A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 2A STUDY TO ASSESS THE EFFICACY AND SAFETY OF REGN3500 MONOTHERAPY AND COMBINATION OF REGN3500 PLUS DUPILUMAB IN ADULT PATIENTS WITH MODERATE-TO-SEVERE ATOPIC DERMATITIS

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

Summary

ID

NL-OMON48003

Source
ToetsingOnline

Brief title
REGN3500

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: farmaceutische industrie

Intervention

Keyword: Atopic Dermatitis, Phase 2a Study, REGN3500 therapy

Outcome measures

Primary outcome

The primary endpoint in the study is the percent change in EASI score from

baseline to week 16.

Secondary outcome

The secondary endpoints are:

* Proportion of patients achieving EASI-50, EASI-75, and EASI-90 (*50%, *75%,

and *90% improvement from baseline) at week 16

* Absolute change in EASI score from baseline to week 16

* Proportion of patients with both an Investigator*s Global Assessment (IGA)

score of 0 or 1 (on a 5-point scale) and a reduction from baseline of *2 points

at week 16

* Change (absolute and percent) from baseline to week 16 in weekly average of

daily peak Pruritus Numerical Rating Scale (NRS)

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

daily peak Pruritus NRS *4 from baseline at week 16

* Time to onset of effect on pruritus during the 16-week treatment period (*4-

point reduction of weekly average of daily peak Pruritus

NRS from baseline)

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

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

involvement

Study description

Background summary

Based on the mechanism of action of REGN3500, inhibition of IL-33, REGN3500 is expected to
be efficacious in treatment of AD. In addition, as some of the inflammatory pathways targeted by
REGN3500 overlap with those targeted by dupilumab, which inhibits IL-4R*, concurrent
treatment with REGN3500 and dupilumab may be additive, further suppressing pathways
associated with allergic inflammation or target pathways not affected by either monotherapy.
These hypotheses will be tested by analysis of the changes from baseline in objective and
subjective measures of skin inflammation after treatment with REGN3500, REGN3500 plus
dupilumab combination, or placebo.

Study objective

The primary objective of the study is to evaluate the efficacy of REGN3500 monotherapy compared with placebo treatment in adult patients with moderate-to-severe atopic dermatitis (AD).
The secondary objectives of the study are:
* To evaluate the efficacy of REGN3500 in combination with
dupilumab compared with placebo treatment in adult patients with

moderate-to-severe AD
* To assess the safety, tolerability, and immunogenicity of subcutaneous (SC) doses of REGN3500 monotherapy and REGN3500 in combination with dupilumab in adult patients with moderate-to-severe AD
* To evaluate the pharmacokinetics (PK) of REGN3500 monotherapy and REGN3500 in combination with dupilumab in adult patients with moderate-to-severe AD
The exploratory objectives of the study are to assess the effects of REGN3500 monotherapy and REGN3500 in combination with dupilumab on skin and blood biomarkers of inflammation, quality of life (QOL), and patient-reported measures of pain and sleep quality in comparison with placebo.

Study design

This is a randomized, double-blind, placebo-controlled, double-dummy, parallel group study to assess the efficacy, safety, tolerability, PK, and immunogenicity of SC treatment with REGN3500 in adult patients with moderate-to-severe AD. Eligible patients must have a documented history of inadequate response or intolerance to treatment with topical AD medications.
After providing informed consent, patients will be assessed for study eligibility at a screening visit (up to 5 weeks [ie, 35 days] prior to randomization). During the screening period, treatments for AD will be washed out, as applicable, according to eligibility requirements. Patients may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions (eg, medication use, concomitant illness, medical condition), unless the reason for the screen failure is related to failing the disease severity inclusion criteria.
Patients will be required to apply moisturizers (bland emollients) at least twice daily for at least the 7 consecutive days immediately before randomization (ie, baseline/randomization visit would be the eighth day) and throughout the study. However, to allow adequate assessment of skin dryness, moisturizers should not be applied on any area(s) of lesional or non-lesional skin designated for such assessments for at least 8 hours before each clinic visit.
Patients who continue to meet eligibility criteria will undergo day 1/baseline assessments and will be randomized in a 1:1:1:1 ratio to receive SC treatment every 2 weeks (Q2W) with REGN3500 300 mg, dupilumab 300 mg, REGN3500 300 mg in combination with dupilumab 300 mg, or placebo. Dupilumab monotherapy will serve as an efficacy and biomarker calibrator arm.
Randomization will be stratified by baseline disease severity (moderate [Investigator*s Global Assessment (IGA=3)] vs. severe [IGA=4] AD). It is planned that at least approximately 50% of patients randomized will have an IGA score of 4. To ensure enrollment according to intended distribution

