A Phase 2, Multi-Center, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of lulizumab pegol vs. Placebo on a Background of Limited Standard of Care in the Treatment of Subjects with Active Systemic Lupus Erythematosus

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

Summary

ID

NL-OMON43900

Source
ToetsingOnline

Brief title
IM128-027

Condition

- Autoimmune disorders

Synonym
Systemic Lupus Erythematosus

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Pharmaceutical Industry

Intervention

Keyword: lulizumab pegol, SLE, Systemic Lupus Erythematosus

Outcome measures

Primary outcome

Primary Objective:

To compare the proportion of subjects who achieve BICLA response (BICLA response rate) at Day 169.

Secondary outcome

Secondary Objectives:

* To evaluate the safety and receptor occupancy (RO) when 6 to 10 subjects per arm reach 29 days (4 weeks).

To assess:

* The safety and tolerability of treatment with BMS-931699 in subjects with active SLE

* The proportion of patients who meet response criteria for the SLE Responder Index (SRI) (4), SRI(5) and SRI(6) at Day 169 following 24-week treatment with BMS-931699 or placebo administered on a stable background therapy.

* The proportion of patients with SLE Responder Index [SRI(4), SRI(5) and SRI(6)] at Day 85 following 12 week treatment with BMS-931699 or placebo administered on a stable background therapy.

* The proportion of subjects with BICLA response at Day 85 following 12-week treatment with BMS 931699 or placebo administered on a stable background therapy
* The improvement in the extent of cutaneous and mucous membrane activity, as measured by the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at Day 85 and Day 169
* Joint tenderness and swellings by American College of Rheumatology (ACR)28 criteria at Day 85 and Day 169
* The other indices of SLE activity measured at Days 29, 57, 85, 113, 141 and 169 including:
* The change from baseline in overall BILAG-2004 score. A major response is defined as described in Yee et al 2010 (A=12; B=8; C=1; D/E=0).
* The change in overall Systemic Lupus Erythematosus Disease Activity Index 2K score (SLEDAI 2K)
* The change from baseline in Physician*s Global Assessment of disease activity (MDGA) score
* The systemic exposure of BMS-931699 in subjects with SLE
* The cumulative corticosteroids use and immunosuppressants use over time
* The immunogenicity of BMS-931699
* Serum biomarkers C3, C4, anti-double-stranded deoxyribonucleic acid (anti-dsDNA), anti-nuclear antibody (ANA) and other autoantibodies at Day 85 and Day 169
* The pharmacodynamics (PD) of BMS-931699, including assessments potentially associated with target engagement (including receptor occupancy [RO]).

* Long term clinical safety, tolerability and efficacy of lulizumab pegol.

Study description

Background summary

Systemic lupus erythematosus (SLE) is a progressive autoimmune disease characterized by multiple organ/tissue involvement. It occurs when patients' antibodies, produced by immune B cells mistakenly attack the body's own cells. SLE leads to organ damage which increases morbidity and mortality. In Europe, the incidence of SLE is estimated at 3.3 to 5.0 per 100,000 persons.
Currently SLE patients are treated with antimalarials, corticosteroids (such as oral prednisone) and immunosuppressive drugs. Although corticosteroids and immunosuppressive drugs are generally effective in temporarily controlling flares and disease progression, their reduced efficacy and serious side effects mean that they cannot be used long term. Non-steroidal anti-inflammatory drugs (NSAIDs) are used to control SLE milder symptoms, but might be contraindicated in SLE patients with severe kidney involvement.
There has only been one new treatment approved for SLE in the past 50 years, hence there is a very high unmet medical need for novel therapies to satisfactorily treat SLE.
BMS 931699 is an anti-human CD28 receptor antagonist domain antibody (dAb). It inhibits the interaction of CD80 and CD86 with CD28. CD28 is the main co-stimulatory receptor of T cells. Interfering with this pathways leads to inhibition of T cell function which makes BMS-931699 a new potential treatment for autoimmune diseases including SLE.
This phase 2 study is needed to further the development of BMS-931699, the data collected will be used to evaluate the safety and efficacy of the four treatment regimens (1.25 mg every other week, 5 mg every other week, 12.5 mg every other week, and 12.5 mg weekly).

