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Skin biomarkers for atopic eczema therapy evaluation study 2

Submission date	Recruitment status
14/07/2022	No longer recruiting
Registration date	**Overall study status**
28/11/2022	Completed
Last Edited	**Condition category**
30/06/2026	Skin and Connective Tissue Diseases

[_] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The first-choice drug treatment for mild-moderate eczema is currently a topical corticosteroid. By topical, we mean the treatment is intended for application directly to the skin. Whilst topical corticosteroids are effective at treating eczema, they have been found to cause unwanted skin changes, such as skin thinning, if used inappropriately over long periods of time. Exactly how much unwarranted thinning is caused by different treatment routines is unclear, so we want to use some new non-invasive ways to measure skin thinning to better understand the problem. One of these ways is to take a 3D image of the skin using a technique called OCT, which is similar to ultrasound. Because the methods are so sensitive, the signs of skin thinning can be seen before the skin becomes visibly damaged.
Crisaborole ointment is a new non-steroidal drug treatment for eczema that appears to be as effective as some topical corticosteroids, and is not expected to cause abnormal skin thinning. Betamethasone valerate cream is one of the most commonly prescribed topical corticosteroids for eczema in the UK, and is available in a number of preparations with different potencies or strengths. Therefore, the aim of the SMART program of studies is to conduct trials in eczema patients involving treatment of separate areas of their skin with either crisaborole ointment or betamethasone valerate cream of different potencies. The effects of the treatments will be assessed using the non-invasive skin imaging techniques.
Both types of treatment have already been tested in clinical trials for clinical efficacy, and so efficacy will not be assessed again here. This study will confirm whether or not crisaborole ointment causes the same unwarranted skin thinning caused by the moderately potent betamethasone valerate 0.025% cream in a direct comparison.

Who can participate?
Patients aged 18 – 64 years, with atopic dermatitis (eczema)

What does the study involve?
Not provided at time of registration

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration

Risks:
In order to determine a set of safety biomarkers it is necessary to characterise an unsafe treatment scenario, which raises important ethical questions about asking participants to undertake a treatment that may cause them harm. It is important to highlight that this study focuses on early transient signs of skin atrophy, and so there is no intention to induce visible adverse effects. We have already established that 4 weeks of treatment with betamethasone valerate 0.1% induces sub-clinical (invisible) skin thinning without inducing visible adverse effects. In this study the less potent topical corticosteroid (TCS), betamethasone valerate 0.025%, will be used following the same regimen.

The regimen proposed for the antecubital fossa and volar forearms (4 weeks twice daily) conforms to the current marketing licence. However, the duration of treatment proposed for the cheeks (2 weeks twice daily) exceeds the guidance in the SmPC, which suggests treatment is restricted to ≤5 days. This is important so that we can better derive this arbitrarily determined treatment cut-off using our precision equipment. The regimen proposed is in line with current clinical practice, making a strong ethical argument to identify any potential harm, or absence of harm, using this product may have under the proposed conditions.

Skin thinning induced during short courses of TCS treatment is transient, with skin returning to pre-treatment thickness within a matter of weeks following cessation, and so the risks of this controlled short burst of treatment are minimal. To further mitigate the risks we will stop treatment on the cheeks after 1 week if epidermal thinning reaches ≥30%. As a precaution we will also review epidermal thickness data collected after the 5th and 10th participants and adjust the treatment duration down if excessive levels of epidermal thinning are observed. This will ensure the study is conducted safely whilst also establishing whether the 5-day limit on application is appropriate for the cheeks. A more detailed justification can be found in the protocol (section 2.8).

Crisaborole:
Crisaborole has been well tolerated across completed clinical studies (28 to date, involving 2558 participates from 3 months to adults >18 years of age). No clinically important systemic safety signals have been identified. Most adverse events (AEs) have been mild, and most considered unrelated or unlikely to be related to study drug. Studies in pregnant or lactating populations have not been conducted, and so this group will be excluded from participation and steps taken to reduce the risk of pregnancy whilst using the study medication.

