ABROCITINIB EXPANDED ACCESS PROTOCOL FOR THE TREATMENT OF ADOLESCENTS AND ADULTS WITH MODERATE TO SEVERE ATOPIC DERMATITIS

Published: 20-04-2021
Last updated: 04-04-2024

Primary:To provide access to abrocitinib to adolescent and adult patients with or without background topical therapy who have inadequate treatment options due to inadequate response or intolerance to available approved medicated topical and systemic...

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

Summary

ID

NL-OMON52169

Source
ToetsingOnline

Brief title
B7451064 (9002/0708)

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: Abrocitinib (PF-04965842), Atopic dermatitis, Expanded Access

Outcome measures

Primary outcome

Not applicable.

Secondary outcome

• Incidence of treatment-emergent adverse events (AEs) and serious adverse

events (SAEs).

• Incidence of serious adverse events (SAEs) and AEs leading to discontinuation.

• Incidence of serious infections, defined as any infection (viral, bacterial,

and fungal) requiring hospitalization or parenteral antimicrobials.

Study description

Background summary

2.2.1. Atopic Dermatitis
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).1,2 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%.3 Earlier reports indicated that, in up to 70% of cases, the disease greatly improves or resolves by late childhood, however more recent findings suggest that disease activity remains manifest for a prolonged period of time. Based on a total of 7,157 patients enrolled in the Pediatric Eczema Elective Registry (PEER) study,

comprising a total of 22,550 person years, it was concluded that symptoms associated with AD seem to persist well into the second decade of life and likely longer.4 At every age, more than 80% of PEER study patients had symptoms of AD and/or were using medication to treat their AD.

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.5,6

Non medicated topical therapies include emollients. Medicated topical therapies for moderate to severe AD include topical corticosteroids (TCS) (eg, betamethasone, clobetasol, fluocinonide), topical calcineurin inhibitors (TCI) (eg, pimecrolimus, tacrolimus), and coal tar preparations. TCS are limited in terms of the treatment duration (eg, corticosteroid use is limited to 2 to 4 weeks) and the body region of treatment due to consistent skin toxicities as well as having risks associated with their broad immunosuppressive actions. TCI have a limited role as a second line treatment due to their limitations in the duration and the body region of treatment.

There are a limited number of approved systemic treatments for moderate to severe AD, and in the US the only approved systemic drugs are corticosteroids and dupilumab. Per the American Academy of Dermatology (AAD) guidelines, the use of steroids should be avoided for the treatment of AD and should be exclusively reserved for acute, severe exacerbations and as a short-term bridge therapy to other systemic, steroid-sparing therapies.7

Dupilumab, an injectable human monoclonal antibody targeting IL 4 and IL 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.8 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.

In Europe, cyclosporine is approved for use in patients with severe AD when systemic therapy is required. Cyclosporine use is associated with several undesirable side effects and due to its narrow therapeutic index, occasional therapeutic drug monitoring is recommended. Known adverse effects include

infections, renal toxicity, hepatotoxicity, skin malignancies, lymphoma, and other malignancies.
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 and effective in patients who have failed other approved medicated topical or systemic treatments. Patients with moderate to severe AD require other systemic treatment options beyond those which are currently approved.
2.2.2. Clinical Overview
Abrocitinib is being developed as an oral treatment for patients with moderate to severe AD based on the existing unmet need in AD, its novel mechanism of action, and the clinical results obtained in Phase 1, Phase 2, and Phase 3 studies. The clinical development program for abrocitinib includes healthy participants as well as participants with psoriasis and with AD.
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 neutralizing antidrug antibodies and may be used intermittently.

Rationale
Abrocitinib is a Janus kinase 1 (JAK1) inhibitor that has been in Phase 3 development since December 2017 treating patients with moderate to severe atopic dermatitis (AD) with or without topical treatment. Recently completed Phase 3 studies B7451012 and B7451013 which evaluated 100 mg once daily (QD) and 200 mg QD abrocitinib in patients aged 12 years and older with moderate to severe AD reported statistically significant improvement in efficacy endpoints in both treatment groups compared to the placebo group with an acceptable safety profile. Based on these data, Pfizer Inc., is filing for marketing authorization for abrocitinib for the treatment of moderate to severe AD in adolescent and adult patients.
This expanded access protocol will provide access to abrocitinib until it becomes commercially available to patients who have inadequate treatment options due to inadequate response or intolerance to available approved medicated topical and systemic therapies, underlying conditions that preclude use of available approved medicated topical and systemic therapies, or lack of availability or access to approved medicated topical and systemic therapies and need abrocitinib as a possible treatment regimen for moderate to severe AD.

