Adjustable brodalumab dosage regimen compared with standard brodalumab treatment for 52 weeks in subjects with moderate-to-severe plaque psoriasis and >=120 kg body weight; ADJUST

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Primary objectiveTo compare the effect on psoriasis symptoms of an adjustable brodalumab dosage regimen to standard brodalumab treatment in subjects with moderate-to-severe psoriasis and a body weight >=120 kg.Secondary objectives:To evaluate the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON56463

Source
ToetsingOnline

Brief title
ADJUST

Condition

- Epidermal and dermal conditions

Synonym
chronic skin condition, plaque psoriasis

Research involving
Human

Sponsors and support

Primary sponsor: Leo Pharma
Source(s) of monetary or material Support: Leo-Pharma A/S

Intervention

Keyword: adjusted dose, body weight >=120 kg, brodalumab, plaque psoriasis

Outcome measures

Primary outcome

Primary endpoint:

• Having at least 90% lower Psoriasis Area and Severity Index (PASI) score

relative to baseline (PASI 90 response) at Week 40.

Secondary outcome

Key secondary endpoint:

• Having static Physician*s Global Assessment (sPGA) score of 0 or 1 at Week 40.

Additional Secondary endpoints:

• Having PASI 90 response at Week 52.

• Having sPGA score of 0 or 1 at Week 52.

• Having sPGAof genitalia (sPGA-G) of 0 or 1 at both Weeks 40 and 52.

• Having sPGA-G of 0 or 1 at Week 40.

• Having sPGA-G of 0 or 1 at Week 52.

• Having PASI 100 response at Week 40.

• Having PASI 100 response at Week 52.

• Change from baseline at Weeks 40 and 52 in PASI score.

• Change from baseline at Weeks 40 and 52 in affected body surface area (BSA).

• Having Dermatology Life Quality Index (DLQI) total score of 0 or 1 at Week 40.

• Having DLQI total score of 0 or 1 at Week 52.

• Change from baseline at Weeks 40 and 52 in DLQI total score.

• Occurrence of adverse events (AEs) up to Week 58.

• AUCtau at Weeks 14-16 and Weeks 40-42.

• Cmax at Weeks 14-16 and Weeks 40-42.

• tmax at Weeks 14-16 and Weeks 40-42.

• Change from baseline in concentration of serum inflammatory biomarkers at

Weeks 16 and 40.

Study description

Background summary

Psoriasis is an inflammatory skin disease that occurs in approximately 2% of the population worldwide . It is a chronic polygenic inherited disease of uncontrolled cutaneous inflammation that manifests, in the majority of subjects, as plaque psoriasis, clinically seen as sharply demarcated, elevated, scaling, erythematous plaques located predominantly on the scalp, extensor sides of elbows and knees, and the sacral region . The skin lesions can be painful, pruritic, and may cause significant emotional and physical discomfort . Psoriatic arthritis is a musculoskeletal inflammatory disease that can be seen as a manifestation of the psoriatic inflammatory process in up to 30% of subjects with chronic plaque psoriasis .
In addition, psoriasis is associated with a range of comorbidities that include cardiovascular disease, traditional cardiovascular risk factors, diabetes mellitus, and psychiatric conditions such as depression and anxiety . Current evidence indicate that obesity is bidirectionally associated with psoriasis, meaning that obesity, through pro-inflammatory pathways, predisposes to the development of psoriasis and that obesity aggravates existing psoriasis.

Inherently, obesity has been shown to increase the risk of major cardiovascular events and cardiovascular mortality . Taken together, severe psoriasis in combination with severe obesity is likely to cause a markedly increased cardiometabolic burden in obese patients.
Thus, a high prevalence of cardiovascular disease is observed in obese psoriasis patients. Therefore, an increased prevalence/incidence of cardiovascular disease is expected in a trial investigating the efficacy and safety of brodalumab relative to previous trials in the psoriasis indication.
The majority of patients with psoriasis has mild to moderate disease and can be treated with topical therapies. In patients with moderate-to-severe psoriasis, phototherapy or systemic treatment, including biologics, are recommended (topicals can be used as an adjunct to
biologics) . It is well known that obesity complicates treatment of psoriasis. Reduced response to systemic and biological treatment has been shown in obese patients and conditions associated with obesity may pose relative contraindications to some traditional systemic agents. Thus, there is an unmet need for effective and safe biological treatment in the population of psoriasis patients with severe obesity.

