CLINICAL STUDY REPORT

Anakinra for **P**ustular psoriasis: **R**esponse in a **Co**ntrolled **T**rial

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Treatment of Pustular Psoriasis with the IL-1 receptor antagonist anakinra: a randomised, placebo controlled trial and associated mechanistic studies.

Sponsor Protocol Code:	162098
EudraCT Number:	2015-003600-23
ISRCTN Number:	ISCRTN13127147
REC Number:	16/LO/0436
Investigational Drugs (IMPs):	Anakinra
Indication:	Palmo-Plantar Pustulosis
Development Phase:	Phase IV
Study Begin (FPFV):	08-AUG-2016
Study End (LPLV):	10-AUG-2020
Report Version & Issue Date:	1.0 (20-SEP-2021)
Sponsor Name and Address:	Guy's and St. Thomas' NHS Foundation Trust King's Health Partners Clinical Trials Office, Floor 16 - Tower Wing, Guys Hospital, Great Maze Pond, London, SE1 9RT.
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Chief Investigator:	Professor Catherine Smith

SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator:

Professor Catherine Smith		20-SEP-2021
Printed name	**Signature**	**Date**

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APPENDICES

1. Ethics

Independent Ethics Committee or Institutional Review Board
The study protocol and amendments were reviewed and approved by a National Research Ethics Service (London - Dulwich Research Ethics Committee).

Ethical conduct of the study
The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

Subject information and consent
Recruitment, IMP delivery and collection of data took place in 16 hospitals across England, Scotland and Wales. Participants were adults (18 years and over) with a diagnosis of palmoplantar pustulosis made by a trained dermatologist, disease duration of greater than 6 months and of sufficient impact and severity to require systemic therapy.

Potentially eligible patients were identified by the following four methods:

> In clinic at participating sites: Potentially eligible patients were identified in clinics and approached directly by a member of the study team and/or clinical care team. The study was explained to the patient and they were provided with the patient information leaflet. Patients were then given as much time as they required (and at least 24 hours) to read the information leaflet and come to a decision regarding their participation.

> Searching existing local healthcare/medical databases at participating sites: Once sites were opened, local study teams identified potentially eligible patients through searching local clinic and pharmacy lists, electronic patient records, referral lists and letters, research databases and other lists (as appropriate). Potential participants were then contacted by their consultant and the research team (by letter, email or phone call) to invite them to participate and provide them with the patient information leaflet.

> Self-referral: Potential study participants identified themselves after becoming aware of the study. On the study website (http://apricot-trial.com/) there was a specific page (which was taken down following the end of recruitment) where patients were invited to register on an interactive web-based patient recruitment questionnaire. These results were automatically sent to the Trial Manager and used as the first line of eligibility screening. If potentially eligible, the patient was then contacted by the Trial Manager/Research Nurse by telephone and email to invite them to participate (and provide them with the patient information leaflet if this had not already been downloaded by the patient from the study website). If the patient remained interested in participating, with their consent, their contact details were provided to the study team geographically closest to them to arrange a formal research consultation.

> Participant Identification Centres (PICs): Potential study participants were identified at PICs following clinic visits or review of local clinic and pharmacy lists, electronic patient records, referral lists and letters, research databases and other lists. They were then contacted by their direct clinical

care team (usually by letter, email, phone call or in person) and then invited to self-refer on the trial website (as detailed above) or (with their agreement) referred directly to the team at their chosen trial site for further information regarding participation.

2. Data Monitoring

Data Monitoring Committee
The Data Monitoring Committee (DMC) was chaired by an independent Chair (Professor Deborah Symmons; Consultant Rheumatologist and Professor of Rheumatology and Musculoskeletal Epidemiology, University of Manchester). The DMC also included: an independent member (Dr Mike Ardern-Jones, University of Southampton), an independent statistician (Professor Simon Skene, University of Surrey), the Chief Investigator of the study (Professor Catherine Smith), the trial statisticians (Dr Suzie Cro, Imperial Clinical Trials Unit and Dr Victoria Cornelius, Imperial Clinical Trials Unit) and the APRICOT Trial Manager.