The skin procedures:
This study involves a series of non-invasive procedures to test the biophysical properties of the skin. These procedures have all been used safely in previous clinical studies, and so the risks of harm are minimal. The OCT and PS-OCT equipment comprises a class 1M laser and Class 3 laser attenuated down to class 1 AEL respectively, making them safe for the proposed testing under normal operating conditions. A regular maintenance plan and risk assessment has been developed to mitigate the risks of participants becoming exposed to the unattenuated Class 3 laser.
Sample collection:
Three types of samples will be collected: (1) superficial stratum corneum (skin) samples by skin tape-stripping (STS), (2) saliva samples by buccal swabbing, and (3) skin biopsy collection. STS is a painless procedure, that removes the dead cells from the surface of the skin that will eventually be lost/shed as a result of normal desquamation. STS will not be performed on broken skin. The collection of skin biopsy samples may cause both physical and psychological harm to participants; however, the risk of any physical harm is minimal due to the procedure being routine in dermatology clinics and being performed by an experienced clinician. Ten adult

participants, out of 40 recruited, are required to provide 2 biopsies each. The procedure will be treated as optional (although it will be compulsory for the final recruits to ensure 10 sets of biopsies are obtained), on a first come first served basis, and require specific consent. Additional remuneration of £100 per biopsy will be provided in recognition of the burden of providing the samples. Obtaining the biopsies is necessary to validate the non-invasive techniques under investigation against histological analysis (current gold standard). By providing a robust validation of the non-invasive techniques under investigation here the need to collect biopsies in future clinical studies could be avoided.
Potential burden:
Due to the number of site visits and the frequency of compliance checks there is a significant burden on participants' time. This burden will be lessened by providing taxi transport to and from the test centre. Participants will also be remunerated for the burden they endure, which may involve time taken out of work.

Where is the study run from?
Sheffield Teaching Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
July 2022 to December 2024

Who is funding the study?
Pfizer (USA)

Who is the main contact?
Dr Simon Danby, s.danby@sheffield.ac.uk

Contact information

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Scientific

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Clinical Trials Information System (CTIS)
2022-000560-21

Integrated Research Application System (IRAS)
1005095

Central Portfolio Management System (CPMS)
54493

Protocol serial number
STH20466

Study information

Scientific Title
Validation of a novel composite of skin biomarkers as a primary outcome measure for evaluating the safety of treatments for atopic dermatitis study 2: a randomised controlled trial (phase 2) comparing the effects of crisaborole 2% ointment to betamethasone valerate 0.025% cream on skin structure and function in participants with atopic dermatitis.

Acronym
SMART2

Study objectives
Primary objective:
To directly compare the effects of crisaborole (2%) ointment to the moderately potent TCS betamethasone valerate (0.025%) cream on the properties of the skin at different anatomical locations (volar forearm, antecubital fossa and cheek) using an established model for quantifying the local adverse effects of TCS.

Secondary objective:
To validate a panel of non-invasive biomarkers of epidermal atrophy/local adverse effects of TCS treatment with future potential for the development and testing of topical treatments for inflammatory skin conditions.

Ethics approval required
Ethics approval required

Ethics approval(s)

Approved 13/10/2022, Yorkshire & The Humber – Sheffield Research Ethics Committee (NHS Blood and Transplant Donor Centre Holland Drive, Newcastle Upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8388; sheffield.rec@hra.nhs.uk), ref: 22/YH/0172

Primary study design
Interventional

Study design
Interventional randomized single blind controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Atopic eczema/dermatitis

Interventions
Twice-daily self-administered application of 1 finger-tip unit (FTU) of either crisaborole (2%) ointment or betamethasone valerate (0.025%) cream to the designated treatment areas on the arms (volar forearm and including the corresponding antecubital fossa) of the respective side of the body for 28 days. Additionally, ¼ FTU of the respective treatment to be applied to the cheek on the same side of the body twice-daily 14 days.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Crisaborole 2% ointment, betamethasone valerate 0.025% cream

Primary outcome(s)
The difference in the change in epidermal thickness (day 29 – day 1) on the volar forearm, measured by structural OCT, between the sites treated with crisaborole (2%) ointment and betamethasone valerate (0.025%) cream.

Key secondary outcome(s)
1. The difference in the change in epidermal thickness (day 29 – day 1) on the antecubital fossa, measured by structural OCT, between the sites treated with crisaborole (2%) ointment and betamethasone valerate (0.025%) cream.
2. The difference in the change in epidermal thickness (day 15 – day 1) on the cheeks, measured by structural OCT, between the sites treated with crisaborole (2%) ointment and betamethasone valerate (0.025%) cream.
3. The difference in the change in epidermal thickness measured by structural OCT and angiographic OCT (superficial plexus depth in µm) during and after 28 days treatment on the volar forearms, antecubital fossae and cheeks on day 1, 15, 29 and day 57 from the volar forearm and antecubital fossa and on day 1, 15, and day 57
4. The difference in the change in visual redness/erythema score and objective redness during and after treatment on day 1, 15, 29 and day 57 from the volar forearm and antecubital fossa

and on day 1, 15, and day 57
5. The difference in the change in TEWL during and after treatment on day 1, 15, 29 and day 57 from the volar forearm and antecubital fossa and on day 1, 15, and day 57
6. The difference in the change in skin barrier integrity/STS (day 29 – day 1) on the volar forearms (TEWLts20) and antecubital fossae (TEWLts10).
7. The difference in the change in visual skin dryness on the volar forearms, antecubital fossae and cheeks during and after treatment on day 1, 15, 29 and day 57 from the volar forearm and antecubital fossa and on day 1, 15, and day 57