Study objective

Primary objective
To compare the effect on psoriasis symptoms of an adjustable brodalumab dosage regimen to standard brodalumab treatment in subjects with moderate-to-severe psoriasis and a body weight >=120 kg.

Secondary objectives:
To evaluate the safety of an adjustable brodalumab dosage regimen in subjects with moderate-to-severe psoriasis and a body weight >=120 kg.

To evaluate pharmacokinetics (PK) of brodalumab in subjects with moderate to severe psoriasis and a body weight >=120 kg.

To explore the effect of brodalumab on systemic inflammation in subjects with moderate-to-severe psoriasis and a body weight >=120 kg.

(Substudy is not applicable in the Netherlands)

Study design

This clinical trial is a randomised, double-blind, controlled, parallel group, multi-centre trial consisting of 3 periods. The individual periods and visit structure are further described below and overviews of the trial design and scheduled procedures are displayed in Sections 3 and 4 of the protocol.
Screening period (-4 weeks to -2 weeks)

A screening visit will take place up to a maximum of 4 weeks and minimum of 2 weeks prior to the treatment period. The objective of the screening period is to enroll eligible and informed subjects. This entails wash-out of specified prohibited medication and specified laboratory testing.
Before any trial-related procedure is started, the subjects will receive the necessary written and verbal information and instructions, including the informed consent form (ICF) and the written subject information sheet. Each subject will receive a unique subject number and the subject*s eligibility will be determined by clinical examination and confirmation of the subject selection criteria.
Treatment period (Week 0 to Week 52)
The start of the treatment period is defined as Week 0 (baseline; Day 1). At this visit, eligibility will be confirmed by re-checking the criteria in subjects who were eligible based on previous examinations, review of sufficient wash-out of prohibited drugs, and review of electrocardiogram (ECG) and central laboratory results from the screening visit. If still eligible, the subject will continue in the trial and receive a unique subject ID number that determines the application scheme of IMP for the individual subject (see Section 9.3 of the protocol).
From Week 0 up to Week 16, all subjects will follow the standard brodalumab regimen of 210 mg at Weeks 0, 1, and 2 and then every second week (Q2W+1) (16-week induction period; see Section 9.2 of the protocol). Including Week 16 and until the last IMP administration at Week 50, the subject will follow an adjustable treatment regimen with additional exposure (+70 mg brodalumab) or placebo Q2W if PASI 90 response is not achieved at any visit from Week 16 to Week 48.
Baseline, efficacy, and safety assessments during the trial are described in Section 11 of the protocol.
Follow-up period (Week 52 to Week 58)
The safety follow-up visit is scheduled at Week 58, approximately 5 half-lives after last IMP administration, provided that the last IMP was administered at Week 50 as per protocol.
In case of early IMP discontinuation, the safety follow-up visit should occur sooner (8 weeks after last dose of IMP), and then the Week 40 visit (Visit 25) may become the last scheduled trial visit (i.e., in case of IMP discontinuation at Week 32 or sooner).
It will be at the discretion of the investigator to ensure the treatment of subjects who discontinue/complete the trial/treatment or ensuring that the subjects are referred to other physician(s) according to standard practice.

Intervention

Kyntheum® (brodalumab)is a recombinant fully human monoclonal immunoglobulin IgG2-antibody that binds with high affinity to human interleukin (IL)-17 receptor A (IL-17RA), thereby blocking the IL-17 pathway. Brodalumab is approved in EU, UK, Canada, Japan, Taiwan, Thailand, Hongkong, China Brazil and the USA for the treatment of moderate-to-severe plaque psoriasis in adult

patients who are candidates for systemic therapy.

Kyntheum® (brodalumab): Solution for subcutaneous injection, Brodalumab formulated at a nominal concentration of 140 mg/mL including the following excipients: Proline, Glutamate, Polysorbate 20, Water for injections . Pre-filled syringe with 210 mg brodalumab in 1.5 mL solution.

Kyntheum® (brodalumab) ; Solution for subcutaneous injection, Brodalumab formulated at a nominal concentration of 140 mg/mL including the following excipients: Proline, Glutamate, Polysorbate 20, Water for injections . Pre-filled syringe with 70 mg brodalumab in 0.5 mL solution.

