A PHASE 3B RANDOMIZED, DOUBLE-BLIND, DOUBLE-DUMMY, ACTIVE CONTROLLED MULTI-CENTER STUDY ASSESSING THE EFFICACY AND SAFETY OF ABROCITINIB COMPARED WITH DUPILUMAB IN ADULT PARTICIPANTS ON BACKGROUND TOPICAL THERAPY WITH MODERATE TO SEVERE ATOPIC DERMATITIS

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Primary:To compare the efficacy of abrocitinib 200 mg once daily (QD) versus dupilumab (as per label guidelines) in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).Key SecondaryTo compare the efficacy...

Ethical review	Not approved
Status	Will not start
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON49637

Source
ToetsingOnline

Brief title
B7451050 (9002/0605)

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 as described in question B6/B7

Intervention

Keyword: Atopic dermatitis, Dupilumab, PF-04965842 (Abrocitinib), Phase 3b

Outcome measures

Primary outcome

- Response based on achieving at least a 4-point improvement in the severity of

Peak Pruritus Numerical Rating Scale (PP-NRS) from baseline at Week 2.

- Response based on achieving the Eczema Area and Severity Index (EASI)-75

(*75% improvement from baseline) at Week 4.

Secondary outcome

Key Secondary

Response based on achieving the Eczema Area and Severity Index (EASI) 75 (*75%

improvement from baseline) at Week 16.

For a complete list of objectives and endpoints, please see section 3 of the

protocol.

Study description

Background summary

Atopic dermatitis (AD), 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 United States (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 in childhood reported to be 34%.
Of the currently available therapies, none offers a cure; therefore, the main aims of existing treatments are to reduce skin lesions, reduce the occurrence of acute flares, to increase the time between relapses, and to reduce pruritus and the resulting sleep disturbance.

The predominant unmet medical need is for a conveniently administered therapy with an acceptable safety profile, for continuous and intermittent use, which is effective for moderate to severe AD. Patients with moderate to severe AD require other systemic treatment options beyond those which are currently approved. Abrocitinib is an oral tablet, providing a more convenient route of administration compared with the subcutaneous injection required for dupilumab and so it does not have the potential risk of injection site reactions. Unlike dupilumab, abrocitinib is a small molecule and there is no anticipated immunogenicity to abrocitinib, and so it is unlikely to generate antidrug antibodies and may be used intermittently.

Dupilumab, an injectable human monoclonal antibody targeting interleukin (IL) -4 and -13, was approved by the FDA in March 2017 and received marketing authorization in Europe in September 2017, for the treatment of moderate to severe AD. Treatment with systemic corticosteroids has known and well documented adverse effects. Treatment with dupilumab has the risk of injection site reactions, allergic reactions, eye and eyelid inflammations and cold sores. Another potential limitation of dupilumab is the possibility for the development of antidrug antibodies, which may result in loss of efficacy over time and the development of safety concerns such as serum sickness-like reactions. Furthermore, dupilumab is delivered via subcutaneous injection, which may not be a method of administration tolerated well by all patients.
During a 1-year, randomized, double-blinded study with dupilumab, in the dupilumab 300 mg every 2 weeks (marketed maintenance dose) plus TCS group, the estimated difference from placebo of the Investigator's Global Assessment (IGA) response rate and Eczema Area and Severity Index (EASI)-75 response rate (*75% improvement from baseline in EASI score) were 26% and 46%, respectively. The placebo response rate for IGA and EASI-75 was 12% and 23%, respectively.9 There

is a need for therapies for those patients who do not respond to dupilumab or who after responding, fail to improve with dupilumab. The development of potential treatments with further improvements in efficacy remains desirable.

Abrocitinib has been in Phase 3 development since December 2017 treating patients with moderate to severe AD with or without topical treatment. The first Phase 3 Study B7451012 that evaluated 100 and 200 mg abrocitinib in patients with moderate to severe AD, which completed in March 2019, reported statistically significant improvement in efficacy endpoints in both treatment groups compared to the placebo group, with an acceptable safety profile.

This Phase 3b study will investigate whether abrocitinib provides comparable or improved efficacy and safety compared with duplilumab in the treatment of moderate to severe AD.

Study objective

Primary:
To compare the efficacy of abrocitinib 200 mg once daily (QD) versus dupilumab (as per label guidelines) in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).

Key Secondary
To compare the efficacy of abrocitinib 200 mg once daily versus dupilumab on additional
efficacy endpoints in adult participants on background topical therapy with moderate to severe atopic dermatitis (AD).

For a complete list of objectives and endpoints, please see section 3 of the protocol.