Study objective

The primary objective of the research is to find out if treatment with BMS-931699 can improve systemic lupus erythematosus (SLE) disease activity. This will be measured by determining the proportion of BICLA responders who achieve BILAG disease activity improvement across all eight involved body systems with no worsening in BILAG or other disease activity indexes at the same time point, and no treatment failure at any time point.

Study design

This is a blinded randomised placebo controlled study. The study will have a short term period (Part 1 and Part 2) and a long term extension.

In the short term treatment period patients will be randomised to one of 5 treatment groups of BMS-931699 or placebo which looks like BMS-931699:
- 1.25 mg every other week
- 5 mg every other week
- 12.5 mg every other week
- 12.5 mg weekly
- Placebo

There will be a total of 350 patients recruited to the short term treatment period. Patients will be randomised on a 1:1:1:1:1 basis so there is an 80% chance of receiving active drug and a 20% chance of placebo.
An interim analysis will be done when a total of 30-50 patients have completed 4 weeks of treatment (Part 1). If the safety and immunosuppression (measured by receptor occupancy) are acceptable at the interim analysis then recruitment will continue until approximately 70 patients per arm have been treated (Part 2). There will be a Part 2 interim analysis for effectiveness when approximately 30 patients per arm have completed 12 weeks of treatment or discontinued. The results from the interim analyses from Part 1 and Part 2 may result in treatment arm modification.
After 24 weeks of treatment patients may be eligible to continue receiving BMS-931699 as part of the Long Term Extension (LTE) phase. If a patient discontinues early or does not go into the LTE then they will be followed for 6 weeks after their last treatment.
The LTE will remain blinded but will no longer have a placebo arm. Patients who were assigned to active drug in part 1 will continue on the same medication. Patients who were assigned to the placebo group will be re-randomised to one of the active BMS-931699 treatment arms. There may be an additional dosing regimen added in the LTE based on interim analysis.
See protocol pages 36 * 40 for detailed information on the study design.
Any modifications to the treatment arms will be prepared as a protocol amendment and will be submitted for approval before being implemented.
There is no defined end date to the LTE however, the LTE provision may be further adjusted based on results from the ongoing development program.

Intervention

The medical intervention for this trial is BMS-931699 or a lookalike placebo which will be administered weekly as a subcutaneous single injection solution. There are no restrictions related to food and fluid intake associated with BMS-931699 known at this point
The composition of the drug product is 12.5 mg/mL BMS-931699 in 20 mM phosphate, pH 5.9, with 5% (w/v) sorbitol. The Pharmacist (or qualified drug preparation person) will know the randomized assignments and will prepare the appropriate dose of active BMS-931699 or placebo accordingly. The prepared drug must be supplied to study personnel in a manner such that neither study personnel nor patients will be aware of whether they receive active drug or placebo.
Every randomized patient will be required to come to the hospital weekly to be

dosed to maintain the blind. Patients randomized to weekly subcutaneous injections of either placebo or BMS-931699 will be dosed weekly as per schedule and subjects randomized to one of the every other week arms will be alternating between receiving a subcutaneous injection of BMS-931699 one week and one of placebo the following week.
Every randomized subject will be required to remain on site for at least 1 hour after each dose to ensure safety.

