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An assessment of the acceptability and practicality of using Janus kinase inhibitors to treat palmoplantar pustulosis

Submission date
19/06/2024

Recruitment status
Recruiting

Registration date
20/11/2024

Overall study status
Ongoing

Last Edited
16/01/2025

Condition category
Skin and Connective Tissue Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Palmoplantar pustulosis (PPP) is a rare, debilitating condition, causing painful, red skin with pus-filled lumps on the hands and feet that are difficult to treat. A new group of drugs called Janus kinase (JAK) inhibitors show promise in the treatment of PPP in some reported cases. However, these drugs also carry a risk of side effects which are more common in people with long-term health conditions. We need to know whether JAK inhibitors are an acceptable treatment for PPP. To do this, we will carry out a small-scale trial investigating whether people with PPP are happy to take JAK inhibitors and whether a larger clinical trial investigating JAK inhibitors in PPP is possible.

Who can participate?
Patients aged 18 years and over with palmoplantar pustulosis

What does the study involve?
Participants will receive a daily tablet of upadacitinib (30 mg once a day) for 8 weeks. The researchers will assess how willing individuals are to participate in the trial, how well they take the medication throughout the trial, and the overall acceptability of the treatment from the perspective of both people with PPP and healthcare professionals. Scoring systems, questionnaires, and in-depth interviews will be used to understand the barriers to running a full-scale clinical trial. Based on the findings from in-depth interviews with people with PPP and healthcare professionals, changes will be made to the recruitment process throughout the trial, identifying strategies that improve recruitment for a future full-scale trial.

What are the possible benefits and risks of participating?
The Medicines and Healthcare products Regulatory Agency (MHRA) has issued guidance regarding the use of JAK inhibitors. An increased risk of major cardiovascular events and malignancy was detected amongst those with pre-existing cardiovascular risk factors who received tofacitinib. The MHRA recommended that these medicines should be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or

stroke), those who smoke or have done so for a long time in the past and those at increased risk of cancer.
The MHRA also recommended using these medicines with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE). The researchers have adapted the exclusion criteria to account for this new guidance. Any decision to treat patients in these cohorts will be made following discussion with the Chief Investigator and will be based on individualised patient factors. Any patients with a history of unprovoked VTE and not on long-term anticoagulation shall be excluded from the trial.
There is a well-established correlation between smoking and palmoplantar pustulosis; it is estimated that 90% of patients with palmoplantar pustulosis are either current or ex-smokers. It will therefore not be feasible to exclude those with a smoking history from this trial, and doing so would greatly reduce the external validity of the trial.
Administration of upadacitinib for this study is not anticipated to induce any potential risk other than the known potential side effects listed below (see SmPC: https://www.medicines.org.uk /emc/product/14871/smpc#gref). During study visits, members of the research team will screen for and record any adverse effects from the medication. The potential side effects of the medication will be made clear to participants as part of the consenting process. This medication is used daily across the field of Dermatology to treat a range of inflammatory conditions, and is generally tolerated well.
Trial participants will need to adhere to a close monitoring schedule, with site visits at Baseline, Week 1, 2, 4, 8, and 12, with a final safety review at Week 20. Blood tests will be taken during screening, baseline, Week 1, 2, 4, 8, and 12. The risks of taking blood include temporary discomfort from the needle in the arm, bleeding, bruising, swelling at the needle site and, in rare instances, infection. Blood tests for safety monitoring are essential during the trial, but every effort will be made to minimise the number of individual needles used for each participant. The need for regular blood tests will be made clear as part of the patient information leaflet and during the consenting process.
Participants will need to attend Guy's and St Thomas' NHS Trust in person for each of the screening and monitoring visits. This is required for accurate scoring of the disease severity, and for safety checks (vital signs, blood tests). This will ensure the safety of all trial participants. The need for in-person reviews will be made clear as part of the patient information leaflet and during the consenting process.
The qualitative interviews will last roughly 60 minutes. These will be carried out either in person or over Microsoft Teams (participant preference) at a time convenient to the participant(s) to minimise the burden. The topics discussed should not be distressing or embarrassing, and should therefore not pose a personal risk to participants.
The study data will be protected by several means keeping data secure and accessible only to appropriate personnel. Access to identifiable data at the local study centre will only be granted following additional checks of delegation logs, and principal investigator approval. Identifiable data visible to the user at the participating centre will be restricted to that from the relevant study. Paper-based CRFs will be stored in a secure locked office at the study site and will be the responsibility of the principal investigator. Every effort will be made to ensure the safety of participants' data, and participants will be informed of any potential data breaches if they occur.
Participants will need to avoid live or live-attenuated vaccines during the 8-week treatment period. This will be discussed with participants during the screening process if they have been invited to receive or require any vaccines.
A chest X-ray (CXR) will be required unless the participant has had one in the previous 12 months. Screening chest x-rays form part of standard care before commencing a systemic immunosuppressant.