The DMC was responsible for monitoring evidence for treatment harm and reviewed all decisions made in relation to the safety aspects of the study. The DMC met on initiation of the project, and agreed the type, frequency and format of data reports. A DMC Charter was constructed and agreed prior to first review of study data.

Trial Steering Committee
The Trial Steering Committee (TSC) included: an independent Chair (Professor Edel O'Toole, Queen Mary University of London), two independent members (Professor Hervé Bachelez, Consultant Dermatologist (with internationally recognised clinical and academic expertise in pustular forms of psoriasis) - University Paris Diderot/Saint-Louis Hospital and Dr Stephen Kelly, Consultant Rheumatologist - Barts Health NHS Trust), an independent patient representative (Mr David Britten), the Chief Investigator of the study (Professor Catherine Smith) and the trial statistician (Dr Victoria Cornelius, Imperial Clinical Trials Unit).

The TSC met as required and was the main decision making body for the study. It had overall responsibility for scientific strategy and direction whilst also providing supervision and advice to study members.

3. Sponsors, Investigators and Trial Sites

Sponsor	**Guy's and St. Thomas' NHS Foundation Trust** King's Health Partners Clinical Trials Office, Floor 16 - Tower Wing, Guys Hospital, Great Maze Pond, London, SE1 9RT. UK.
Chief Investigator:	**Professor Catherine Smith** St. John's Institute of Dermatology, 9th Floor - Tower Wing, Guys Hospital, Great Maze Pond, London, SE1 9RT. UK.

4. Co-Investigator(s), Statistician, Laboratories, Database Management

Co-Investigators, Statisticians and Laboratories	**Professor Jonathan Barker** St. John's Institute of Dermatology, 9th Floor - Tower Wing, Guys Hospital, Great Maze Pond, London, SE1 9RT. UK. **Dr Andrew Pink** St. John's Institute of Dermatology, 1st Floor - Counting House, Guys Hospital, Great Maze Pond, London, SE1 9RT. UK. **Dr. Francesca Capon** Department of Medical & Molecular Genetics, King's College London, London, SE1 9RT. UK. **Dr. Victoria Cornelius** Imperial Clinical Trials Unit, Imperial College London, London, W12 7RH, UK.

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5. Study Synopsis

Title of clinical trial	**A**nakinra for **P**ustular psoriasis: **R**esponse in a **Co**ntrolled **T**rial
Protocol Short Title/Acronym	APRICOT
Study Phase	Phase IV
Sponsor name	Guy's and St. Thomas' NHS Foundation Trust
Chief Investigator	Professor Catherine Smith
Eudract number	2015-003600-23
REC number	16/LO/0436
IRAS project ID	162098
Medical condition or disease under investigation	Palmo-Plantar Pustulosis
Purpose of clinical trial	Determine efficacy of anakinra in the treatment of palmo-plantar pustulosis (PPP).
Primary objective	The primary objective of the study was to determine the efficacy of anakinra (compared to placebo) in the treatment of adults with palmoplantar pustulosis.
Secondary objective (s)	1) Determine the treatment group difference in fresh pustule count, adjusted for baseline. 2) Determine the treatment group difference in total pustule count, adjusted for baseline. 3) Determine the time to response of palmoplantar pustulosis (defined as a 75% reduction in fresh pustule count compared to baseline), and relapse rate (defined as return to baseline fresh pustule count) with anakinra compared to placebo. 4) Determine the proportion of randomised participants who achieved clearance of palmoplantar pustulosis with anakinra compared to placebo by 8 weeks. 5) Determine the treatment effect on the development of a disease flare (>50% deterioration in PP-PASI compared to Baseline) at 8 weeks. 6) Determine any treatment effect of anakinra in pustular psoriasis at non acral sites as measured by change in percentage area of involvement at 8 weeks compared to baseline. 7) Determine any treatment effect of anakinra in plaque type psoriasis (if present) measured using