Placebo; Solution for subcutaneous injection, The placebo solution is similar to the active brodalumab solution except that it does not contain any active substance. Pre-filled syringe with 0.5 mL solution.

Study burden and risks

A high body weight is associated with increased morbidity and poorer treatment outcomes in patients with psoriasis . Thus, the subjects included in this trial are a difficult-to-treat population, as indicated by the lower treatment effect observed with the standard brodalumab
dosage in subjects with moderate-to-severe psoriasis and a body weight >=120 kg (see Section 12 of the protocol).
Population PK exposure modelling supports that the adjustable brodalumab dosage regimen in this trial may be associated with increased efficacy in subjects with moderate-to-severe psoriasis and a body weight >=120 kg, assuming that a higher exposure translates into higher efficacy.
The adjustable brodalumab dosage regimen explored in this trial will lead to increased systemic exposure in subjects where the dosage is adjusted, compared to subjects where the dose is not adjusted, which may be associated with increased risk. However, the systemic
exposure in dose-adjusted subjects is expected to be similar to the systemic exposure previously seen in subjects weighing 80 kg. The benefit/risk profile is maintained by ensuring that only subjects who achieve suboptimal efficacy with the standard regimen will receive an increased brodalumab dosage (or placebo).
The only adverse events (AEs) that showed dose dependency in the phase 3 development programme were infections and neutropenia. These may occur with increased frequency in patients receiving a higher dose of brodalumab. However, the expected systemic steady state exposure of brodalumab in subjects >=120 kg receiving treatment with 280 mg every 2 weeks (Q2W) does not exceed the exposure predicted in subjects <=80 kg receiving treatment with 210 mg Q2W (see Panel 20), and therefore no change in the safety profile due to increased exposure is expected in this trial.
Altogether, the risks associated with participating in this clinical trial are considered low and outweighed by the benefit of a potentially improved

treatment option for subjects with a body weight >=120 kg.

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

* Signed and dated informed consent has been obtained prior to any protocol-related procedures.
* Age >=18 to <75 years at the time of screening.
* Diagnosed with chronic plaque psoriasis at least 6 months before randomisation as determined by the investigator.
* Body weight >=120 kg at the time of screening.
* Moderate-to-severe plaque psoriasis as defined by: BSA >=10% and PASI >=12 at screening and baseline.
* No evidence of active or latent tuberculosis according to local standard of

care for patients requiring initiation of a biologic treatment

Exclusion criteria

* Diagnosed with erythrodermic psoriasis, pustular psoriasis, guttate psoriasis, medication-induced psoriasis, or other skin conditions (e.g.,eczema) that would interfere with evaluations of the effect of theinvestigational medicinal product (IMP) on subjects with plaque psoriasis.
* Clinically important active infections or infestations, chronic, recurrent or latent infections or infestations, or is immunocompromised (e.g., human immunodeficiency virus, hepatitis B, and hepatitis C).
* Any systemic disease considered by the investigator to be uncontrolled and either immunocompromising the subject and/or placing the subject at undue risk of intercurrent diseases (including, but not limited to, renal failure, heart failure, liver disease, diabetes, and anaemia).
* Known history of Crohn*s disease.
* Myocardial infarction or stroke, or unstable angina pectoris within the past 12 months.
* Any active malignancy.
* History of malignancy within 5 years, except for treated and considered cured cutaneous squamous or basal cell carcinoma, in situ cervical cancer, or in situ breast ductal carcinoma.
* History of suicidal behaviour (i.e., *actual suicide attempt*, *interrupted attempt*, *aborted attempt*, or *preparatory acts or behaviour*) based on the Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire at screening or at baseline.
* Any suicidal ideation of category 4 or 5 (*active suicidal ideation with some intent to act, without specific plan* or * active suicidal ideation with specific plan and intent*) based on the C-SSRS questionnaire at screening or at baseline.
* A Patient Health Questionnaire (PHQ)-8 score of >=10 corresponding to moderate-to-severe depression at screening or at baseline.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	21-07-2022
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kyntheum 210 mg
Generic name:	brodalumab 210 mg
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kyntheum 70 mg
Generic name:	brodalumab 70 mg
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	15-09-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	08-10-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	04-05-2021

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-05-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-004998-13-NL
ClinicalTrials.gov	NCT04306315
CCMO	NL73011.056.20