Where is the study run from?
1. King’s College London (UK)
2. Guy’s and St Thomas’ NHS Trust (UK)

When is the study starting and how long is it expected to run for?
June 2024 to September 2026

Who is funding the study?
National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
1. Dr David Gleeson, David.gleeson@kcl.ac.uk
2. Prof. Catherine Smith, Catherine.smith@kcl.ac.uk

Contact information

Type(s)
Public, Principal Investigator

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Type(s)
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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
346783

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
3643JAKPPPOT, IRAS 346783, CPMS 64148

Study information

Scientific Title
JAnus Kinase inhibitors in PalmoPlantar PustulOsis: a mixed-methods feasibiliTy trial

Acronym
JAKPPPOT

Study objectives
Primary Objective:
Assess the feasibility of JAK inhibitor therapy in palmoplantar pustulosis (PPP), to inform the viability of a future adequately-powered randomised controlled trial (RCT) via a composite assessment of three domains: recruitment rate, adherence, and acceptability, using qualitative and quantitative measures.

Secondary Objectives:
1. Identify trial recruitment optimisation strategies for a future RCT.
2. Generate an indication of the effect size to be used in a future sample size calculation for a definitive trial of JAK inhibitor therapy in PPP, as measured by a change in objective disease severity at 8 weeks from baseline, using the palmoplantar pustulosis psoriasis area and severity index (PP-PASI).

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/09/2024, Newcastle North Tyneside 2 Research Ethics Committee (2 Redman Place, Health Research Authority, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8086; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 24/NE/0147

Study design
Non-randomized feasibility study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Efficacy

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Palmoplantar pustulosis

Interventions
This is a single-arm study in which all participants will receive the oral JAK inhibitor updacitinib 30 mg once a day for 8 weeks. In certain patient cohorts, outlined in Section 4.4. of the SmPC, the dose will be moderated to 15 mg once a day. Participants will be followed up for 12 weeks after completion of the 8-week intervention period. There is no randomization process as this is a single-arm study.

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy, Others (Feasibility assessment comprised of a composite assessment of recruitment, adherence and acceptability. Trial recruitment optimisation strategies for a future full randomised-controlled trial will also be identified.)

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Upadacitinib

Primary outcome measure
1. Overall proportion of potential participants identified who enrolled in the trial, termed the ‘recruitment rate’
2. Overall proportion of participants achieving ‘good adherence’ (proportion of days covered >80%) during the trial
3. Overall proportion of participants who view JAK inhibitor therapy in PPP to be ‘acceptable’

Assessed at 24 months, or when the recruitment target of 20 participants is achieved (whichever occurs first)

