (*5/10 on subject completed Numeric Response Scale)
5. Systemically active disease, ESSDAI *5 points.;SEX
6. Male and female subjects; females of child bearing potential are eligible if using effective contraception:
Female subject is eligible to participate if she is not pregnant (as confirmed by a negative urine human chorionic gonadotropin (hCG) test), not lactating, and at least one of the following conditions applies:
a. Non-reproductive potential defined as:
* Pre-menopausal females with one of the following:
* Documented tubal ligation
* Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
* Hysterectomy
* Documented Bilateral Oophorectomy
* Postmenopausal defined as 12 months of spontaneous amenorrhea [in questionable cases a blood sample with simultaneous follicle stimulating hormone (FSH) and estradiol levels consistent with menopause (refer to laboratory reference ranges for confirmatory levels)]. Females on hormone

replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the highly effective contraception methods if they wish to continue their HRT during the study; otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment.
b. Reproductive potential and agrees to follow one of the options listed below in the GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) requirements from 30 days prior to the first dose of study medication up to Week 68 after Day 0.
GSK Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP);This list does not apply to FRP with same sex partners, when this is their preferred and
usual lifestyle or for subjects who are and will continue to be abstinent from penilevaginal intercourse on a long term and persistent basis.
* Contraceptive subdermal implant that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
* Intrauterine device or intrauterine system that meets the SOP effectiveness criteria including a <1% rate of failure per year, as stated in the product label
* Combined estrogen and progestogen oral contraceptive
* Injectable progestogen
* Contraceptive vaginal ring
* Percutaneous contraceptive patches
* Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject.
These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label.
The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.
INFORMED CONSENT
7. Ability to understand and comply with the protocol-required procedures and provision of informed consent.

Exclusion criteria

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. Diagnosis of secondary Sjögren*s syndrome.
2. Active life-threatening or organ-threatening complications of SS disease at the time of screening based on treating physician evaluation including but not restricted to (a) vasculitis with renal, digestive, cardiac, pulmonary or CNS involvement characterized as severe, (b) active CNS or PNS involvement requiring high dose steroids, (c) severe renal involvement defined by objective measures, (d) lymphoma.
3. History of major organ transplant (including hematopoietic stem cell transplant).
4. History of malignancy within past 5 years [with the exception of adequately treated: (a) cervical carcinoma Stage 1B or less, (b) non-invasive basal cell and squamous cell skin carcinoma].
5. History of infection requiring long term systemic therapy including: (a) history of

positive HIV serology, (b) positive serology for Hepatitis C (HCV), (c) positive serology for Hepatitis B (HB), defined as: (i) HB surface antigen positive (HBsAg+) OR (ii) HB core antibody positive (HBcAb+).
6. Previous serious opportunistic or atypical infections or hospitalization for treatment of infection within 364 days of Day 0 or use of parenteral (IV or IM) antibacterials, antivirals, anti-fungals, or anti-parasitic agents within 364 days of prior to Day 0.
7. Patients in a severely immunocompromised state.
8. History of an anaphylactic reaction to parenteral administration of contrast agents, human or murine proteins or monoclonal antibodies.
9. History of significant medical illness (or planned surgical procedure) which in the opinion of the investigator would interfere with the study procedures and / or assessments - including but not limited to IgG4 disease or prior head or neck irradiation.
10. Severe heart failure (New York Heart Association, Class IV) or other severe, uncontrolled cardiac disease.
11. Tuberculosis (TB), defined as: (a) prior history of TB infection, (b) suspicion of TB infection or (c) current TB infection.
12. At risk of suicide, as indicated by a lifetime history of attempted suicide or significant suicidal ideation over the 6 months prior to the screening visit; or, if in the Investigator*s judgment, the subject is at risk for a suicide attempt.
13. Neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML) - not otherwise explained - or confirmed PML.
14. Electrocardiogram (ECG) showing a clinically significant abnormality at Screening or showing an average QTcB or QTcF interval *450 msec (*480 msec for subjects with a Bundle Branch Block) over 3 consecutive ECGs (refer to Section 7.4.5)
15. ALT >2xULN and bilirubin >1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%).
16. Current or chronic history of liver disease, or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones);CONCOMITANT MEDICATIONS
17. Use of systemic immunosuppressive or immunomodulatory agents including methotrexate, azathioprine, leflunomide, mycophenolate (including mycophenolate mofetil, mycophenolate mofetil hydrochloride, and mycophenolate sodium), mizoribine, calcineurin inhibitors (e.g., tacrolimus, cyclosporine), sirolimus, 6-mercaptopurine, or thalidomide) within 60 days prior to Day 0.
18. Have received cyclophosphamide within 180 days prior to Day 0.
19. Have received anti-BLyS, anti-CD 20, anti-CD22 or anti-CD52 or any other B-cell depleting agent within 364 days prior to Day 0.
20. Have received abatacept or any biologic agent within 180 day prior to Day 0
21. Have received IVIG or plasmapheresis within 90 days prior to Day 0.
22. Have received oral steroid >10 mg prednisone equivalent/day within 30 days prior to Day 0 or oral steroid >20 mg prednisone equivalent / day for a minimum of two consecutive weeks within 60 days prior to Day 0. Have received parenteral steroid within 60 days prior to Day 0.
23. Have received a live vaccine within 30 days of Day 0.
24. Current participation in any other interventional trial.
25. Planned blood donation during the treatment and follow up periods of the study.

RELEVANT HABITS
26. Subjects who are unable or unwilling to administer, or to have a caregiver administer subcutaneous injections.
27. Drug or alcohol abuse or dependence.
CONTRAINDICATIONS
28. History of hypersensitivity to belimumab and/or rituximab or known to have titers of human anti-mouse antibody or human anti-chimeric antibody or history of hypersensitivity reactions when treated with other diagnostic or therapeutic monoclonal antibodies.
DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
29. Have an IgA deficiency (IgA level <10 mg/dL).
30. Any of the following screening laboratory values:
* White blood cells (WBC) <2 x 109/L
* Neutrophils <1.5 x 109/L
* Circulating IgG < 550 mg / dL
* Aspartate aminotransferase (AST) >2.0 times the upper limit of normal
* Alkaline phosphatase (ALP) >1.5 times the upper limit of normal
* Bilirubin >1.5 times the upper limit of normal (unless direct bilirubin fraction is < 35%)
* CD19+ B-lymphocyte counts <0.1 x 109/L (applies only to subjects previously exposed to B cell depleting therapies)

Study design

Design

Study phase:	2
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):	30-03-2016
Enrollment:	9

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Belimumab
Generic name:	Benlysta®
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Rituximab
Generic name:	MabThera®
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-12-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-12-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-07-2016

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-05-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-07-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-08-2017
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
Other	clinicaltrials.gov
EudraCT	EUCTR2015-000400-26-NL
CCMO	NL54687.100.15