A phase 3 study investigating the efficacy, safety, and tolerability of Dupilumab administered to adult patients with severe atopic dermatitis who are not adequately controlled with or are intolerant to oral cyclosporine A, or when this treatment is not medically advisable

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The primary objective of the study is to evaluate the efficacy of 2 dose regimens of dupilumab compared to placebo, administered with concomitant topical corticosteroids (TCS), in adult patients with severe AD who are not adequately controlled with...

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

Summary

ID

NL-OMON43809

Source
ToetsingOnline

Brief title
R668-AD-1424 (0456/0050)

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: Regeneron Pharmaceuticals;Inc.

Intervention

Keyword: atopic dermatitis, cyclosporine A, Dupilumab

Outcome measures

Primary outcome

Endpoints

Primary: The primary endpoint in the study is: the proportion of

patients with Eczema Area and Severity Index (EASI) 75 (*75% improvement from

baseline) at week 16.

Secondary outcome

Secondary: The secondary endpoints are:

Efficacy

* Proportion of patients with EASI 75 (*75% improvement from baseline) at week

16 for patients with prior CSA use

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

from baseline of *2 points at week 16

* Percent change from baseline to week 16 in the pruritus numerical rating

scale (NRS)

* Proportion of patients with improvement (reduction) of pruritus NRS *3 at

week 16

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

* Change from baseline to week 16 in percent body surface area (BSA)

* Percent change from baseline to week 16 in the SCORing Atopic Dermatitis

(SCORAD)

*

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

*

* Change from baseline to week 16 in the Hospital Anxiety and Depression Scale

(HADS)

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

* Percent change from baseline to week 2 in the pruritus NRS

* Topical treatment for AD * medication-free days to week 16

* Mean weekly dose of TCS through week 16

* Proportion of patients with EASI 75 (*75% improvement from baseline) at week

24

* Proportion of patients with EASI 75 (*75% improvement from baseline) at week

24 for patients with prior CSA use

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

from baseline of *2 points at week 24

* Percent change from baseline to week 24 in the pruritus NRS

* Proportion of patients with improvement (reduction) of pruritus NRS *3 at

week 24

* Percent change from baseline to week 24 in the EASI score

* Change from baseline to week 24 in percent BSA

* Percent change from baseline to week 24 in the SCORAD

* Proportion of patients with SCORAD 50 (*50% improvement from baseline) at week 24

* Change from baseline to week 24 in the DLQI

* Change from baseline to week 24 in the HADS

* Change from baseline to week 24 in the POEM

* Topical treatment for AD * medication-free days to week 24

* Change from baseline to week 24 in the Hospital Anxiety and Depression Scale (HADS)

* Mean weekly dose of TCS through week 24

Safety and tolerability

* Incidence of skin infection treatment-emergent adverse events (TEAEs) (excluding herpetic infections) from baseline through the on-treatment period

* Incidence of treatment-emergent serious adverse events (TESAEs) from baseline through the on-treatment period

* Incidence of TEAEs leading to treatment discontinuation from baseline through the on-treatment period

* Overall incidence of TEAEs from baseline through the on-treatment period

Study description

Background summary

A Phase 3 Study Investigating the Efficacy, Safety, and Tolerability of Dupilumab Administered to Adult Patients with Severe Atopic Dermatitis who are not Adequately Controlled with or are Intolerant to Oral Cyclosporine A, or when this Treatment is not Medically Advisable.

The study will be executed in approximately 125 study sites in countries where systemic cyclosporine A (CSA) is approved for the treatment of atopic dermatitis (AD).

The duration of the study for a patient is approximately 40 weeks, including the screening period.

See also section C4 and section of the protocol: Introduction and Rationale.

Study objective

The primary objective of the study is to evaluate the efficacy of 2 dose regimens of dupilumab compared to placebo, administered with concomitant topical corticosteroids (TCS), in adult patients with severe AD who are not adequately controlled with, or are intolerant to, oral CSA, or when this treatment is currently not medically advisable.
The secondary objective of the study is to assess the safety and tolerability of 2 dose regimens of dupilumab compared to placebo, administered with concomitant TCS, in adult patients with severe AD who are not adequately controlled with, or are intolerant to, oral CSA, or when this treatment is currently not medically advisable.

