An open-label, multi-centre drug-drug interaction trial to investigate the effects of tralokinumab on the pharmacokinetics of selected cytochrome P450 (CYP) substrates in adult subjects with moderate-to-severe atopic dermatitis

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Primary objectiveTo evaluate if tralokinumab after 14 weeks of treatment (at steady state) changes the metabolism of substrates of CYP 1A2, 2C9, 2C19, 2D6, or 3A4 pathways in subjects with moderate-tosevere atopic dermatitisSecondary objectivesTo...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin and subcutaneous tissue disorders NEC
Study type	Interventional

Summary

ID

NL-OMON46290

Source
ToetsingOnline

Brief title
Drug-drug interaction tralokinumab in moderate-to-severe atopic dermatitis

Condition

- Skin and subcutaneous tissue disorders NEC

Synonym
atopic dermatitis, Eczema

Research involving

Human

Sponsors and support

Primary sponsor: Leo Pharma
Source(s) of monetary or material Support: Leo Pharma

Intervention

Keyword: Atopic dermatitis, Drug-drug interaction, Pharmacokinetics, Tralokinumab

Outcome measures

Primary outcome

- Ratio of the AUClast at Week 15 (after multiple doses of tralokinumab,

AUClast,MD) to that on Day -7 (at baseline, AUClast,Base) for each of the 5

substrates

- Ratio of the Cmax at Week 15 (Cmax,MD) to that on Day -7 (Cmax,Base) for each

of the 5 substrates

Secondary outcome

- Ratio of the AUClast on Day 8 (after a single dose of tralokinumab,

AUClast,SD) to that on Day -7 (AUClast,Base) for each of the 5 substrates

- Ratio of the Cmax on Day 8 (Cmax,SD) to that on Day -7 (Cmax,Base) for each

of the 5 substrates

- Ratio of the AUCinf on Day 8 (AUCinf,SD) to that on Day -7 (AUCinf,Base) for

each of the 5 substrates

Study description

Background summary

Because AD is associated with elevated proinflammatory cytokines, and because

increased levels of certain cytokines during chronic inflammation can alter the formation of cytochrome P450 (CYP) enzymes, there is potential for AD disease-drug-drug interaction.

The current draft guidance for drug interaction studies (FDA 2017) recommends conducting clinical trials to determine the effect of a therapeutic protein on CYP enzymes in the target patient population if the investigational therapeutic protein is a cytokine or cytokine modulator. This is the case with tralokinumab, the investigational medicinal product (IMP) in this trial.

Study objective

Primary objective

To evaluate if tralokinumab after 14 weeks of treatment (at steady state) changes the metabolism of substrates of CYP 1A2, 2C9, 2C19, 2D6, or 3A4 pathways in subjects with moderate-tosevere atopic dermatitis

Secondary objectives

To evaluate if a single dose of tralokinumab changes the metabolism of substrates of CYP 1A2, 2C9, 2C19, 2D6, or 3A4 pathways in subjects with moderate-to-severe atopic dermatitis

To evaluate the safety and tolerability of tralokinumab in subjects with moderate-to-severe atopic dermatitis

Study design

The trial will consist of a screening period of 2*5 weeks (Week -6 to Day -7), a 1-week pre-IMP period (Day -7 to Day 1), a 16-week treatment period (Day 1 to Week 16), and a 14-week safety follow-up period (Week 16 to Week 30).
Eligible subjects may enter the open-label, long-term extension trial (LP0162-1337, ECZTEND) at Week 16 or later.
Following the pre-IMP period, all subjects will be dosed with tralokinumab 600 mg (4 mL) on Day 1, then with tralokinumab 300 mg (2 mL) every 2 weeks. The last dose of tralokinumab will be administered at Week 14.
After administration of the 5 substrates (caffeine, warfarin, omeprazole, metoprolol, and midazolam [CYP cocktail]) on Day -7, Day 8, and Week 15, plasma samples will be collected for up to 7 days after the cocktail dosing for measurement of plasma concentrations of the substrates.
For each of the 5 substrates, the pharmacokinetic (PK) parameters on Day -7 (baseline) will be compared with the PK parameters on Day 8 (after a single dose of tralokinumab) and at Week 15 (after multiple doses of tralokinumab).
Plasma concentrations of tralokinumab will be measured at the cocktail dosing visits on Day 8 and at Week 15. Additionally, plasma concentrations of

tralokinumab will be measured before administration of tralokinumab at Weeks 4 and 14, and 2 weeks after the last administration of tralokinumab, that is, at Week 16.
All subjects will use an emollient twice daily (or more, as needed) for at least 14 days before baseline and will continue this treatment throughout the trial (including the safety follow-up period).

