A phase 3 randomized withdrawal, double-blind, placebo-controlled, multi-center study investigating the efficacy and safety of PF-04965842 in subjects aged 12 years and over, with moderate to severe atopic dermatitis with the option of rescue treatment in flaring subjects.

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Primary Objective- To evaluate and compare the maintenance of effect of two doses of PF-04965842 (200 mg and 100 mg once daily [QD]) and placebo in subjects aged 12 and above with moderate to severe atopic dermatitis who respond to an initial open-...

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

Summary

ID

NL-OMON48910

Source
ToetsingOnline

Brief title
B7451014 (9002/0547)

Condition

- Epidermal and dermal conditions

Synonym
Atopic dermatitis, atopic eczema

Research involving
Human

Sponsors and support

Primary sponsor: Pfizer
Source(s) of monetary or material Support: The sponsor;Pfizer inc.

Intervention

Keyword: Atopic dermatitis, PF-04965842, Phase 3

Outcome measures

Primary outcome

Loss of response requiring rescue treatment will be evaluated and compared among groups during the blinded treatment period. Loss of response is denoted as flare and is defined as a loss of at least 50% of the Eczema Area and Severity Index (EASI) response at Week 12 and an Investigator*s Global Assessment (IGA) score of 2 or higher.

Secondary outcome

Key Secondary Endpoint

1. Loss of response based on an IGA score of 2 or higher.

Clinical Efficacy Assessments :

1. Response based on the IGA at all scheduled time points.

2. Response based on EASI total score at all scheduled time points.

3. Response based on achieving *4 point improvement in the severity of pruritus Numerical Rating Scale (NRS) from baseline at all scheduled time points.

4. Change from baseline in percent Body Surface Area (BSA) at all scheduled time points.

5. Change from baseline in SCORing Atopic Dermatitis (SCORAD) subjective assessments of itch and sleep loss at all scheduled time points.

6. Proportion of subjects achieving a *50% and *75% improvement in SCORAD (SCORAD 50, SCORAD 75) from baseline at all scheduled time points.

Clinical Efficacy Assessments in Subjects Requiring Rescue Treatment:

1. Response based on the IGA at the end of rescue therapy.

2. Response based on the EASI total score at the end of rescue therapy.

3. Response based on achieving *4 point improvement in the severity of pruritus Numerical Rating Scale (NRS) at the end of rescue therapy relative to the start of rescue therapy baseline value.

4. Change from percent Body Surface Area (BSA) at the end of rescue therapy relative to the start of rescue therapy baseline value.

5. Change in SCORAD subjective assessments of itch and sleep loss at the end of rescue therapy relative to the start of rescue therapy baseline value.

6. Proportion of subjects achieving a *50% and *75% improvement in SCORAD (SCORAD 50, SCORAD 75) at the end of rescue therapy relative to the start of rescue therapy baseline value.

For additional endpoints please refer to section 2 of the study protocol.

Study description

Background summary

Atopic dermatitis, also known as atopic eczema, is a common, chronic, inflammatory skin disorder characterized by flaky skin lesions, intense pruritus, and a general deterioration in quality of life. Over the past 50 years, AD has become more prevalent, especially in industrialized, temperate countries such as the US. AD is one of the most common, chronic, relapsing childhood dermatoses, impacting 15 30% of all children in the US and many have disease that persists into adulthood with a lifetime prevalence of those affected beyond childhood reported to be 34%

There are a limited number of treatments available for AD and those that are available have multiple limitations. The medicated topical therapies have drawbacks related to the duration of use due to the potential for local and systemic side effects and to the body regions of use. For AD patients not responding to medicated topical therapies and phototherapy, on- and off label use of systemic agents, which include oral corticosteroids or oral immunosuppressants, remain the last viable treatment option. Systemic therapy options are associated with potentially severe adverse effects and require careful monitoring. The risk of toxicity and side effects remain a concern when systemic agents are used. For these reasons the use of these agents is limited to short courses or intermittent therapy.

PF 04965842 is an orally bioavailable small molecule that selectively inhibits JAK1 by blocking the ATP binding site. A variety of pro inflammatory cytokines such as IL 4, IL 13, IL 22, IL 31 and IFN-y, have been suggested to have a role in the pathogenesis of AD. Many of these pathogenic cytokines use the JAK1 for signaling. Therefore, JAK1 is an attractive therapeutic target for AD as an innovative oral therapeutic agent.

Study objective

Primary Objective
- To evaluate and compare the maintenance of effect of two doses of PF-04965842 (200 mg and 100 mg once daily [QD]) and placebo in subjects aged 12 and above with moderate to severe atopic dermatitis who respond to an initial open-label run-in treatment of 200 mg PF-04965842 QD.

Secondary Objectives
- To evaluate and compare the effect of PF-04965842 on additional efficacy endpoints and patient-reported outcomes over time in subjects aged 12 years and older with moderate to severe atopic dermatitis.
- To assess the efficacy of open-label rescue treatment consisting of 200 mg PF-04965842 in combination with topical therapy per standard of care in cases

of flare (per protocol definition).