Study objective

Primary:
To provide access to abrocitinib to adolescent and adult patients with or without background topical therapy who have inadequate treatment options due to inadequate response or intolerance to available approved medicated topical and systemic therapies, underlying conditions that preclude use of available

approved medicated topical and systemic therapies, or lack of availability or access to approved medicated topical and systemic therapies and need abrocitinib as a possible treatment regimen for moderate to severe AD.

Secondary:
To gain additional safety and tolerability data for abrocitinib 100 mg and 200 mg once daily (QD) with or without background topical therapy in adolescent and adult participants with moderate to severe AD in a *real world* clinical setting.

Study design

• This is an open label, non-comparative, multi-center, expanded access study of abrocitinib in adolescents and adults with moderate to severe AD who have inadequate therapeutic options. The study will be conducted in countries where there is an intent to register abrocitinib for a marketing authorization.
• Participants who meet eligibility criteria at Baseline will undergo Day 1 assessments and be assigned to receive abrocitinib 100 mg QD or 200 mg QD at the investigator*s discretion. Participants may have their dose up- or down-titrated by the investigator during the course of the study (minimum 100 mg QD, maximum 200 mg QD) for efficacy or safety reasons. Participants may also have dosing temporarily interrupted for safety reasons for up to 30 consecutive days.
• Medicated and non-medicated topical treatments for AD are permitted throughout the study and should be administered in accordance with local practice and regulations. Concomitant systemic treatments for AD are not permitted except as part of rescue therapy (Refer to Rescue Therapy for Atopic Dermatitis section). Concomitant medication for AEs or other non-AD concomitant medical conditions are permitted throughout the study, unless listed as a prohibited medication.
• Laboratory tests will be performed throughout this study as detailed in the SoA. Investigators will follow the instructions for more frequent monitoring detailed in the Monitoring and Discontinuation Criteria appendix if the specified laboratory values reach the listed thresholds.

Intervention

• Abrocitinib 100 mg (1 x 100 mg tablet) or 200 mg (2 x 100 mg tablet) will be administered orally QD at the investigator*s discretion pursuant to instructions in the protocol. Refer to Section 6 Study Intervention of the main protocol for complete information on abrocitinib administration instructions and guidance.
• The maximum total treatment duration for individual participants may differ, as a participant may continue to receive abrocitinib until availability of commercial product in his/her country or until the sponsor terminates the study in that country.

• The study will be comprised of 1) a Screening period of up to 28 days, 2) a Study Intervention period during which participants will complete scheduled onsite visits at Baseline, Week 4, Week 12, and every 12 weeks thereafter until the End of Treatment visit, and a 4-week Follow-up period.

Study burden and risks

Benefit/Risk Assessment
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 and B7451013 studies. The potential risks of treatment include those that were noted in Phase 2b and Phase 3 studies and those based on the pharmacology of 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. 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 of abrocitinib in the treatment of adolescent and 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 Abrocitinib (PF-04965842) Investigator*s Brochure.

Benefit Assessment
Participation in study B7451064 will provide adolescent and adult patients with moderate to severe AD who have inadequate treatment options for their moderate to severe AD with the potential benefit of receiving early access treatment with abrocitinib (100 mg and 200 mg) which has demonstrated efficacy and an acceptable safety profile in Phase 3 studies. While it is possible that a study participant*s AD symptoms may improve during treatment with abrocitinib, there is no guarantee of benefit. Participants may also benefit from protocol participation by gaining knowledge about their health status through study tests (eg, physical examinations, laboratory assessments, vital sign measurements) conducted at regular intervals during the trial.

Overall Benefit/Risk Conclusion
Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with abrocitinib are justified by the anticipated benefits that may be afforded to participants with moderate to severe AD who have inadequate treatment options. The study will also collect safety data and exploratory efficacy data in a population representative of those who will receive the drug if approved by regulatory authorities.