Intervention

Tralokinumab

CYP cocktail:
- Caffeine
- Warfarin
- Omeprazole
- Metoprolol
- Midazolam

Study burden and risks

There is an unmet medical need for new therapies for use in subjects with moderate-to-severe AD because current immunosuppressive medications, such as cyclosporine, methotrexate, and azathioprine, are associated with long-term toxicities. Although 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 moderate-to-severe AD 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 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.

Contacts

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Trial sites

Listed location countries

France, Netherlands, United States of America

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 or for whom topical treatments are otherwise medically inadvisable.
* AD involvement of *10% body surface area at screening and baseline.
* Stable dose of emollient twice daily (or more, as needed) for at least 14 days before baseline.
* Willingness to abstain from consumption of any 1 or more of the following items in the periods specified:
o ±7 days within each cocktail dosing visit (that is, between the Day -14 and Day 15 visits and between the Week 14 and Week 16 visits): foods/beverages that affect the CYP system:
- Grapefruit or grapefruit juice, Seville oranges or orange juice, starfruit, pomegranate and cranberry juices, red wine, red grape extract.
- Cruciferous vegetables, including but not limited to broccoli, cabbage, cauliflower, kale, Brussels sprout, radish, turnip, horseradish.
- Chargrilled meat.
o ±48 hours within each cocktail dosing visit: caffeinated beverages, foods/drugs that contain

caffeine, including coffee, tea (black and green), coca cola, energy drinks, and chocolate.

Exclusion criteria

* Administration, within 14 days or 5 half-lives (whichever is longer) prior to Day -7, of any medication that is a known inducer or inhibitor of 1 or more of the following CYP enzymes: CYP3A, CYP2C19, CYP2C9, CYD2D6, and CYP1A2.
* Subjects who are poor metabolisers of CYP2C9, CYP2C19, or CYP2D6, based on genotyping.
* Any contraindication to 1 or more of the following drugs, according to the applicable labelling: caffeine, warfarin, omeprazole, metoprolol, or midazolam.
* Consumption of any 1 or more of the following items in the periods specified:
o From Day -14 (±7 days within each cocktail dosing visit):
foods/beverages that affect the CYP system:
- Grapefruit or grapefruit juice, Seville oranges or orange juice, starfruit, pomegranate and cranberry juices, red wine, red grape extract.
- Cruciferous vegetables, including but not limited to broccoli, cabbage, cauliflower, kale, Brussels sprout, radish, turnip, horseradish.
- Chargrilled meat.
o From Day -9 (±48 hours within each cocktail dosing visit):
caffeinated beverages, foods/drugs that contain caffeine, including coffee, tea (black and green), coca cola, energy drinks, and chocolate.
* Nausea or diarrhoea 1 week prior to Day -7.
* Active dermatologic conditions that may confound the diagnosis of AD.
* Use of tanning beds or phototherapy within 5 weeks prior to Day -7.
* Treatment with systemic immunosuppressive/immunomodulating drugs and/or systemic corticosteroid within 3 weeks prior to Day -7.
* Treatment with topical corticosteroids, topical calcineurin inhibitors, or topical phosphodiesterase 4 inhibitors within 1 week prior to Day -7.
* Receipt of any marketed biological therapy (that is, immunoglobulin or anti-immunoglobulin E) including dupilumab or investigational biologic agents:
o Any cell-depleting agents, including but not limited to rituximab: within 6 months prior to baseline (Day -7), or until lymphocyte count returns to normal, whichever is longer.
o Other biologics: within 3 months or 5 half-lives, whichever is longer, prior to baseline (Day -7).
* Active skin infection within 1 week prior to Day -7.
* Clinically significant infection within 4 weeks prior to Day -7.
* 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 type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Caffein
Generic name:	Caffein
Product type:	Medicine
Brand name:	Metoprolol
Generic name:	Metoprolol Tartrate
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Midazolam
Generic name:	Midazolam
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Omeprazole
Generic name:	Omeprazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tralokinumab
Generic name:	N.A.

Ethics review

Approved WMO Date:	18-02-2019
Application type:	First submission
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	2018-000534-35
ClinicalTrials.gov	NCT03556592
CCMO	NL68628.056.18

Study results

Results posted: 22-07-2021

First publication
22-07-2021