Completion date
31/12/2024

Eligibility

Key inclusion criteria
1. Volunteers with AD, defined according to the UK working party diagnostic criteria, not currently undergoing, or requiring, active drug treatment at baseline (visit 1)
2. Male or female aged 18-64 years old at baseline (Visit 1)
3. Volunteer understands the purpose, modalities and potential risk of the trial
4. Participants able to read and understand English
5. Participants willing to sign the informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Upper age limit
64 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Participants with a known allergy/hypersensitivity to any of the excipients of the trial preparations.
2. Participants with acne, suntan, birth marks, multiple nevi, tattoos, blemishes or dense body hair that obstruct the test areas.
3. Investigator assessment of eczema severity at the measurement (anatomical) sites on the volar forearm and cheek is almost clear or greater (score ≥1) based on the Investigators static

global assessment (ISGA) scale at screening and baseline. At the start of the study the skin of the volar forearm and cheek measurement sites will therefore be clear (0) of the signs of eczema.
4. Investigator assessment of eczema severity at the measurement (anatomical) sites on the antecubital fossae is moderate or severe (score ≥3) based on the Investigators static global assessment (ISGA) scale at screening and baseline. At the start of the study the skin of the antecubital fossa measurement sites will therefore be clear (0) of the signs of eczema, almost clear (1) or mild (2).
5. Participants with a condition that in the opinion of the investigator contradicts participation in the study.
6. Pregnant female participants; breastfeeding female participants; and female participants of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for at least 28 days after the last dose of investigational product.
7. Use of any topical product on the test areas within 7 days prior to Baseline/Day 1, including cosmetic moisturizers and sunscreen. Participants using any topical products on the test areas within 7 days at the screening visit will be eligible if they are willing and able to wash-out these products for 7 days in total and for the duration of the trial. Such participants will be potentially eligible at screening and will be confirmed as eligible if adequate washout is confirmed at visit 1. Use of moisturizers and/or sunscreen is permitted during the study to manage dry skin and sun exposure in areas surrounding but not on or overlapping the test areas.
8. Participants who have used a tanning bed within 28 days of baseline (visit 1). Participants who have used a sunbed within 28 days at the screening visit will be eligible if they are willing and able to wash-out for 28 days in total and for the duration of the trial. Such participants will be potentially eligible at screening and will be confirmed as eligible if adequate washout is confirmed at visit 1.
9. Participants who have used any medication that could interfere with the trial aim prior to the start of the study (baseline/visit 1). Participants using such medication at the screening visit will be eligible if they are willing and able to wash-out these treatments for the applicable washout period as defined by in section 8.8 ‘Prior and Concomitant Medication’ and for the duration of the trial. Such participants will be potentially eligible at screening and will be confirmed as eligible if adequate washout is confirmed at visit 1.
10. Participants currently participating in another interventional clinical trial.
11. Volunteer is incapable of giving fully informed consent.
12. Participants judged by the PI to be inappropriate for the trial.

Date of first enrolment
01/11/2022

Date of final enrolment
31/08/2023

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
-

-
England
-

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Industry

Funder Name
Pfizer

Alternative Name(s)
Pfizer Inc., Pfizer Consumer Healthcare, Davis, Charles Pfizer & Company, Warner-Lambert, King Pharmaceuticals, Wyeth Pharmaceuticals, Seagen, Pfizer Inc

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
Data that supports the findings of this study is available upon reasonable request and subject to review from the study sponsor, Sheffield Teaching Hospitals NHS Foundation Trust. Subject to certain criteria, conditions and exceptions, the sponsor may also provide access to the related individual de-identified participant data.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		29/06/2026	29/06/2026	No	No
HRA research summary			26/07/2023	No	No
Protocol file	version 2.0	30/09/2022	20/03/2026	No	No
Statistical Analysis Plan	version 1.0	12/12/2023	26/03/2026	No	No