Contacts

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Scientific
Pfizer

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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

Participants are eligible to be included in the study only if all of the following criteria apply:
Age:
1. Participants 12 years of age or older at the time of signing the informed consent. Adolescent participants below the age of 18 years(or country -specific age of majority) will only be enrolled if approved by the country regulatory/health authority. If these approvals have not been granted, only participants 18 years of age (or country-specific age of majority) or older at the time of signing of informed consent may be enrolled.
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 6months prior to Day 1 and has confirmed atopic dermatitis at the Screening and Baseline visits according to Hanifin and Rajka criteria for AD.10 Refer to protocol. -Inadequate treatment options for moderate to severe AD due to history of inadequate response or intolerance to treatment with available approved medicated topical and systemic therapies for the treatment of AD, underlying conditions that preclude use of available approved medicated topical and systemic therapies for the treatment of AD, or lack of availability or access to approved medicated topical and systemic therapies for the treatment of AD.
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 as indicated by meeting at least 1of the following on the day of the baseline visit: IGA >=3; EASI >=16.
3. Participants who are ineligible for participation in any ongoing clinical trial of abrocitinib, including lack of access due to geographical limitations.
4. Participants and, as applicable, parents/legal guardians of age of minority participants who are willing and able to comply with all scheduled visits, treatment plan, laboratory tests, lifestyle considerations, and other study procedures.
Sex:
5. 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. Refer to protocol.
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) (Refer to the definition in the Contraceptive Guidance appendix).
OR
- Is a WOCBP.A WOCBP who is sexually active must use a contraceptive method that is highly effective, with a failure rate of <1%, as described in Contraceptive Guidance appendix during the intervention period and for at least 28 days after the last dose of abrocitinib. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of abrocitinib.
- A WOCBP must have a negative highly sensitive(refer to the Clinical Laboratory Tests appendix)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 abrocitinib and at every site visit including the EOT and Follow-up/EOS 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.
Please refer to section 5.1 of the protocol for a complete list of inclusion criteria

Exclusion criteria

Medical Conditions:
1. Other medical or psychiatric condition including recent(within the past year)or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator*s judgment, make the participant inappropriate for the study.
2. The participant must 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 information from the screening period indicate:
- Suicidal ideation associated with actual intent and a method or plan in the past year for adults or at any time in their lifetime for adolescents ages >=12 and <18years: *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 for adults or at any time in their lifetime for adolescents ages >=12 and <18 years: *Yes* answer (in the past 5 years for adults or at any time in their lifetime for adolescents) 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 for adults or>=10for adolescents ages >=12 and <18years.
- 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. Have increased risk of developing venous thromboembolism, eg, deep vein thrombosis or pulmonary embolism:
- History of venous thromboembolism, or
- First-degree relative with unprovoked venous thromboembolism (ie, without known underlying cause such as trauma, surgery, immobilization, prolonged travel, pregnancy, hormone use, or plaster cast), that would suggest participant is at increased risk of inherited coagulation disorder (eg,Factor V Leiden).
4. A current or past medical history of conditions associated with thrombocytopenia, coagulopathy, or platelet dysfunction.
5. Receiving anti-coagulants or medications known to cause thrombocytopenia

(unless considered safe to stop and washout for the duration of the study).
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 6months prior to Day1;
- Have active chronic or acute skin infection requiring treatment with systemic antimicrobials within 2weeks prior to Day1, or superficial skin infections within 1week prior to Day1;
- A participant known to be infected with human immunodeficiency virus (HIV), Hepatitis B, or Hepatitis C.
• Screening for Hepatitis B will include testing for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (HBcAb). Participants who are HBsAg negative and HBcAb positive will have testing for HBsAb. Participants who are HBsAg negative, HBcAb positive, and HBsAb positive at Screening will have testing for hepatitis B Virus (HBV) deoxyribonucleic 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 assigned to abrocitinib on Study Day 1 but will have HBV DNA testing repeated at the Q12 week visits, at the End of Treatment (EOT) visit, and at the Follow-up/End of Study visit
8. 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.
9. Have a known immunodeficiency disorder.
10. 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.
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
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-10-2021
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Abrocitinib
Generic name:	n/a

Ethics review

Approved WMO Date:	20-04-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-06-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-07-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-07-2022
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	EUCTR2020-003610-12-NL
ClinicalTrials.gov	NCT04564755
CCMO	NL76952.100.21