A randomized, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis.

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Primary objective:To demonstrate the efficacy of dupilumab administered concomitantly with TCS through week 16 in adult patients with moderate-to-severe atopic dermatitis (AD).Secondary objectives:Evaluate long-term efficacy of dupilumab when...

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

Summary

ID

NL-OMON42019

Source
ToetsingOnline

Brief title
Dupilumab for adult patients with moderate to severe atopic dermatitis.

Condition

- Epidermal and dermal conditions

Synonym
atopic dermatitis; eczema

Research involving
Human

Sponsors and support

Primary sponsor: Regeneron Pharmaceuticals, Inc.
Source(s) of monetary or material Support: Door de industrie zoals is opgegegevn bij vraag B6/B7

Intervention

Keyword: atopic, dermatitis, dupilumab

Outcome measures

Primary outcome

Proportion of patients with EASI-75 response (reduction of EASI score by >=75%

from baseline) at week 16.

Proportion of patients with both an IGA 0 or 1 (on a 5-point scale) and a

reduction from baseline of >=2 points at week 16.

Secondary outcome

Key Secondary Endpoints:

* Proportion of patients with EASI-75 response (reduction of EASI score by *75%

from baseline) at week 16 (this is not a secondary efficacy endpoint for the EU

and EU reference market countries, and Japas, as it is already a co-primary

endpoint)

* Percent change from baseline to week 16 in weekly average of peak daily

Pruritus Numerical Rating Scale (NRS)

* Proportion of patients with improvement (reduction) in weekly average of peak

daily Pruritus NRS *4 from baseline to week 16

* Proportion of patients with IGA 0 or 1 and a reduction from baseline of >=2

points at week 52

* Proportion of patients with EASI-75 response at week 52

* Proportion of patients with improvement (reduction) in weekly average of peak daily Pruritus NRS >=3 from baseline to week 16.

* Percent change from baseline to week 52 in weekly average of peak daily Pruritus NRS.

Other secondary endpoints:

* Percent change in EASI score from baseline to week 16.

* Change from baseline to week 16 in percent BSA

* Percent change in SCORing Atopic Dermatitis (SCORAD) from baseline to week 16

* Percent change from baseline to week 16 in Global Individual Sings Score (GISS) (erythema, infiltration/papulation, excoriations, lichenification)

* Change from baseline to week 16 in Dermatology Life Quality Index (DLQI)

* Change from baseline to week 16 in Patient Oriented Eczema Measure (POEM)

* Change from baseline to week 16 in Hospital Anxiety and Depression Scale (HADS)

* Reduction in topical AD medication use through week 16 (determined by the amount of TCS and/or topical calcineurin inhibitors (TCI) used since previous visit in weight).

* Proportion of patients with improvement (reduction) in weekly average of peak daily Pruritus NRS *3 from baseline to week 52

* Proportion of patients with improvement (reduction) in weekly average of peak daily Pruritus NRS *4 from baseline to week 52

* Percent change in EASI score from baseline to week 52.

* Change from baseline to week 52 in percent BSA

* Percent change in SCORAD from baseline to week 52

* Percent change from baseline to week 52 in GISS (erythema,

infiltration/papulation, excoriations, lichenification)

* Change from baseline to week 2 in weekly average of peak daily Pruritus NRS

* Number of flares through week 52

* Change from baseline to week 52 in DLQI

* Change from baseline to week 52 in POEM

* Change from baseline to week 52 in HADS

* Incidence of skin-infection treatment-emergent adverse events (TEAEs)

requiring systemic treatment from baseline through week 56

* Incidence of serious TEAEs through week 56

* Indicence of TEASs leading to study drug discontinuation from baseline

through week 56

Study description

Background summary

Atopic dermatitis (AD) is a chronic/relapsing inflammatory skin disease characterized by intense pruritus (eg, itchiness), and by scaly and dry eczematous lesions. It is often associated with other atopic disorders, such as allergic rhinitis and asthma. Severe disease can be extremely disabling due to several factors: major psychological problems, significant sleep loss, and impaired quality of life (QOL) that leads to a high socioeconomic cost. An estimated 15% to 30% of children and 2% to 10% of adults are affected by AD.

