A randomised, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy and safety of tralokinumab in combination with topical corticosteroids in subjects with moderate-to-severe atopic dermatitis who are candidates for systemic therapy

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Primary objective:To demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with TCS in treating moderate-to-severe AD.Secondary objectives:To evaluate the efficacy of tralokinumab in combination with TCS on...

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

Summary

ID

NL-OMON46483

Source
ToetsingOnline

Brief title
ECZTRA 3

Condition

- Epidermal and dermal conditions

Synonym
atopic dermatitis, eczema

Research involving
Human

Sponsors and support

Primary sponsor: TFS Trial Form Support BV
Source(s) of monetary or material Support: Leo Pharma

Intervention

Keyword: atopic dermatitis, blisters, eczema, skin disease

Outcome measures

Primary outcome

* Investigator*s Global Assessment (IGA) score of 0 (clear) or 1 (almost clear)

at Week 16.

At least 75% reduction in Eczema Area and Severity Index (EASI) score from

baseline (EASI75) at Week 16.

Secondary outcome

* Change in Scoring Atopic Dermatitis (SCORAD) from baseline to Week 16.

* Reduction of Worst Daily Pruritus numeric rating scale (NRS) (weekly average)

of at least 4 from baseline to Week 16.

Change in Dermatology Life Quality Index (DLQI) from baseline to Week 16.

Study description

Background summary

Treatment recommendations for AD include topical therapies, the main being TCS. Unfortunately, TCS and topical calcineurin inhibitors (TCIs) have limited efficacy in patients with moderate to severe disease. TCS and non-biologic systemic therapies (e.g. cyclosporine, azathioprine) are all associated with toxicities with long-term use (*16-*18). The recently approved biological agent dupilumab exhibits an acceptable benefit-risk ratio in clinical trials

investigating subjects with moderate to-severe AD, however there is limited experience with long-term dupilumab use in the post marketing setting.
The purpose of this phase 3 trial is to provide evidence of the efficacy and safety of tralokinumab in combination with TCS in the treatment of subjects with moderate-to-severe AD inadequately controlled with topical therapies. Such subjects would be candidates for systemic therapy.
Since TCS represent the mainstay of pharmacological treatment of AD, many patients may use tralokinumab in combination with TCS and this trial is intended to inform about treatment and maintenance with concomitant use of tralokinumab and TCS. After a 16 week initial treatment period, the trial will evaluate 2 different treatment options for additional 16-weeks of maintenance therapy in the continuation treatment period (tralokinumab 300 mg Q2W and 300 mg every 4 weeks [Q4W]).
The primary objective of this trial is to demonstrate that tralokinumab in combination with TCS provides more effective control of the skin manifestations of AD than placebo in combination with TCS. The trial will evaluate the percentage of subjects achieving IGA response of 0 (clear) or 1 (almost clear) and the percentage of subjects achieving at least 75% reduction in EASI score (EASI75) at Week 16, with secondary endpoints addressing symptom scores and extent of AD (SCORAD), itch severity, and health-related quality of life (HRQoL) measures related to AD.
Thus, the trial will further contribute to the characterisation of the benefit-risk profile of tralokinumab.

Study objective

Primary objective:
To demonstrate that tralokinumab in combination with TCS is superior to placebo in combination with TCS in treating moderate-to-severe AD.
Secondary objectives:
To evaluate the efficacy of tralokinumab in combination with TCS on severity and extent of AD, itch, and health-related quality of life compared with placebo in combination with TCS.
To assess safety of tralokinumab in combination with TCS when used to treat moderate-to-severe AD for 32 weeks.

Study design

The trial will consist of a screening period of 2 to 6 weeks (Weeks 6/ 2 to 0), an initial treatment period of 16 weeks (Weeks 0 to 16), a continuation treatment period of 16 weeks (Weeks 16 to 32), and a 14-week off treatment follow-up period for the assessment of safety (Weeks 32 to 46).
Subjects will be randomised in a 2:1 ratio to receive multiple subcutaneous (SC) doses of tralokinumab (300 mg) or placebo every 2 weeks (Q2W) following a loading dose of 600 mg on Day 0 (or 4 mL placebo). Randomisation will be stratified by region and baseline disease severity.

At Week 16, subjects will continue into continuation treatment until Week 32 (the last dose of investigational medicinal product [IMP] will be given at Week 30). The treatment during the continuation treatment period will depend on the regimen received in the initial treatment period and on the subject*s clinical response at Week 16 (defined as IGA of 0 or 1 on a 5 point scale ranging from 0 [clear] to 4 [severe], or EASI75).
Subjects randomised to tralokinumab in the initial treatment period and with a clinical response at Week 16 will be re-randomised 1:1 to one of the following Q2W maintenance regimens stratified by region and IGA response at Week 16 (IGA 0/1 or IGA >1):
* Tralokinumab 300 mg Q2W.
* Alternating dose administrations tralokinumab 300 mg and placebo (tralokinumab Q4W).
Subjects randomised to placebo in the initial treatment period and with a clinical response at Week 16 will receive placebo Q2W in the continuation treatment period. Non responders at Week 16 in the tralokinumab and placebo groups will receive tralokinumab 300 mg Q2W.
The primary endpoints are assessed at Week 16, and the final efficacy assessment will be conducted at Week 32.
Starting on Day 0 (baseline), all subjects will be allowed to initiate treatment once daily with a supplied TCS on lesional skin and continue as needed throughout the treatment period. TCS use will be monitored throughout the trial.
All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before randomisation and will continue this treatment throughout the trial (including safety follow-up). On lesional skin, emollients should only be applied at a time where TCS is not applied; on TCS-untreated areas, the emollients may be applied at all times.