Study design

The study comprises a 2-week screening period, a 2-week medium-potency TCS standardization period, a 24-week treatment period, and a 12 week safety follow up period. This study is being done to evaluate dupilumab treatment in these patients with severe AD who have also previously demonstrated inadequate response to TCS. All patients will receive concomitant medium-potency TCS as background concomitant therapy to reflect standard of care treatment of this severe population.
After providing informed consent, patients will be assessed for study eligibility at the screening visit. Patients will undergo screening between day -28 and day -15, prior to randomization. During this 2-week screening period, TCS treatment is allowed at the discretion of the investigator.
Starting on day -14, all patients will initiate a standardized TCS treatment regimen, and will continue the standardized medium-potency regimen through the end of the treatment period (week 24). During the 12 week follow-up period, they may continue to receive TCS at the discretion of the investigator, for intolerable AD disease activity.
Patients will also be required to apply moisturizers at least twice daily for

at least the 7 consecutive days immediately before randomization (baseline/day 1) and continue at least twice daily throughout the study.

Patients who continue to meet eligibility criteria at baseline (day 1) will undergo assessments and will be randomized in a 1:1:1 ratio to receive either once-weekly (qw) or every 2 week (q2w) subcutaneous (SC) injections of 300 mg dupilumab (following an SC loading dose of 600 mg on day 1), or matching injectable placebo, including the placebo for the loading dose. During weeks in which dupilumab is not administered (in the q2w regimen), patients will receive injectable placebo. In order to maintain blinding, all patients will receive an injection (active or placebo) each week from day 1 to week 24 (treatment period).
The patients will be stratified by: 1) Baseline assessment of disease severity (Investigator*s Global Assessment [IGA] 3 vs IGA 4) and 2) documented history of no prior CSA exposure and not currently a candidate for CSA treatment or CSA prior exposure that should not be continued or restarted.
Patients will be followed up for an additional 12 weeks for safety after the end of the treatment period. Starting at week 24, patients may be rolled over into an open-label extension (OLE) study, if they are considered eligible. Patients who discontinued prematurely (ie, patients who did not complete the protocol-defined end-of-treatment [EOT] visit) cannot enroll into the OLE study before the date when the EOT visit would have normally occurred.

Intervention

Treatments
Study Drug
Dose/Route/Schedule: Patients will receive either qw SC injections of 300 mg dupilumab (following a loading dose of 600 mg on day 1), or q2w SC injections of 300 mg dupilumab (following a loading dose of 600 mg on day 1) during the 24 week treatment period. During weeks in which dupilumab is not administered (in the q2w regimen), patients will receive injectable placebo.

Placebo
Route/Schedule: Patients will receive weekly injections of matching placebo (following a placebo *loading dose* on day 1) during the 24-week treatment period.

Background Treatment
Dose/Route/Schedule: TCS:
Starting on day -14, all patients are required to undergo treatment with TCS using a standardized regimen according to the following guidelines:
* Apply medium-potency TCS once daily to areas with active lesions
* Low-potency TCS should be used once daily on areas of thin skin (face, neck, intertriginous, and genital areas, areas of skin atrophy, etc) or for areas where continued treatment with medium-potency TCS is considered unsafe
* Monitor the patient for signs of local or systemic TCS toxicity and stop

treatment as necessary
During the 24-week placebo-controlled study treatment period, medium potency TCS dosing frequency will be symptom-based (IGA score) adjusted every 4 weeks (q4w) as per the protocol-specified tapering algorithm.
Emollients:
All patients are required to apply moisturizers (emollients) at least twice daily for at least the 7 consecutive days immediately before randomization (baseline/day 1) and to continue through the end of the follow-up period. 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. All types of moisturizers are permitted, but patients may not initiate treatment with prescription moisturizers or moisturizers containing additives during the screening period or during the study. Patients may continue using stable doses of prescription moisturizers or moisturizers containing additives, if initiated before the screening visit.
Rescue Treatment
Dose/Route/Schedule: If medically necessary (ie, to control intolerable AD symptoms), rescue treatment for AD may be provided to study patients at the discretion of the investigator. If possible, investigators should attempt to limit the first step of rescue therapy to high-potency TCS, and escalate to systemic medications only for patients who do not respond adequately after at least 7 days of topical treatment. Investigators should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety labs) immediately before administering any rescue treatment. An unscheduled visit may be used for this, if necessary.