The goal in treating AD is reducing skin inflammation. Up-regulation of IL-4 and IL-13 has been implicated as an important inflammatory component of AD disease progression. Dupilumab targets the IL-4R*, and thus interferes with the signaling cascade. Inhibition of this Th2 inflammatory pathway is currently

being and has previously been evaluated with other agents.

Dupilumab is being developed for the treatment of moderate-to-severe AD in patients intolerant of, or not adequately controlled with, topical treatments. Phase 1 and phase 2 data with dupilumab have, to date, demonstrated promising efficacy, safety, and tolerability in a patient population with moderate* to-severe AD. In many cases, treatment-benefit occurred during the first week of treatment; this early response is similar to the time of onset observed with cyclosporine treatment, but without the apparent risk for cardiovascular and renal side effects.

Study objective

Primary objective:
To demonstrate the efficacy of dupilumab administered concomitantly with TCS through week 16 in adult patients with moderate-to-severe atopic dermatitis (AD).

Secondary objectives:
Evaluate long-term efficacy of dupilumab when administered concomitantly with TCS for up to 52 weeks.
Evaluate long-term safety of dupilumab when administered concomitantly with TCS for up to 52 weeks.

Research objectives:
Assess the relationship between long-term exposure to dupilumab and potential biomarkers of AD.

Study design

This is a 64-week (52-week treatment period and 12 week follow up), randomized, double-blind, placebo-controlled, parallel group study to confirm the efficacy and safety of dupilumab administered concomitantly with TCS in adults with moderate-to-severe AD. After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening within 35 days prior to randomization. During the screening period, treatments for AD will be washed out for at least 7 days prior to baseline (except moisturizers). Patients will be required to apply moisturizers (emollients) twice daily for at least the 7 consecutive days immediately before randomization and continue throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on the area(s) of non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.

Patients who continue to meet eligibility criteria at baseline will undergo day 1/baseline assessments and will be randomized in a 3:1:3 ratio to receive qw or

q2w SC injections of 300 mg dupilumab, following a loading dose of 600 mg on day 1 (during weeks when dupilumab is not administered, patients will receive placebo), or matching placebo including the loading dose. In order to maintain blinding, all patients will receive an injection each week from day 1 to week 51. Randomization will be stratified by baseline disease severity (moderate [IGA = 3 vs. severe [IGA = 4] AD) and by region. Eligible patients must have a documented history of inadequate response to treatment with topical AD medication. Patients will have the option to self administer study drug outside the study site during weeks in which no clinic visit is scheduled. Patients (and/or caregivers) will be trained on injecting study drug at visits 2 (day 1) through visit 4 (week 2), or until competency has been demonstrated. Patients will remain at the study site for a minimum of 30 minutes after each of the first 3 weekly injections. Patients who do not want to self-inject may have the clinic staff administer all the study drug injections in the clinic.
Starting on day 1/baseline, all patients will initiate treatment with TCS using a standardized regimen and continue the standardized regimen through the end of the study.
After week 2, if needed to control intolerable symptoms, patients will be eligible to receive rescue treatment with any locally approved AD treatments at the discretion of the investigator. If rescue is needed after week 2, investigators will be encouraged to provide rescue therapy in a staged fashion, using a greater intensity of treatment compared to that which the patient was using (eg, increasing the potency of TCS, treating with oral corticosteroids, systemic nonsteroid immunosuppressants, or phototherapy). Patients who experience worsening of disease between scheduled visits should return to the clinic (unscheduled visit) for IGA, Eczema Area and Severity Index (EASI), and body surface area (BSA) of involvement of AD assessments before starting treatment escalation. Patients may receive rescue after week 2 with TCS and continue treatment with study drug. If a patient receives rescue with a systemic nonsteroid immunosuppressant, systemic corticosteroids, or phototherapy, the patient must stop study drug, but may be eligible to restart treatment with study drug after discontinuing such rescue treatment. Patients who are discontinued from study drug are considered treatment failures, but will remain in the study and continue with the study visits and assessments. Use of all concomitant topical products, medications, and procedures will be documented.
The end of treatment period visit will occur at week 52, 1 week after the last dose of study drug. The duration of the 12-week follow-up period is based on the time expected for drug levels to reach zero (below the lower limit of quantification) in most patients after the last dose of dupilumab. The end of study visit will occur at week 64
Patients who complete this study may be eligible to enroll in a subsequent open-label extension study in which they may receive treatment with dupilumab. Safety, laboratory, and clinical assessments will be performed at specified clinic visits as noted.