Study burden and risks

As part of the trial, patients will be expected to attend multiple hospital visits where they will undergo physical examinations, vital sign measurements, blood tests for safety assessment, pregnancy testing (for females of child bearing potential), monitoring for adverse events, as well as extensive assessments of their SLE.
Blood will also be collected at certain visits for research purposes (PK, immunogenicity and biomarker studies). The frequency of visits and number of procedures carried out during this trial would typically be considered over and above standard of care. The procedures are carried out by trained medical professionals and every effort will be made to minimise any risks or discomfort to the patient.
Ongoing assessment of safety will be performed by an independent Data Monitoring Committee (DMC) and an internal safety monitoring team. Both entities may make recommendations to the Sponsor regarding conduct of study and dose adjustment based on safety observations.
The following is a summary of the side effects reported in the clinical studies (Phase I studies in healthy subjects) and an explanation of the potential risks associated with the use of BMS-931699.
* Serious infections: Subjects receiving BMS-931699 have a higher chance of getting infections including upper respiratory infections and other infections caused by viruses or bacteria. Call your study doctor right away if you develop the following symptoms of infection, which may be early signs of a serious infection (fever, feeling very tired, having a cough, having flu-like symptoms, warm, red, or painful skin, burning sensation during urination). Frequency observed in Phase I: 1.6%
* Allergic reactions: Allergic reactions can happen on the day of treatment or the day after receiving BMS-931699. Although serious, these allergic reactions are usually not immediately life-threatening. Tell your doctor or get emergency medical help right away if you have hives, swollen face, eyelids, lips, tongue, throat, or trouble breathing. Frequency observed in Phase I: 0.8%
* Vaccinations: Patients should not receive BMS-931699 at the same time as live vaccines as BMS-931699 may cause some vaccines to be less effective.
* Subcutaneous Injection-Related Reactions: Patients may experience pain, bleeding, irritation or infection at the site of the puncture. Acute injection-related side effects (adverse reactions occurring within 1 hour of the start of the injection) have been reported more frequently with BMS-931699 compared to placebo. Injection-related side effects reported were redness at

the site of injection swelling, and tenderness. Frequency observed in Phase I: 8.3%

Other side effects of BMS-931699 observed in Phase I studies:
* Nausea. Frequency observed in Phase I: 4.8%
* Flushing. Frequency observed in Phase I: 4.0%
* Cough, wheezing. Frequency observed in Phase I: 2.4%
* Rash, urticaria (hives). Frequency observed in Phase I: 1.6%
* Headache. Frequency observed in Phase I: 16.7%
* Dizziness. Frequency observed in Phase I: 2.4%

Since the study drug is investigational when it is taken alone or in combination with other medications, there may be other risks that have not yet been identified. All drugs have a possible risk of an allergic reaction, which if not treated promptly, could become life threatening.
Possible side effects from blood drawing include pain, bruising, swelling, bleeding, irritation or infection at the site of the puncture, dizziness or faintness. .
Although there is a placebo arm to the study, all patients will continue to receive a background of limited standard of care medications.
The benefits from participation in this study include the possibility of treating SLE and of making a contribution to medical knowledge which may help other people with SLE. However, there is no guarantee that patients will benefit from participating in this study.

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

* Male and female subjects, ages 18-70 years inclusive
* Satisfying the SLE classification criteria of the American College of Rheumatology (1982), as revised by the College in 1997, with elevated titer of anti nuclear antibodies at Screening, active features of SLE, including at least one adjudicated BILAG B or greater due to arthritis and/or inflammatory skin disease.
* Unless intolerant, subjects must be on background therapy for 12 weeks, on a stable dose for at least 8 weeks, with at least one steroid sparing agent, including azathioprine (AZA), leflunomide, methotrexate (MTX), anti-malarial agents, mycophenolate mofetil/ mycophenolic acid, which must remain on stable dose throughout the study.
* Prednisone is not required; however, if subject is taking prednisone (or prednisone-equivalent), the maximum dose must not exceed 30mg/day of prednisone (or prednisone equivalent) at screening for a subject to be eligible and must be at a maximum of 10mg/day for at least 5 days prior to Day 1. Subjects must not have SLE manifestations or other disorders expected to require increase in corticosteroids (CS) during the study.
* Any other immunossuppressive or biologic drug will require washout periods indicated in Appendix 2 of the protocol prior to signing consent.
* If subjects receive chronic therapy with NSAIDs (including marketed COX-2 inhibitors), doses must be stable for 14 days prior to first dose of study medication on Day 1 (randomization) and are recommended to remain stable throughout the study.