Study burden and risks

See section E9

Contacts

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Regeneron Pharmaceuticals, Inc.

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US

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. Severe, Chronic AD, (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]) ;3. EASI score *20 at the screening and baseline visits ;4. IGA score *3 (on the 0 to 4 IGA scale) at the screening and baseline visits ;5. *10% body surface area (BSA) of AD involvement at the screening and baseline visits ;6. Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with TCS;7. Have applied a stable dose of topical emollient (moisturizer) twice daily for at least the 7 consecutive days immediately before the baseline visit;8. Documented history by a physician of either:;A. No prior CSA exposure and not currently a candidate for CSA treatment due to:;* medical contraindications (eg, uncontrolled hypertension on medication), or;* use of prohibited concomitant medications (eg, statins, digoxin, macrolide;* antibiotics, barbiturates, anti-seizure, nonsteroidal anti-inflammatory drugs,;* diuretics, angiotensin-converting-enzyme inhibitors, St John*s Wort, etc), or;* increased susceptibility to CSA-induced renal damage (elevated creatinine) and;* liver damage (elevated function tests), or;* increased risk of serious infections, or ;* hypersensitivity to CSA active substance or excipients, ;OR;B. Previously exposed to CSA, and CSA treatment should not be continued or restarted due to:;* intolerance and/or unacceptable toxicity (eg, elevated creatinine, elevated liver function tests, uncontrolled hypertension, paraesthesia, headache, nausea, hypertrichosis, etc), or;* inadequate response to CSA (defined as flare of AD on CSA tapering after a maximum of 6 weeks of high dose [5 mg/kg/day] to maintenance dose [2 to 3 mg/kg/day] or a flare after a minimum of 3 months on maintenance dose). Flare is defined as increase in signs and/or symptoms leading to escalation of therapy, which can be an increase in dose, a switch to a higher-potency class of TCS, or the start of another systemic non-steroidal immunosuppressive drug. Or;* requirement for CSA at doses >5 mg/kg/day, or duration beyond those specified in the prescribing information (>1 year).

Exclusion criteria

1. Participation in a prior dupilumab clinical study ;2. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, prior to screening;3. Hypersensitivity and/or intolerance to corticosteroids or to any other ingredients contained in the TCS product used in the study;4. Systemic CSA, systemic corticosteroids, or phototherapy within 4 weeks prior to screening, and azathioprine (AZA), methotrexate (MTX), mycophenolate mofetil (MMF), or Janus Kinase (JAK) inhibitors within 8 weeks prior to screening.;5. Treatment with TCI within 1 week prior to screening visit ;6. Treatment with biologics as follows:;* Any cell-depleting agents including but not limited to rituximab: within 6 months before the screening visit, or until lymphocyte count returns to normal, whichever is longer;* Other biologics: within 5 half-lives (if known) or 16 weeks prior to the screening visit, whichever is longer;7. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the screening visit ;8. Treatment with a live (attenuated) vaccine within 12 weeks before the screening visit;9. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the screening visit;or superficial skin infections within 1 week before the screening visit. NOTE: patients may be rescreened no sooner than 2 weeks after infection resolves. ;10. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis [TB], histoplasmosis, Listeriosis, coccidioidomycosis, pneumocystosis, aspergillosis) despite infection resolution; or unusually frequent, recurrent, or prolonged infections, per investigator judgment;11. Presence of any 1 of the following TB criteria: ;a. A positive tuberculin skin test at the screening visit;b. A positive blood QuantiFERON®-TB or T-Spot test at the screening visit;c. Chest x-ray (posterior-anterior and lateral views) at screening or within 3 months before the screening visit (radiology report must be available) with results consistent with prior TB infection (including but not limited to apical scarring, apical fibrosis, or multiple calcified granuloma). This does not include non-caseating granulomata.;NOTE: Any of these 3 TB tests will be performed on a country-by-country basis according to local guidelines only if required by regulatory authorities or ethics boards.;12. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening;13. Positive hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBc Ab), or hepatitis C antibody (HCV Ab) at the screening visit.

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):	25-04-2016
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dupilumab
Generic name:	REGN668/SAR231893

Ethics review

Approved WMO Date:	20-10-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-02-2016
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	22-03-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	15-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-04-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-09-2016
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-03-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2015-002653-35-NL
CCMO	NL55127.028.15