Safety Objective
- To assess the safety and tolerability of PF 04965842 during open label and double blind treatment in subjects aged 12 and over with moderate to severe AD.

Pharmacokinetic Objective
- To evaluate the PK of PF 04965842 in subjects aged 12 years and older with moderate to severe atopic dermatitis following 12 weeks of maintenance treatment.

Exploratory Objective
Collection of banked biospecimens for exploratory research unless prohibited by local regulations or ethics committee decision.

Study design

This is a randomized, responder-enriched, double-blind, placebo-controlled, Phase 3 withdrawal trial to evaluate the efficacy and safety of PF-04965842 monotherapy in subjects aged 12 years and older with moderate to severe AD as defined per the inclusion criteria and a body weight * 40 kg.

After providing informed consent, subjects are assessed for study eligibility at the screening visit. During the screening period, treatments for AD are washed out, as applicable, according to eligibility requirements. Subjects may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions unless the reason for the screen failure is related to failing the disease severity inclusion criteria. A baseline (Day 1) visit occurs within 28 days after the screening visit.
The trial consists of an open-label run-in period to determine responder status to an initial induction treatment with PF-04965842 (200 mg, QD), a randomized, placebo-controlled, double-blinded PF-04965842 maintenance treatment period, and a 4 week untreated follow-up safety period. Subjects who meet the protocol definition of flare during blinded treatment enter an open-label rescue treatment period.

Enrolled subjects initiate the 12-week, open-label run-in period to identify responders who have a positive clinical response to induction treatment with 200 mg PF-04965842 QD. Responder criteria are defined as:
a) achieving an IGA of clear (0) or almost clear (1) (on a 5-point scale),
b) a reduction from IGA baseline of *2 points, and
c) reaching an EASI-75response compared to baseline.
Baseline is defined as the IGA score and EASI score obtained prior to dosing on Day 1. Subjects meeting all of the responder criteria may be eligible for randomization. Subjects who do not reach the response threshold required for randomization are declared non-responders after completion of the open label run-in period. Non-responders are not eligible for randomization in the

B7451014 study, but may choose to enroll into the PF-04965842 Long Term Extension (LTE) study B7451015 providing they remain eligible; otherwise they are permanently discontinued from treatment and enter the 4-week untreated follow-up period in B7451014.

Subjects with a positive clinical response to PF-04965842 induction treatment at the end of the 12 week open label run-in period enter a 40 week, double-blind, maintenance treatment period in which they are randomized into 1 of 3 treatment arms in a 1:1:1 ratio:
1. 100 mg PF-04965842 QD;
2. 200 mg PF-04965842 QD;
3. Placebo.

Randomization is stratified by age category, i.e., <18 years and *18 years. Eligible subjects must have a documented history of inadequate response with topical AD medications or have required systemic therapies for control of their disease. Medicated topical and/or systemic standard of care therapies are not allowed during the open-label run-in and blinded treatment periods. Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over-the-counter [OTC] or prescription only product).

Following completion of 40 weeks of blinded treatment, all subjects are to be assessed for eligibility to enter the PF-04965842 LTE study B7451015. If a subject discontinues prematurely or is not eligible or willing to participate in B7451015, then the subject enters the 4-week untreated follow-up period in B7451014.

During the blinded treatment period, subjects meeting the protocol definition of flare enter an open-label rescue period during which they receive another 12-week course of 200 mg PF-04965842 QD with topical therapy per local standard of care (SOC). After completing the full 12-week rescue period, subjects may enter the LTE study B7451015, if eligible. Subjects discontinuing early from treatment or who are otherwise ineligible for the LTE study enter the 4 week untreated follow-up period in B7451014.

An investigator can temporarily interrupt dosing for up to a maximum of 28 consecutive days for a subject, for safety reasons or while monitoring abnormal laboratory tests if the investigator judges that this is necessary. The investigator should use their judgement with regard to unscheduled visits/laboratory/clinical assessments required to monitor the subject during this time-frame. If within this timeframe the investigator judges that it is safe to restart dosing, then the subject may restart investigational product. If the investigator judges that it is not safe to restart dosing within this timeframe then the subject must be permanently discontinued from treatment, have an End of Treatment visit and enter the 4-week follow-up period. Doses not taken for the reasons mentioned above do not constitute protocol deviations or

medication errors and should not be considered dosing errors, but should be noted in the dosing log with the reason for reduced drug consumption clearly described.

The total study duration if a subject does not flare is 52 weeks (12 weeks open-label induction treatment + 40 weeks blinded maintenance treatment). The potential maximum study duration is 64 weeks. This would only be achieved if a subject flared on the last day of the maintenance treatment period (52 weeks + 12 weeks rescue). If subjects do not intend to enroll in the LTE study, the above durations are extended by + 4 weeks of an untreated follow-up safety period.

Intervention

Subjects with a positive clinical response to PF-04965842 induction treatment at the end of the 12 week open label run-in period enter a 40 week, double-blind, maintenance treatment period in which they are randomized into 1 of 3 treatment arms in a 1:1:1 ratio:
1. 100 mg PF-04965842 QD;
2. 200 mg PF-04965842 QD;
3. Placebo.

