Randomized, Double-Blind, Placebo-Controlled, Multicenter, Exploratory Phase II Study to Compare Three Dose Regimens of GLPG0259 vs Placebo, in Combination with Methotrexate, Administered for 12 Weeks to Subjects with Active Rheumatoid Arthritis and an Inadequate Response to Methotrexate

Published: 21-06-2010
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Primary Objective:To preliminarily evaluate the efficacy of GLPG0259 compared with placebo in terms of the proportion of subjects achieving ACR20 at Week 12 (Visit [V]7).Secondary Objectives:•To evaluate the efficacy of GLPG0259 compared with...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON34069

Source
ToetsingOnline

Brief title
GLPG0259 vs placebo in combination with MTX in subjects with RA

Condition

- Other condition
- Autoimmune disorders

Synonym
inflammation of the joints

Health condition

chronische gewrichtsaandoening

Research involving
Human

Sponsors and support

Primary sponsor: Galapagos NV
Source(s) of monetary or material Support: sponsor Galapagos

Intervention

Keyword: exploratory phase II, GLPG0259, Rheumatoid Arthritis

Outcome measures

Primary outcome

Primary: The primary efficacy endpoint will be the number and percentage of

subjects in each GLPG0259 dose group and placebo group achieving an American

College of Rheumatology (ACR)20 (ACR20 response rate) at Week 12 (Visit [V] 7).

Secondary outcome

Secondary: The secondary efficacy endpoints will be:

• ACR20 response rate at Weeks 1, 2, 4, and 8 (V3, 4, 5, and 6);

• Time from randomization to ACR20 response;

• Number and percentage of subjects achieving ACR50 (ACR50 response rate) at

Weeks 1, 2, 4, 8, and 12 (V3, 4, 5, 6, and 7);

• Number and percentage of subjects achieving ACR70 (ACR70 response rate) at

Weeks 1, 2, 4, 8, and 12 (V3, 4, 5, 6, and 7);

• ACR-N response at Weeks 1, 2, 4, 8, and 12 (V3, 4, 5, 6, and 7);

• Change from baseline in Disease Activity Score 28 (DAS28) at Weeks 1, 2, 4,

8, and 12 (V3, 4, 5, 6, and 7); and

• Change from baseline in the core components of the ACR response and DAS28 at

Weeks 1, 2, 4, 8, and 12 (V3, 4, 5, 6, and 7).

The secondary safety endpoints will include:

• Incidence and severity of adverse events (AEs);

• Vital signs (supine heart rate and blood pressure [systolic and diastolic]);

• 12-lead electrocardiogram (ECG); and

• Clinical laboratory tests (hematology, serum chemistry, coagulation, and

urinalysis).

The secondary pharmacokinetic (PK) endpoints will include:

• Area under the curve (AUC);

• Average plasma concentration (Cave);

• Trough plasma concentration (Ctrough); and

• Terminal half life (t1/2,z).

Study description

Background summary

Despite the recent advances in RA treatment, there is still a need for orally administered novel therapies that can effectively reduce the signs and symptoms of the disease. GLPG0259 is a small molecule for oral daily administration that has shown promising properties as a potentially safe and effective RA treatment.
Study GLPG0259-CL-201 is an exploratory Phase II study, where the safety and tolerability and the preliminary efficacy of different doses of GLPG0259 will be evaluated for the first time in patients with RA. PK assessments will be also performed.

Study objective

Primary Objective:

To preliminarily evaluate the efficacy of GLPG0259 compared with placebo in terms of the proportion of subjects achieving ACR20 at Week 12 (Visit [V]7).

Secondary Objectives:

•To evaluate the efficacy of GLPG0259 compared with placebo in terms of ACR response criteria, time to response, and disease status (DAS28);
•To evaluate the safety and tolerability of GLPG0259 in comparison with placebo in terms of AEs, laboratory test abnormalities, vital signs and ECGs; and
•To characterize the population pharmacokinetics of GLPG0259 and determine the impact of covariates on PK parameter estimates of GLPG0259.