Study design

This is a randomized, double-blind, double-dummy, active controlled, multi-center study to assess the efficacy and safety of abrocitinib 200 mg QD compared with dupilumab (administered per label guidelines) in adult participants on background topical therapy, with moderate to severe AD. The treatment duration is 26 weeks. A total of approximately 600 participants will be enrolled from approximately 220 sites globally. There are primary efficacy assessments at Week 2 and Week 4, and a key secondary efficacy assessment at Week 16. Efficacy and safety endpoints will be assessed throughout the entire study.

Participants who complete the study through the Week 26 visit and are deemed eligible will enter the long-term extension (LTE) Study B7451015. A study design schematic is presented in Section 1.2.

After providing informed consent, participants will be assessed for study eligibility at the screening visit. Participants will undergo screening within approximately 28 days prior to randomization. Use of screening procedures exceeding 28 days prior to randomization should be discussed with the Pfizer Medical Monitor. During the screening period, systemic treatments for AD will be washed out, as applicable, according to eligibility requirements. Eligible participants must have a documented history, within 6 months of the screening visit, of inadequate response to treatment with medicated topical therapy for at least 4 weeks or must have required systemic therapies for control of their disease within the previous year. Eligible participants must meet the eligibility criteria, which includes being dupilumab naïve, at baseline. In addition, participants must be willing and able to use standardized background topical therapy, as per protocol guidelines, throughout the duration of the study. Participants may be re-screened once if they fail the screening evaluation for reasons related to incidental transitory conditions. Participants for whom screen failure is related to failing the disease severity (including extent of disease) inclusion criterion and who subsequently experience worsening AD, which in the investigator*s judgement would make them eligible for participation, may be considered for re-screening. Such cases should be discussed with the Pfizer Medical Monitor (or designee) to determine if re-screening is appropriate.

Participants who continue to meet eligibility criteria at baseline will undergo Day 1 assessments and be randomized in a 1:1 ratio to receive abrocitinib 200 mg QD with dupilumab-matching placebo administered every other week or dupilumab 300 mg administered every other week (with a loading dose of 600 mg at baseline) with abrocitinib-matching placebo administered QD. Investigators, participants, and the sponsor study team will be blinded to treatment group assignment.

The total treatment period is 26 weeks. Participants discontinuing early from treatment, or who are otherwise ineligible for the LTE study, will undergo a 4-week follow-up period in study B7451050.

Intervention

1. Abrocitinib 200 mg (2 x 100 mg tablets) administered orally QD and dupilumab-matching placebo administered by subcutaneous injection every other week (2 injections at baseline; to dummy the loading dose) from Day 1 to Week 26 (the last injection of dupilumab-matching placebo will occur at Week 24).
2. Dupilumab 300 mg administered by subcutaneous injection every other week (with a loading dose of 600 mg at baseline) and abrocitinib-matching placebo administered orally QD from Day 1 to Week 26 (the last injection of dupilumab will occur at Week 24).

Study burden and risks

There was clinically meaningful benefit demonstrated with abrocitinib in the Phase 2b POC study in adult patients with moderate to severe AD and the completed Phase 3 B7451012 study. The potential risks of treatment include those that were noted in Phase 2b and Phase 3 studies and those based on the pharmacology of Janus kinase (JAK) inhibitors and include viral reactivation, serious and opportunistic infections, hematopoietic effects (including reduced platelet count), and malignancy and immunoproliferative disorders. The most common events were gastrointestinal disorders, nervous system disorders, and skin/subcutaneous tissue disorders. In Study B7451001, 2 participants discontinued from the study due to AEs. One participant in the abrocitinib 100 mg group discontinued due to an AE of second-degree atrioventricular block, which was considered as non-treatment-related and was attributed to a pre-existing condition by the investigator. Appropriate risk evaluation and mitigation strategies have been incorporated into this protocol.

Overall, there is a favorable benefit-risk profile to support the continued development in Phase 3 of abrocitinib in the treatment of adult participants with AD for both the 100 mg and 200 mg doses.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of abrocitinib may be found in the IB, which is the single reference safety document (SRSD) for this study. The SRSD for the comparator agent, dupilumab, is the United States Package Insert (USPI).

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

Participants are eligible to be included in the study only if all of the following criteria apply:

Age
1. Participants must be 18 years of age or older inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics
2. Participants who meet all of 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 for AD. Refer to Appendix 9.
* 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 consecutive weeks, or who have required systemic therapies for control of their disease within the past year. 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 prescribed product).
* Moderate to severe AD (BSA * 10%, IGA * 3, EASI * 16, and PP-NRS severity score * 4 on the day of the baseline visit).