	psoriasis area and severity index (PASI) at 8 weeks compared to baseline. 8) Determine the impact of anakinra on patients' symptoms and quality of life compared to placebo at 8 weeks, adjusted for baseline, as assessed using the: Palmoplantar Quality of life instrument (PPQoL), Dermatology life Quality Index (DLQI), Participants Global assessment (PGA) and EQ53-3L. 9) Determine the proportion of randomised participants who found the treatment acceptable or, "worthwhile." 10) Determine the proportion of randomised participants that adhered to treatment. 11) Determine whether there are any treatment group differences in episodes of serious infections, as defined by any infection leading to death, hospital admission or requiring intra-venous antibiotics. 12) Determine whether there are any treatment group differences in neutropenia (neutrophil count of ≤1.0 x 10^9/l on at least one occasion). 13) Collect data on the adverse event profile and adverse reactions induced by anakinra compared to placebo to evaluate the safety and tolerability of anakinra in the treatment of palmoplantar pustulosis.
Trial Design	Double blind, randomised, placebo controlled study with two stages and an adaptive element followed by an Open Label Extension.
Endpoints	**Primary Endpoints** The primary endpoint was change in disease activity at 8 weeks, adjusted for baseline, measured using PP-PASI. Determination of the efficacy of anakinra (compared to placebo) in the treatment of adults with palmoplantar pustulosis, measured by an independent blinded assessor using Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) across 1, 4 and 8 weeks. **Secondary Endpoints** **Investigator Assessed** 1) Total pustule count on palms and soles across 1, 4, 8 weeks adjusted for baseline (visit 1). 2) Investigator's Global Assessment (PPP-IGA) at 1, 4 and 8 compared to baseline (visit 1). 3) Time to response of PPP (defined as a 75%

	reduction in fresh pustule count compared to baseline), and relapse rate (defined as return to baseline fresh pustule count). 4) Achievement of 'clear' on PPP-IGA by 8 weeks 5) Development of a disease flare (ie: >50% deterioration in PPPASI compared to baseline, visit 1). 6) Pustular psoriasis at non acral sites as measured by change in percentage area of involvement at 8 weeks compared to baseline (visit 1). 7) Plaque type psoriasis (if present) measured using Psoriasis Area and Severity Index (PASI) at 8 weeks compared to baseline (visit 1). 8) Serious infection as defined by any infection leading to death, hospital admission or requiring IV antibiotics. 9) Neutropenia (ie: neutrophil count of 1.0 x 10^9/l on at least one occasion) **Patient Reported Outcomes** 1) Patient's Global Assessment (clear, nearly clear, mild, moderate, severe, very severe) across 1, 4, 8 weeks compared to baseline (visit 1). 2) Palmoplantar Quality of Life Instrument score in randomised patients at 8 weeks compared to baseline (visit 1). 3) Dermatology Life Quality Index at 8 weeks compared to baseline (visit 1). 4) EQ5D-3L score at 8 weeks compared to baseline (visit 1). 5) Treatment acceptability (i.e.: whether the treatment is 'worthwhile') evaluated using a brief questionnaire with a response scale of 1-5 at study end. 6) Adherence to treatment measured by responses to daily text message over 8 weeks of treatment. **Exploratory Endpoints** 1) Expression levels of IL-1 related transcripts in blood, skin and keratinocytes derived from hair plucks. 2) Disease-associated mutations.