Study burden and risks

Please refer to appendix D of the subject information sheet for an overview of the side effects and possible risks of the study.

Contacts

Public
Pfizer

East 42nd street 235
New York NY 10017
US
Scientific
Pfizer

East 42nd street 235
New York NY 10017
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Evidence of a personally signed and dated informed consent document indicating that the subject, or his/her legally acceptable representative/ parent(s) or legal guardian, if a minor, have been informed of all pertinent aspects of the study.
2. Male or female subjects of 12 years of age or older, at the time of informed consent and body weight *40 kg. Adolescent subjects below the legal age of majority (legal adulthood) in the subject*s country will only be enrolled in this study if instructed by the sponsor and approved by the country*s regulatory/health authority. If these approvals have not been granted, only subjects * the legal age of majority (legal adulthood) in the subject*s country will be enrolled.
3. Meet all the following atopic dermatitis criteria:
* Clinical diagnosis of chronic atopic dermatitis (also known as atopic eczema) for at least 1 year prior to Day 1 and has confirmed atopic dermatitis at the screening and baseline visits according to Hanifin and Rajka criteria of AD.
* Documented recent history (within 6 months before the screening visit) of inadequate response to treatment with medicated topical therapy for AD for at least 4 weeks, or who have required systemic therapies for control of their disease.
NOTE: Medicated topical therapy is defined as a topical product that contains an active pharmaceutical ingredient indicated for the treatment of AD (irrespective of whether it is an over-the-counter [OTC] or prescription only product).
* Moderate to severe AD (affected BSA *10%, IGA *3, EASI *16 and pruritus NRS severity *4 on the day of the baseline visit).
4. Willing and able to comply with scheduled visits, treatment plan, laboratory tests and other study procedures.
5. Female subjects who are of child-bearing potential (which includes adolescents aged 12 years and older regardless of whether they have experienced menarche) must not be intending to become pregnant, currently pregnant, or lactating. The following conditions apply:

a. Female subjects of childbearing potential must have a confirmed negative pregnancy test prior to treatment with investigational product;
b. Female subjects of childbearing potential must agree to use a highly effective method of contraception for the duration of the active treatment period and for at least 28 days after the last dose of investigational product.
NOTE: Sexual abstinence, defined as completely and persistently refraining from all heterosexual intercourse (including during the entire period of risk associated with study treatments) may obviate the need for contraception ONLY if this is the preferred and usual lifestyle of the subject.
6. Female subjects of non-childbearing potential must meet at least 1 of the following criteria:
* Have undergone a documented hysterectomy and/or bilateral oophorectomy;
* Have medically confirmed ovarian failure; or
* Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause and have a serum follicle-stimulating hormone (FSH) level confirming the postmenopausal state.
All other female subjects (including female subjects with tubal ligations) are considered to be of childbearing potential.
7. Must agree to avoid prolonged exposure to the sun and not to use tanning booths, sun lamps or other ultraviolet light sources during the study.

Exclusion criteria

1. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
2. Any psychiatric condition including recent or active suicidal ideation or behavior that meets any of the following criteria:
* Suicidal ideation associated with actual intent and a method or plan in the past year: *Yes* answers on items 4 or 5 of the Columbia suicide severity rating scale (C-SSRS);
* Previous history of suicidal behaviors in the past 5 years: *Yes* answer (for events that occurred in the past 5 years) to any of the suicidal behavior items of the C-SSRS;
* Any lifetime history of serious or recurrent suicidal behavior;
* Suicidal behaviors questionnaire * revised (SBQ-R) total score *8;
* Clinically significant depression: patient health questionnaire * 8 items (PHQ-8) total score *15;
* The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria;
* In the opinion of the investigator or Pfizer (or designee) exclusion is required.
3. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy or platelet dysfunction.
4. Receiving anti-coagulants or medications known to cause thrombocytopenia (unless considered safe to stop and washout for the duration of the study).
5. Currently have active forms of other inflammatory skin diseases, i.e., not AD or have

evidence of skin conditions (e.g., psoriasis, seborrheic dermatitis, Lupus) at the time of Day 1 that would interfere with evaluation of atopic dermatitis or response to treatment.
6. Vaccinated or exposed to a live or attenuated vaccine within the 6 weeks prior to the first dose of investigational product, or is expected to be vaccinated or to have household exposure to these vaccines during treatment or during the 6 weeks following discontinuation of investigational product.
7. Adolescent subjects 12 to <18 years old without documented evidence of having received at least one dose of the varicella vaccine in countries where the vaccine is approved and standard of care or those who do not have evidence of prior exposure to varicella zoster virus (VZV) based on serological testing (i.e., varicella zoster virus immunoglobulin G antibody [VZV IgG Ab]) at screening.
8. Subjects who have received prior treatment with any JAK inhibitors.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-04-2019
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not yet known
Generic name:	not yet known

Ethics review

Approved WMO Date:	06-07-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-02-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-05-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	04-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-09-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2018-000501-23-NL
CCMO	NL65557.100.18