of disease severity, alerts will be built into the interactive voice/web response system to limit enrolling patients with an IGA score <4.
Following the initial dose of study drug administered SC on day 1 (ie, REGN3500/REGN3500-matching placebo plus loading dose of dupilumab/dupilumab-matching placebo), study treatment will be administered SC Q2W through week 14. The last study treatment will be administered at week 14. If medically necessary (ie, to control intolerable AD symptoms), patients may receive rescue treatment for AD (eg, systemic and topical corticosteroids) at the discretion of the investigator.
Patients will remain at the study site for 2 hours after administration of study drug. During the 16-week
treatment period, patients will have study visits every other week. The endof-treatment visit will occur at week 16, which is 2 weeks after the last dose of study drug. The primary endpoint will be determined at week 16. Posttreatment follow-up visits will occur every 4 weeks from week 20 through
week 36.

Intervention

Patients will be randomly assigned to one of four treatment groups:
* REGN3500 : 2 injections of REGN3500 150 mg plus 2 injections of dupilumab matching placebo on Day 1 and then 2 injections of REGN3500 150 mg plus 1 injection of dupilumab-matching placebo every 2 weeks through Week 14.
* Dupilumab: 2 injections of dupilumab 300mg plus 2 injections of REGN3500-matching placebo on Day 1 and then 1 injection of dupilumab 300 mg plus 2 injections of REGN3500-matching placebo every 2 weeks through Week 14
* REGN3500 plus Dupilumab Combination: 2 injections of REGN3500 150 mg plus 2 injections of dupilumab 300 mg on Day 1 and then 2 injections of REGN3500 150 mg plus 1 injection of dupilumab 300 mg every 2 weeks through Week 14
* Placebo: 2 injections of REGN3500-matching placebo plus 2 injections of dupilumab-matching placebo on Day 1 and then 2 injections of REGN3500-matching placebo plus 1 injection of dupilumab-matching placebo every 2 weeks through Week 14.

Study burden and risks

In general, study subjects can experience physical or psychological discomfort through examination tests, research procedures and questionnaires. In addition, subjects can experience side effects from the study medication.

The study subjects undergo the following extra invasive procedures in the context of the study:
- Blood collection: 12 times
- Subcutaneous injection: 25 times
- Skin biopsy (optional): maximum 2 times

In addition, the subjects undergo the following extra non-invasive interventions in the context of the study:
- Visits to the doctor: 15 visits
- Physical examination: 4 times
- Eye examination: 1 time
- ECG: 3 times
- Questionnaires: 15 times
- Complete the diary: 36-41 weeks
- Urine samples: 10 times

Testing for the presence of HIV, tuberculosis and hepatitis is also performed and a pregnancy test is performed for women.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

A patient must meet the following criteria to be eligible for inclusion in the study:
1. Male or female, 18 to 75 years
2. Chronic AD, according to American Academy of Dermatology Consensus Criteria (Eichenfield, 2014), that has been present for at least 3 years before the screening visit
3. EASI score *16 at the screening and baseline visits
4. IGA score *3 (on the 0 to 4 IGA scale, in which 3 is moderate and 4 is severe) at screening
and baseline visits
5. *10% BSA of AD involvement at the screening and baseline visits
6. Baseline peak Pruritus NRS score for maximum itch intensity *4
NOTE: Baseline peak Pruritus NRS score for maximum itch intensity will be determined
based on the average of daily NRS scores for maximum itch intensity (the daily score
ranges from 0 to 10) during the 7 days immediately preceding randomization. A minimum
of 4 daily scores out of the 7 days is required to calculate the baseline average score. For
patients who do not have at least 4 daily scores reported during the 7 days immediately
preceding the planned randomization date, randomization should be postponed until this
requirement is met, but without exceeding the 35-day maximum duration for screening.
7. Documented recent history (within 6 months before the screening visit) of inadequate
response to topical AD medication(s) or for whom topical treatments are medically
inadvisable (eg, intolerance, because of important side effects, or safety risks).
NOTE:
* Inadequate response is defined as failure to achieve and maintain remission or a low
disease activity state (comparable to IGA 0<=clear to 2<=mild) despite treatment with a
daily regimen of topical corticosteroids (TCS) of medium to higher potency (± topical
calcineurin inhibitors [TCI] as appropriate), applied for at least 28 days or for the
maximum duration recommended by the product prescribing information (eg, 14 days for super-potent TCS), whichever is shorter.
* Patients with documented systemic treatment for AD (eg, systemic