Sex
3. Male or Female
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:
No contraceptive measures are required.

b. Female participants:
A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
* Is not a woman of childbearing potential (WOCBP) (see definition in Appendix 4)
OR
* Is a WOCBP (all female participants, regardless of whether or not they have experienced/reported menarche, are considered WOCBP unless they are permanently sterile or confirmed infertile). A WOCBP who is sexually active must use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Appendix 4 during the intervention period and for at least 28 days after the last dose of study intervention. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.
* A WOCBP must have a negative highly sensitive (Appendix 2) serum pregnancy test at the screening visit. A urine pregnancy test with a sensitivity of at least 25 mIU/mL, will be performed before the first dose of study intervention and at every site visit including the EOT and follow-up visits to confirm the participant has not become pregnant. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
* The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

4. Capable of giving signed informed consent as described in Appendix 1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5. For the treatment of AD, the participant may use low- or medium-potency medicated and non-medicated topical therapy, with response to treatment remaining inadequate at baseline. The participant must also be willing and able to comply with standardized background topical therapy, as per protocol guidelines Section 6.5.1, throughout the remainder of the study.

6. Participants willing and able to comply with scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.

7. Participants must agree to avoid prolonged exposure to the sun and to refrain from the use of tanning booths, sun lamps, and other sources of ultraviolet light during the study.

8. If participants are receiving concomitant medications for any reason other than AD, these participants must be on a stable regimen, which is defined as not starting a new drug or changing dosage within 7 days or 5 half-lives (whichever is longer) prior to Day 1. Administration of these stable regimen

concomitant medications will be allowed to continue throughout the study.

Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions
1. Other acute or chronic medical condition including laboratory abnormality that may increase the risk associated with study participation or study intervention administration or may interfere with the interpretation of study results and, in the judgement of the investigator, would make the participant inappropriate for entry into this study.

2. The participant should have a risk assessment done by a qualified mental health professional (MHP) to assess whether it is safe to participate in the trial if the participant*s responses on any of the screening instruments or other screening information indicate:
* 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 (non-suicidal self-injurious behavior is not a trigger for a risk assessment unless in the investigator*s judgement it is indicated).
* Clinically significant depression: Patient Health Questionnaire 8 items (PHQ-8) when the total score is *15.
* The presence of any current major psychiatric disorder that is not explicitly permitted in the inclusion/exclusion criteria.
* In the investigator*s judgment a risk assessment or 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 (ie, not AD) or have evidence of skin conditions (eg, psoriasis, seborrheic dermatitis, Lupus) at the time of Day 1 that would interfere with evaluation of AD or response to treatment.

6. Have a history of any lymphoproliferative disorder such as Epstein Barr virus (EBV), related lymphoproliferative disorder, history of lymphoma,

leukemia, or signs or symptoms suggestive of current lymphatic or lymphoid disease.

7. Infection history:
* Have a history of systemic infection requiring hospitalization, parenteral antimicrobial therapy, or as otherwise judged clinically significant by the investigator within 6 months prior to Day 1;
* Have a known helminth infection;
* Have active chronic or acute skin infection requiring treatment with systemic antimicrobials within 2 weeks prior to Day 1, or superficial skin infections within 1 week prior to Day 1;
* A participant known to be infected with human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C.
* Participants who are hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (HBcAb) positive, and hepatitis B surface antibody (HBsAb) positive at Screening will have reflex testing for hepatitis B Virus (HBV) deoxyribose nucleic acid (DNA). Participants who have HBV DNA above the lower limit of quantification (LLQ) are excluded. Participants who have HBV DNA negative or below LLQ may be randomized but will have HBV DNA testing repeated at Week 16 and Week 26 End of Treatment (EOT) visit, or Early Discontinuation (ED) visit, whichever is sooner.
* Have a history (single episode) of disseminated herpes zoster or disseminated herpes simplex, or a recurrent (more than one episode of) localized, dermatomal herpes zoster.

8. Have a known immunodeficiency disorder or a first-degree relative with a hereditary immunodeficiency.

9. Have a history of alcohol or substance abuse within 6 months prior to Day 1 that in the opinion of the investigator will preclude participation in the study.

10. Have any malignancies or have a history of malignancies with the exception of adequately treated or excised non-metastatic basal cell or squamous cell cancer of the skin, or cervical carcinoma in situ.

11. Require treatment with prohibited concomitant medications (refer to Section 6.5) or have received a prohibited concomitant medication within the specified timeframe prior to the first dose of study intervention(s).

Please refer to section 5.2 of the protocol for a complete list of exclusion criteria.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	8
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Dupixent
Generic name:	Dupilumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n/a
Generic name:	Abrocitinib

Ethics review

Approved WMO

Date:	29-04-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Not approved

Date:	04-09-2020
Application type:	First submission
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	EUCTR2019-004013-13-NL
CCMO	NL73212.100.20