Intervention

Tralokinumab (human recombinant IL 13 monoclonal antibody)
150 mg/mL solution for SC injection in an accessorised pre filled syringe, 1.0 mL fill volume. Each kit contains 1 syringe.
Placebo
Placebo solution for SC injection in an accessorised pre-filled syringe, 1.0 mL fill volume. Each kit contains 1 syringe.

Study burden and risks

There is an unmet medical need for new therapies for use in subjects with moderate-to-severe AD as current immunosuppressive medications, such as cyclosporine, methotrexate, and azathioprine, have associated long-term toxicities. Albeit dupilumab exhibits an acceptable benefit-risk ratio in clinical trials in AD, the long-term efficacy and safety experience with dupilumab is currently limited.

Tralokinumab has already demonstrated efficacy in both moderate-to-severe AD as well as in a severe asthma population in phase 2 trials, and has shown an acceptable safety profile in AD, asthma, ulcerative colitis, idiopathic pulmonary fibrosis, and in trials with healthy subjects. The evidence discussed in Section *5.2 further supports the hypothesis that individuals with AD may benefit from treatment with tralokinumab.
In the clinical trials completed to date, tralokinumab was well tolerated. A number of theoretical potential risks have been identified that are described in the current version of the Investigator*s Brochure, including hypersensitivity reactions, immune complex disease, severe infections, malignancies, and interference with reproductive function; measures are in place in this trial to protect participating subjects as follows:
* Close monitoring of subjects during the trial with trial visits every 2 weeks during the treatment period (see the schedule of procedures in Section *4).
* Close monitoring of subjects during the post dosing period at the first 3 investigational medicinal product (IMP) dosing visits in the initial treatment period (i.e., Weeks 0, 2, and 4) and after re-randomisation (i.e., Weeks 16, 18, and 20) as a precautionary measure against hypersensitivity reactions (further details are given in Section *9.1.3.1).
* Monitoring of subjects for clinical manifestations that may be associated with the development of specific antibodies to tralokinumab (i.e., immune complex disease).
* Exclusion of subjects with untreated systemic helminth infestations or subjects who have failed to respond to standard of care therapy; neutralisation of IL 13 might theoretically cause a worsening of parasitic infestation, in particular prevention of expulsion of gastrointestinal worms (helminths) (*19).
* Exclusion of subjects with a history of tuberculosis requiring treatment within 12 months prior to the screening visit.
* Exclusion of subjects with a history of a clinically significant infection (defined as a systemic or serious skin infection requiring parenteral antibiotics, antiviral, or anti-fungal medication; see Section *8.3) within 4 weeks prior to baseline which, in the opinion of the investigator or sponsor*s medical expert, may compromise the safety of the subject in the trial.
In conclusion, previous clinical experience with tralokinumab shows no major safety or tolerability concerns and appropriate measures have been instituted in this trial to protect subjects from potential risks that have been previously identified and to closely monitor each subject. The current risk/benefit ratio is favourable and supports the administration of tralokinumab in combination with TCS therapy for the purposes of achieving the objectives of this trial.

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

* Age 18 and above.
* Diagnosis of AD as defined by the Hanifin and Rajka (1980) criteria for AD.
* History of AD for *1 year.
* Subjects who have a recent history of inadequate response to treatment with topical medications.
* AD involvement of *10% body surface area at screening and baseline.
* An EASI score of *12 at screening and 16 at baseline.
* An IGA score of *3 at screening and at baseline.
* A Worst Daily Pruritus NRS average score of *4 during the week prior to baseline.
* Stable dose of emollient twice daily (or more, as needed) for at least 14 days before randomisation.

Exclusion criteria

* Subjects for whom TCSs are medically inadvisable e.g., due to important side effects or

safety risks in the opinion of the investigator.
* Active dermatologic conditions that may confound the diagnosis of AD.
* Use of tanning beds or phototherapy within 6 weeks prior to randomisation.
* Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 4 weeks prior to randomisation.
* Treatment with TCS, TCI, or topical phosphodiesterase 4 (PDE-4) inhibitor within 2 weeks prior to randomisation.
* Receipt of any marketed biological therapy (i.e. immunoglobulin, anti- immunoglobulin E) including dupilumab or investigational biologic agents.
* Active skin infection within 1 week prior to randomisation.
* Clinically significant infection within 4 weeks prior to randomisation.
* A helminth parasitic infection within 6 months prior to the date informed consent is obtained.
* Tuberculosis requiring treatment within the 12 months prior to screening.
* Known primary immunodeficiency disorder.

Study design

Design

Study phase:	3
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):	14-08-2018
Enrollment:	43
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Mometasone Furoate
Generic name:	Momecutan Fettcreme
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tralokinumab
Generic name:	NA

Ethics review

Approved WMO Date:	24-01-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-04-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-06-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-12-2018

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-01-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-002065-21-NL
CCMO	NL64045.091.18