immunosuppressant
drugs like cyclosporine, methotrexate, corticosteroids, etc) in the past 6 months are also
considered to be inadequate responders to topical treatments and are potentially eligible
for treatment with dupilumab and REGN3500 after appropriate washout.
* Important side effects or safety risks are those that outweigh the potential treatment
benefits and include intolerance to treatment, hypersensitivity reactions, significant
skin atrophy, and systemic effects, as assessed by the investigator or by the patient*s
treating physician.
* Acceptable documentation includes contemporaneous chart notes that record topical
medication prescription and treatment outcome, or investigator documentation based
on communication with the patient*s treating physician. If documentation is inadequate, potential patients may be offered a course of treatment with a daily regimen
of TCS of medium or higher potency (±TCI as appropriate), applied for at least 28 days
during the screening period or for the maximum duration recommended by the product
prescribing information, whichever is shorter. Patients who demonstrate inadequate
response during this period, as defined above, will be eligible for inclusion in the study
following appropriate washout.
8. Have applied a stable dose of topical bland emollient (moisturizer) at least twice daily for
at least the 7 consecutive days immediately before randomization
(ie, baseline/randomization visit would be the eighth day; see exclusion criterion 7
regarding restrictions on the kind of emollients permitted during the study).
9. Willing and able to comply with all clinic visits and study-related procedures
10. Provide informed consent signed by study patient or legally acceptable representative
11. Able to understand and complete study-related questionnaires

Exclusion criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Prior participation in an anti-IL-33 class antibody (including not limited to REGN3500) or anti-IL4R* class antibody (including but not limited to dupilumab) clinical study; past treatment with or current treatment with dupilumab or another anti-IL4R* treatment
2. Body mass index <16 kg/m2
3. Treatment with an investigational drug within 8 weeks or within 5 half-lives (if known), whichever is longer, before the baseline visit
4. Having used any of the following treatments within 4 weeks before the baseline visit or any condition that, in the opinion of the investigator, is likely to require such treatment(s) during the first 4 weeks of study treatment:
- Immunosuppressive/immunomodulating drugs (eg, systemic corticosteroids, cyclosporine, mycophenolate-mofetil, IFN-*, Janus kinase inhibitors, azathioprine, methotrexate, etc)
- Phototherapy for AD
5. Treatment with TCS, TCI, or topical crisaborole within 1 week before the baseline visit
6. Treatment with biologics as follows:
- Any cell-depleting agents including but not limited to rituximab: within 6 months before the baseline visit, or until lymphocyte count returns to normal, whichever is longer
- Other biologics: within 5 half-lives (if known) or 16 weeks prior to baseline visit, whichever is longer
7. Initiation of treatment of AD with prescription moisturizers or moisturizers containing additives such as ceramide, hyaluronic acid, urea, or filaggrin degradation products during the screening period (patients may continue using stable doses of such moisturizers if initiated before the screening visit)
8. Regular use (more than 2 visits per week) of a tanning booth/parlor within 4 weeks of the baseline visit
9. Planned or anticipated use of any prohibited medications and procedures during study treatment
10. Treatment with a live (attenuated) vaccine within 12 weeks before the baseline visit
11. Active chronic or acute infection requiring treatment with systemic antibiotics, antivirals, antiparasitics, antiprotozoals, or antifungals within 2 weeks before the baseline visit, or superficial skin infections within 1 week before the baseline visit
NOTE: patients may be re-screened after infection resolves
12. 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
*Patients with a positive TB QuantiFERON test result at screening will be excluded from the study.
13. History of human immunodeficiency virus (HIV) infection or positive HIV serology at screening
14. Positive with hepatitis B surface antigen (HBsAg), hepatitis B core