Study design

This will be an exploratory, Phase II, double-blind, placebo-controlled, multicenter study in a maximum of 200 randomized subjects with active rheumatoid arthritis (RA) who have an inadequate response to methotrexate. The study consists of two parts:
Part A: Thirty eligible subjects will be randomized in a 2:1 allocation ratio to a once-daily dose of 50 mg of GLPG0259 or placebo in addition to their stable dose of methotrexate (20 subjects will receive GLPG0259 and 10 subjects will receive placebo). During the course of treatment, the study drug dose may be split (twice-daily dose of 25 mg each) or reduced to 25 mg/day based on the individual subject*s drug tolerability. An interim analysis will be performed at the end of Part A to assess the efficacy and tolerability of GLPG0259 versus (vs) placebo. The number of subjects who required their dose to be split/reduced in Part A will also be evaluated in order to determine the highest dose (either 50mg/day or 25 mg/day) and dose regimen (either once or twice daily) to be used in Part B. The number of subjects required to be randomized to the highest dose selected will then be determined.
Part B: If the interim analysis at the end of Part A shows a clinical advantage of GLPG0259 over placebo and the study progresses into Part B, depending on the highest dose selected at least 150 additional subjects will either be randomized to GLPG0259 50 mg/day, GLPG0259 25 mg/day, GLPG0259 12.5 mg/day, or matching placebo; or to GLPG0259 25 mg/day, GLPG0259 12.5 mg/day, GLPG0259 6 mg/day, or matching placebo at the baseline visit.
At the end of the study, it is planned that 45 subjects will have been exposed to the each of the three different doses of GLPG0259 or placebo.

Intervention

The investigational product will consist of two 25 mg capsules of GLPG0259 for

oral administration in Part A. All subjects will start Part A on a 50 mg/day dose; the dose may subsequently be split so that one 25 mg capsule is taken twice daily or, in the case of dose reduction, one 25 mg capsule will be taken once daily.
In Part B, two capsules of 6.25, 12.5, and 25 mg (or 3, 6.25, and 12.5 mg depending on the highest dose selected for Part B), will be taken either once or twice daily for 12 weeks.
Depending on the outcome of Part A, final doses and dose regimens for Part B may still be adapted.

Matching placebo capsules for oral administration will be taken for 12 weeks as a reference

Study burden and risks

Thirty eligible subjects will be randomized in a 2:1 allocation ratio to a once-daily dose of 50 mg of GLPG0259 or placebo in addition to their stable dose of methotrexate (20 subjects will receive GLPG0259 and 10 subjects will receive placebo). During the course of treatment, the study drug dose may be split (twice-daily dose of 25 mg each) or reduced to 25 mg/day based on the individual subject*s drug tolerability. An interim analysis will be performed at the end of Part A to assess the efficacy and tolerability of GLPG0259 versus (vs) placebo. The number of subjects who required their dose to be split/reduced in Part A will also be evaluated in order to determine the highest dose (either 50mg/day or 25 mg/day) and dose regimen (either once or twice daily) to be used in Part B. The number of subjects required to be randomized to the highest dose selected will then be determined.
Part B: If the interim analysis at the end of Part A shows a clinical advantage of GLPG0259 over placebo and the study progresses into Part B, depending on the highest dose selected at least 150 additional subjects will either be randomized to GLPG0259 50 mg/day, GLPG0259 25 mg/day, GLPG0259 12.5 mg/day, or matching placebo; or to GLPG0259 25 mg/day, GLPG0259 12.5 mg/day, GLPG0259 6 mg/day, or matching placebo at the baseline visit.
At the end of the study, it is planned that 45 subjects will have been exposed to the each of the three different doses of GLPG0259 or placebo.

Please refer to question E4 and the flow chart on page 45 of the protocol for all study procedures

Please refer to question E9 and the patient information for all possible risks and adverse events

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) 18-70 years of age on the day of signing informed consent
2) Fulfill the 1987 revised ACR criteria for the classification of RA, but must not be wheelchair or bed bound (functional class IV)
3.Have active RA as shown by five or more swollen joints (from the 66-joint count), five or more tender joints (from 68-joint count), and a serum C-reactive protein (CRP) >=1.5 mg/dL;
4.Have received methotrexate for six months or longer and at a stable dose of 7.5 to 25 mg/week for >=12 weeks prior to screening and willing to continue on this regimen for the duration of the study;
5.If taking oral steroids, these should be at a dose <=10 mg/day of prednisone or prednisone equivalent and stable for at least four weeks prior to screening;
6.If taking non-steroidal anti-inflammatory drugs (NSAIDs), these must be at a stable dose for at least two weeks prior to screening;
7.The results of the following laboratory tests performed at the central laboratory at screening must be within the limits specified below:
a. Hemoglobin >=8.5 g/dL (International System of Units [SI]: >=85 g/L);