Secondary outcome measures
1. Total number of potential participants who have contact with the research team assessed at 24 months, or when the recruitment target of 20 participants is achieved (whichever occurs first)
2. Overall speed of participant identification assessed at 24 months, or when the recruitment target of 20 participants is achieved (whichever occurs first)
3. Overall speed of participant recruitment assessed at 24 months, or when the recruitment

target of 20 participants is achieved (whichever occurs first)
4. Total number of ineligible participants assessed at 24 months, or when the recruitment target of 20 participants is achieved (whichever occurs first)
5. Reasons for ineligibility assessed at 24 months, or when the recruitment target of 20 participants is achieved (whichever occurs first)
6. Recruitment of 20 participants assessed at 24 months, or when the recruitment target of 20 participants is achieved (whichever occurs first)
7. Overall mean change in palmoplantar pustulosis psoriasis area and severity index (PP-PASI) over the 8-week treatment period, adjusted for baseline (visit 1)
8. Change in recruitment rate with each phase of the QRI approach assessed at the end of each phase of the QRI approach (new phase for every 20 eligible patient participants approached throughout the trial).

Overall study start date
14/06/2024

Completion date
15/09/2026

Eligibility

Key inclusion criteria
Main Investigational Trial:
1. Adults (aged 18 years and over) with a diagnosis of palmoplantar pustulosis* (PPP) made by a trained dermatologist with disease of sufficient impact and severity to require systemic therapy
2. Disease duration of >6 months, not responding to an adequate trial of topical therapy including very potent corticosteroids
3. Evidence of active pustulation on palms and/or soles to ensure sufficient baseline disease activity to detect efficacy
4. At least moderate disease based on a PalmoPlantar Pustulosis Investigator Global Assessment (PPP-IGA)
5. Who have given written, informed consent to participate
6. Willing and able to comply with scheduled visits, treatment plans, laboratory tests and other study procedures

*Different forms of psoriasis can co-present together (e.g. chronic plaque psoriasis, Acrodermatitis of Hallopeau, generalised pustular psoriasis). A concomitant diagnosis of a different type of psoriasis will not be a contra-indication to eligibility.

Integrated Qualitative Study:
Trial Participants and Trial Decliners:
1. Must be eligible for enrolment in the clinical trial aspect of the study
2. Able to give written informed consent to participate

Healthcare Professionals:
1. Involved in the recruitment and delivery of the trial
2. Able to give written informed consent to participate

Participant type(s)
Patient, Health professional

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
20

Key exclusion criteria
Main Investigational Trial:
1. A history of malignancy of any organ system (other than treated, localised non-melanoma skin cancer), treated or untreated, within the past 5 years
2. With a known history of provoked or unprovoked venous thrombo-embolism (deep vein thrombosis or pulmonary embolism), unless actively treated with long-term anticoagulation
3. Previous treatment with a JAK inhibitor
4. A history of recurrent bacterial, fungal or viral infections which, in the opinion of the principal investigator, present a risk to the patient
5. Evidence of active infection or untreated latent TB
6. HIV positive
7. Active or untreated Hepatitis B or C
8. Use of therapies with potential or known efficacy in psoriasis during or within the following specified timeframe before treatment initiation as listed in the washout section (section 8.6.1)
9. With moderate renal impairment [CrCl <50ml/min]
10. With neutropenia (<1.5x109/L)
11. With thrombocytopenia (<150x109/L)
12. With known moderate hepatic disease and/or raised hepatic transaminases (ALT/AST) > 2 x ULN at baseline. Patients who fail this screening criterion may still be considered following review by a hepatologist and confirmed expert opinion that study entry is clinically appropriate.
13. Live vaccinations within 3 months prior to the start of study medication, and willing to not have live vaccinations during the trial and up to 3 months following the last dose.
14. Women who are pregnant, breastfeeding or of childbearing potential* not on adequate contraception**
15. Male participants who are not willing to use highly effective methods of contraception** when engaging in sexual activity with a female of childbearing potential
16. Any condition where, in the opinion of the investigator, the IMP would present risk to the patient.
17. Unable to give written, informed consent.
18. Unable to comply with the study visit schedule.
19. Known hypersensitivity to upadacitinib and/or its excipients (SmPC 6.1)
20. Receipt of any of the following within the specified timeframe before treatment initiation (baseline, visit 1):
20.1. Topical treatments likely to impact signs and symptoms of psoriasis (e.g. potent/very potent corticosteroids, vitamin D analogues, calcineurin inhibitors) within 2 weeks
20.2. Systemic immunosuppressants (e.g. methotrexate, ciclosporin, acitretin) within 4 weeks
20.3. Phototherapy (UVB TL01, UVB, PUVA, UVA1) within 4 weeks
20.4. Etanercept or adalimumab within 4 weeks
20.5. Other biologic therapies (infliximab, certolizumab, ustekinumab, secukinumab, ixekizumab,