antibody (HBcAb), or hepatitis C virus antibody (HCV Ab) at the screening visit
15. At baseline, presence of any conditions listed as criteria for study drug discontinuation
16. Presence of skin comorbidities that may interfere with study assessments
17. History of cancer, with the exceptions of:
- Patients with adequately treated basal cell carcinoma or carcinoma in situ of the cervix.
- Patients with other malignancies that have been successfully treated for >10 years prior to screening where, in the judgement of both the investigator and the treating physician, appropriate follow-up has revealed no evidence of recurrence through time of screening.
18. Diagnosed active endoparasitic infections; suspected or high risk of endoparasitic infection, unless clinical and (if necessary) laboratory assessment have ruled out active infection before randomization
19. History of alcohol or drug abuse within 2 years of the screening visit
20. Severe concomitant illness(es) that, in the investigator*s judgment, would adversely affect the patient*s participation in the study.
Examples include, but are not limited to, patients with short life expectancy, patients with uncontrolled diabetes (hemoglobin A1c *9%), patients with uncontrolled cerebrocardiovascular conditions (eg, myocardial infarction, unstable arterial hypertension, unstable angina, cerebrovascular accident, and stage III or IV cardiac failure according to the New York Heart Association classification), severe renal conditions (eg, patients on dialysis), hepatobiliary conditions (eg, Child-Pugh class B or C), neurological conditions (eg, demyelinating diseases), active major autoimmune diseases (eg, lupus, inflammatory bowel disease, rheumatoid arthritis, etc), other severe endocrinological, gastrointestinal, metabolic, pulmonary, or lymphatic diseases. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, case report forms [CRFs], etc)
21. Any other medical or psychological condition (including relevant laboratory abnormalities at screening) that, in the opinion of the investigator, may suggest a new and/or insufficiently understood disease, may present an unreasonable risk to the study patient as a result of his/her participation in this clinical study, may make patient*s participation unreliable, or may interfere with study assessments. The specific justification for patients excluded under this criterion will be noted in study documents (chart notes, CRFs, etc).
22. Planned or anticipated major surgical procedure during the patient*s participation in this study
23. Patient is a member of the investigational team or his/her immediate family
24. Pregnant or breastfeeding women, or women planning to become pregnant or breastfeed during the study
25. Women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment, during the study, and for at least 20 weeks after the last dose of study drug. Highly effective contraceptive measures include:
a. stable use of oral contraceptives associated with inhibition of ovulation

(such as contraceptives containing estrogen/progesterone or high dose progesterone) initiated 2 or more menstrual cycles prior to screening
b. intrauterine device (IUD); intrauterine hormone releasing system (IUS)
c. bilateral tubal ligation
d. vasectomized partner with confirmed sterility (ie, patient*s medical record)
e. and/or sexual abstinence*, *
f. contraception for male patients is not required§
*Postmenopausal women must be amenorrheic for at least 12 months (without an alternative medical cause) in order not to be considered of childbearing potential. Amenorrheic status should be confirmed by demonstrating follicle-stimulating hormone (FSH) levels consistent with postmenopausal status according to laboratory ranges. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.
* Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The
reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient
*Periodic abstinence (calendar, symptothermal, postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception. Female condom and male condom should not be used together.
§Based on the known target biology of the study drugs and the extremely low levels of study drug expected to reach the fetus via seminal fluid, the use of contraception in treated males to prevent female partner and/or fetal exposure is considered unnecessary.
26. Known sensitivity to doxycycline and/or tetracycline or to any of the components of the investigational product formulation
27. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities will be excluded from this study (as required by country regulations).

Study design

Design

Study phase:	2
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):	12-11-2018
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	dupilumab
Generic name:	Dupixent
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	REGN3500
Generic name:	REGN3500

Ethics review

Approved WMO Date:	12-03-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-07-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	02-08-2019

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	15-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-10-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	29-11-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-03-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2018-001543-30-NL
ClinicalTrials.gov	NCT03736967
CCMO	NL67735.041.19