b. White blood cells >=3.0 x 103 cells/mm3 (SI: >=3.0 x109 cells/L);
c. Neutrophils >=1.5 x 103 cells/mm3 (SI: >=1.5 x109 cells/L);
d. Platelets >=100 x 103 cells/mm3 (SI: >=100 x109 cells/L);
e. Serum ALT and aspartate aminotransferase (AST) <=1.5 x ULN;
f. Total bilirubin level <=1.25 x ULN; and
8.Female subjects must have a negative pregnancy test unless they are surgically sterile or have been post-menopausal for at least one year (12 consecutive months without menses);
9.Women of childbearing potential must use a medically acceptable means of birth control and agree to continue its use during the study and for at least 12 weeks after the last dose of study drug. Women who have had a complete surgical hysterectomy or are postmenopausal are exempt from this requirement. Medically acceptable forms of birth control include oral contraceptives, injectable or implantable methods, intrauterine devices, tubal ligation (if performed more than one year before screening), or double barrier contraception. Sexually active men must agree to use a medically acceptable form of contraception during the study and continue its use for at least 12 weeks after the last dose of study drug; and
10.Able and willing to sign the informed consent prior to screening evaluations and agree to schedule of assessments.

Exclusion criteria

1. Treatment with DMARDs other than background methotrexate, including oral or injectable gold,sulfasalazine, hydroxychloroquine, azathioprine, or D penicillamine within four weeks prior to screening, cyclosporine within eight weeks prior to screening, and leflunomide within three months prior to screening;
2.Current or previous RA treatment with a biological agent, with the exception of biologics administered in a clinical study setting more than six months prior to screening (12 months for rituximab or other B cell depleting agents);
3.Previous treatment at any time with a cytotoxic agent, other than methotrexate, before screening. These agents include, but are not limited to, chlorambucil, cyclophosphamide, nitrogen mustard, or other alkylating agents;
4.Receipt of an intra-articular or parenteral corticosteroid injection within four weeks prior to screening;
5.Current regular use of aspirin or any other anti-coagulant medication;
6.Known hypersensitivity to study drug ingredients or a significant allergic reaction to any drug as determined by the Investigator, such as anaphylaxis, requiring hospitalization;
7.Positive serology for human immunodeficiency virus (HIV)1 or 2 or hepatitis B or C, or any history of HIV or hepatitis from any cause with the exception of hepatitis A;
8.History of any inflammatory rheumatological disorders other than RA;
9.Have undergone surgical treatments for RA including synovectomy and arthroplasty within three months prior to screening and/or a joint surgery is planned within the next months;
10.Symptoms of clinically significant illness other than RA (including but not limited to cardiopulmonary, renal, metabolic, hematologic, or psychiatric disorders) within three months prior to screening;
11.History of active infections requiring intravenous antibiotics within the past four weeks;
12.History of malignancy within the past five years (except for basal cell carcinoma of the

skin or carcinoma in situ of the cervix that has been treated with no evidence of recurrence);
13.History of tuberculosis (TB) infection as determined by:
a.a positive diagnostic TB test result (defined as a positive QuantiFERON TB Gold test), and
b.a chest radiograph (both posterior-anterior and lateral views), taken within three months prior to screening and read by a qualified radiologist, with evidence of current active TB or old inactive TB.
14.Administration of a live vaccine within four weeks prior to screening;
15.Participation in any investigational drug/device clinical study within four weeks prior to screening, in biological agents clinical studies within six months prior to screening, and B cell-depleting agent clinical studies within 12 months prior to screening;
16.History within the previous two years or current evidence of drug or alcohol abuse;
17.Pregnant or lactating women; and
18.Any condition or circumstances which in the opinion of the Investigator may make a subject unlikely or unable to complete the study or comply with study procedures and requirements, or may pose a risk to the subject*s safety.

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:	Will not start
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GLPG0259

Generic name:	GLPG0259

Ethics review

Approved WMO Date:	21-06-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	10-12-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2009-015898-12-NL
CCMO	NL32768.058.10