risankizumab, bimekizumab, brodalumab, tildrakizumab) within 3 months
20.6. Other investigational drugs within 4 months or 5 half-lives (whichever is longer)
20.7. Other immunosuppressant/immunomodulatory therapies including intra-articular steroids within 30 days or 5 half lives (whichever is longer)

In line with the Medicines and Healthcare products Regulatory Agency's (MHRA) recent advice, upadacitinib will only be used in the following cohorts if no suitable treatment alternatives are available:
1. 65 years or older
2. Patients with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as past long-term smokers)
3. Patients with malignancy risk factors (e.g. current malignancy or history of malignancy)
Any decision to treat patients in these cohorts will be made following discussion with the Chief Investigator and will be based on individualised patient factors.

*Women of child-bearing potential defined as: fertile, following menarche and until being post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A post-menopausal state is defined as no menses for 12 months without an alternative medical cause.

**Effective methods of contraception include:
1. Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
2. Progestogen-only hormonal contraception (oral, injectable, implantable)
3. Intrauterine device
4. Intrauterine hormone-releasing system
5. Bilateral tubal occlusion
6. Vasectomised partner (only considered highly effective if partner is the sole partner of the participant) and the vasectomised partner has received medical assessment of the surgical success
7. Male or female condom with or without spermicide
8. Cap, diaphragm, or sponge with spermicide
9. A combination of male condom with either cap, diaphragm or sponge with spermicide (double barrier methods)

Integrated Qualitative Study:
Healthcare Professionals:
Members of the research team involved in the qualitative analysis of the data will be excluded for pragmatic reasons

Date of first enrolment
14/11/2024

Date of final enrolment
15/09/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Guys Hospital
Guys Hospital
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Sponsor information

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Sponsor type
University/education

Website
http://www.kcl.ac.uk/index.aspx

ROR
https://ror.org/0220mzb33

Organisation
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Sponsor type
Hospital/treatment centre

Website
http://www.guysandstthomas.nhs.uk/Home.aspx

ROR
https://ror.org/00j161312

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. Peer-reviewed scientific journals
2. Conference presentation
3. Publication on website

4. Access to raw data and right to publish freely by all investigators in the study or by an Independent Steering Committee on behalf of all investigators
5. Other

It is anticipated that the full protocol and all results will be available as open access according to the principles of the funding body, the National Institute of Health and Care Research (NIHR).

All participants will be asked for their consent for the secure sharing of their de-identified data with research collaborators (including those outside the UK) in the future during the consent process. During any transfer of data, only non-identifiable participant data will be transferred electronically.

Intention to publish date
01/07/2027

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be available upon request from the research team (Professor Catherine Smith, Chief Investigator, Catherine.smith@kcl.ac.uk) for ethically approved projects, subject to approval by the Chief Investigator and both cosponsors (KCL and GSTT). Any collaborations will be compliant with the co-sponsor's data-sharing policies and in coordination with both co-sponsors' Research and Development functions. The researchers will seek participant consent in the informed consent form for their deidentified study data to be shared with research collaborators running other research studies in our organisation or in other organisations. These organisations may be universities, NHS organisations or companies (i.e. industry partners and/or vendors) involved in health and care research in this country or abroad. This information will not identify participants and will not be combined with other information in a way that could identify them. The information will only be used for the purpose of health and care research and cannot be used to contact participants, affect their care, or to make decisions about future services available to them, such as insurance. Appropriate data agreements will be put in place to govern terms prior to data transfers. Data will be available once the final analysis is complete and a minimum of 6 months after publication of the main results paper.

IPD sharing plan summary
Available on request