Exclusion criteria

* Subjects with drug-induced SLE, rather than *idiopathic* SLE.
* Subjects with other autoimmune disease.
* Subjects with primary anti-phospholipid antibody syndrome as the sole or primary feature of their SLE or SLE-like syndrome.
* Any major surgery within 6 weeks of study drug administration (Day 1) or any elective surgery planned during the course of the study.
* Subjects with any history or risk for tuberculosis (TB).
* Subjects with active or unstable lupus neuropsychiatric manifestations, including but not limited to any condition defined by BILAG *A* criteria, with the exception of mononeuritis

multiplex and polyneuropathy, which are allowed.
* Subjects with active, severe, lupus nephritis (WHO class III, IV) which requires or may require treatment with cytotoxic agents or high dose corticosteroids.
* Subjects with herpes zoster that resolved less than 2 months prior to screening.
* Subjects with evidence (as assessed by the Investigator) of active or latent bacterial or viral infections at the time of potential screening, including subjects with evidence of Human Immunodeficiency Virus (HIV) infection as defined by positivity of HIV-1 and HIV 2 antibody.
* Subjects currently on hydroxychloroquine or chloroquine with evidence of retinopathy within 6 months of screening or who have had no ophthalmologic evaluation within one year of screening and will not have this examination done or who are unwilling or unable to have regular ophthalmologic examinations while participating in the study.
* Concomitant illness that, in the opinion of the investigator, is likely to require additional systemic glucocorticosteroid therapy during the study
* Female subjects with a breast cancer screening suspicious for malignancy, and in whom the possibility of malignancy cannot be reasonably excluded following additional clinical, laboratory or other diagnostic evaluations.
* Subjects with a history of cancer within the last five years (other than non-melanoma skin cell cancers cured by local resection). Existing non-melanoma skin cell cancers must be removed prior to randomization (Day 1 treatment). Carcinoma in situ, treated with definitive surgical intervention, is allowed.
* Subjects with any acute and/or chronic serious bacterial or viral infection (such as pneumonia, renal infection and sinusitis).
* Donation of blood to a blood bank or in a clinical study (except a screening visit) within 4 weeks of study drug administration (within 2 weeks for plasma only)
* Blood transfusion within 4 weeks of study drug administration.
* Any other sound medical, psychiatric and/or social reason as determined by the investigator.
* Evidence of organ dysfunction or any clinically significant deviation from normal in physical examination, vital signs, ECG or clinical laboratory determinations beyond what is consistent with the target population.
* Positive hepatitis-B surface antigen
* Positive hepatitis-C antibody with positive Recombinant ImmunoBlot Assay (RIBA) or Polymerase Chain Reaction (PCR)
* White blood cells (WBC) < 1,200/mm3 (1.2 x 109/L)
* Platelets < 50,000/mm3 (50 x 109/L)
* Hemoglobin < 8g/dL or < 7g/dL if due to hemolytic anemia related to SLE
* Proteinuria > 3.0g/day (3000 mg/day) or equivalent level of proteinuria as assessed by protein/creatinine ratio (3 mg/mg or 339 mg/mmol).
* serum creatinine > 2.0 mg/dL
* Active urinary sediment
* Serum alanine aminotransferase (ALT) > 2x upper limit of normal (ULN), unless explicitly related to lupus based on the Investigator*s judgment.
* Serum aspartate aminotransferase (AST) > 2xULN, unless explicitly related to lupus based on the Investigator*s judgment.
* Positive urine screen for illegal drugs of abuse
* Any other laboratory test results that, in the opinion of the Investigator, might place subject at unacceptable risk for participating in this study.

* Women of childbearing potential (WOCBP) must not be nursing or pregnant and must be using an acceptable method of contraception for at least 4 weeks before dosing. WOCBP must have a negative pregnancy test within 24 hours prior to dosing with study medication.

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):	15-06-2016
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	lulizumab pegol
Generic name:	lulizumab pegol

Ethics review

Approved WMO

Date:	03-09-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	22-12-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-07-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	2014-002184-14

Register	ID
EudraCT	EUCTR2014-002184-14-NL
CCMO	NL53415.042.15