Approximately 700 patients will be enrolled.

Intervention

Subcutaneous dupilumab injection OR subcutaneous placebo injection:

Patients will receive a loading dose of 400 mg (2 injections each containing 200 mg dupilumab in a 2 mL volume) on day 1 followed by 200 mg in 2 mL qw from week 1 through week 52.
OR
Patients will receive a loading dose of 600 mg (2 injections, each containing 300 mg dupilumab in a 2 mL volume), on day 1 followed by 300 mg in 2 mL q2w from week 2 through week 50 (even-numbered weeks). During weeks in which dupilumab is not administered (odd-numbered weeks), patients will receive placebo injections (see below).

The last dose of study drug for both regimens will be at week 51.

OR
Placebo:
Matching placebo SC injection. Loading dose for the placebo arm consists of 2 injections, each containing placebo formulation in a 2 mL volume, administered at day 1 followed by qw injections of 2 mL placebo formulation from week 1 through week 52 (last dose of study drug will be at week 51).

Study burden and risks

Dupilumab is bestudeerd bij ruim 400 menselijke proefpersonen, bestaande uit gezonde vrijwilligers en patiënten met atopische dermatitis, astma en neuspoliepen. Op grond van de momenteel beschikbare gegevens zijn er geen vastgestelde risico's bepaald die rechtstreeks verband houden met dupilumab.

Patients are closely monitored on AEs, ECGs vital functions and lab results to ensure patient safety and to support the evaluation of the safety profile.

The risks and burden for the patient are thought to be in perspective to the treatment of the patient and the necessity to study new compounds with additional benefits. Patients are given the choice to either go to the researchcenter for the weekly injection or to learn to do it at home.

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. Male or female, 18 years or older
2. Chronic AD, (according to the American Academy of Dermatology Consensus Criteria),that has been present for at least 3 years before the screening visit.
3. Patients with documented recent history (within 6 months before the screening visit) of inadequate response to a sufficient course of outpatient treatment with topical AD medication(s), or for whom topical AD therapies are medically inadvisable.

Exclusion criteria

1. Prior treatment with dupilumab.
2. Important side effects of topical medication (e.g., tolerance to treatment, hypersensitivity reactions, significant skin atrophy, systemic effects), as assessed by the investigator or patient's treating physician.
3. At baseline visit >=30% of the total lesional surface located on areas of thin skin that cannot be safely treated with medium or higher potency TCS (e.g., face, neck, intertriginous areas, genital areas, areas of skin atrophy)
4. Recent treatment (within specific time windows before the baseline visit) with systemic

corticosteroids, immunosuppressive agents, topical corticosteroids and calcineurin inhibitors, live (attenuated) vaccine, other investigational drugs.
5. History of human immunodeficiency virus (HIV) infection.
6. HIV or viral hepatitis positive serology at screening.
7. Known or suspected immunosuppression
8. Recent infections requiring antiinfectious treatment
9. Recent history or high risk of clinical endoparasitoses, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization.
10. High risk populations (low life expectancy, severe concomitant diseases, etc.)
11. Pregnant or breast-feeding women
12. Patients of reproductive potential and sexually active who are unwilling to use adequate contraceptives

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):	06-02-2015
Enrollment:	120
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dupilumab
Generic name:	nvt

Ethics review

Approved WMO Date:	20-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-07-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-09-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-003254-24-NL
CCMO	NL48219.018.14