	3) Patient immune phenotypes. 4) Complete clinical, DNA, RNA, serum datasets (with optional tissue samples [skin and hair pluck]) on patients with pustular psoriasis.
Planned number of subjects	Stage 1: 24 Stage 2: 40 Total sample size: 64
Summary of eligibility criteria	**Key Inclusion Criteria:** i. Adults (18 years and over) with diagnosis of PPP made by a trained dermatologist with disease of sufficient impact and severity to require systemic therapy. ii. Disease duration of >6 months, not responding to an adequate trial of topical therapy including very potent corticosteroids. iii. Evidence of active pustulation on palms and /or soles to ensure sufficient baseline disease activity to detect efficacy iv. At least moderate disease on the PPP Investigator's Global Assessment (PPP-IGA). v. Women of child bearing potential who are on adequate contraception, who are not pregnant or not breast feeding. vi. Who have given written, informed consent to participate.
IMP, dosage and route of administration	Anakinra (Kineret) 100mg/0.67ml daily, self-administered, sub-cutaneous injection.
Active comparator product(s)	No active comparator. Non-active comparator: placebo injection (0.67ml vehicle)
Maximum duration of treatment of a subject	8 weeks for the double blind, randomised, placebo controlled study and then an optional further 8 weeks for the open label extension.
Version and date of protocol amendments	Version 1.0: 17-DEC-2015 Version 1.1: 31-MAR-2016 Version 2.0: 28-APR-2016 Version 3.0: 01-SEP-2016 Version 3.1: 05-DEC-2016 Version 4.0: 03-APR-2017 Version 4.1: 09-JUN-2017 Version 4.2: 01-NOV-2017 Version 5.0: 01-MAR-2018 Version 5.1: 06-JUN-2018 Version 5.2: 29-AUG-2018 Version 6.0: 15-NOV-2018 Version 6.1: 03-JUN-2019

6. Glossary of terms

ACH	Acrodermatitis Continua of Hallopeau
AE	Adverse event
APP	Acral Pustular Psoriasis
CACE	Complier Average Causal Effect
CAPS	Cryopyrin-Associated Periodic Syndromes
CPP	Chronic Plaque Psoriasis
CXR	Chest X-ray
DEGs	Differentially Expressed Genes
GPP	Generalised Pustular Psoriasis
IGA	Investigator Global Assessment
MTIS	Medical Toxicology and Information Service
OLE	Open Label Extension
PASI	Psoriasis Area Severity Index
PPI	Patient and Public Involvement
PPP	Palmo-Plantar Pustulosis
PP-PASI	Palmoplantar Pustulosis Psoriasis Area Severity Index
PPP-IGA	Palmo-Plantar Pustulosis - Investigators Global Assessment
PROM	Patient Reported Outcome Measures
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SD	Standard Deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis

7. Publication (reference)

Cornelius V, Wilson R, Cro S, Barker J, Burden D, Griffiths C, et al. A small population, randomised, placebo-controlled trial to determine the efficacy of anakinra in the treatment of pustular psoriasis: study protocol for the APRICOT trial. *Trials*. 2018 Aug. 19 (1), 465. This can be found: https://doi.org/10.1186/s13063-018-2841-y

Cro S, Smith C, Wilson R, Cornelius V. Treatment of pustular psoriasis with anakinra: a statistical analysis plan for stage 1 of an adaptive two-staged randomised placebo-controlled trial. *Trials*. 2018 Oct. 19 (1), 534. This can be found: https://doi.org/10.1186/s13063-018-2914-y

Cro S, Patel P, Barker J, Burden D, Griffiths C, Lachmann H, et al. A randomised placebo controlled trial of anakinra for treating pustular psoriasis: statistical analysis plan for stage two of the APRICOT trial. *Trials*. 2020 Feb. 21 (1), 158. This can be found: https://doi.org/10.1186/s13063-020-4103-z

8. Study period (years)

Recruitment took place between October 2016 and January 2020. First patient first visit occurred on 08-AUG-2016 (a protocol deviation) and last patient last visit occurred on 10-AUG-2020.

Patient recruitment was completed on 30-JAN-2020.

9. Phase of development

APRICOT was a phase IV, two-staged, adaptive, double-blind, randomised, placebo-controlled trial followed by an Open Label Extension (OLE) aiming to recruit 64 participants (24 to Stage 1 and 40 to Stage 2). Analysis at the end of Stage 1 was used to compare treatment arms to ensure sufficient efficacy and safety in order to progress to the Stage 2. The primary outcome for Stage 2 was also selected out of two pre-specified candidate outcomes (PP-PASI or fresh pustule count) based on assessments of reliability and discriminatory ability using Stage 1 data.

10. Objectives

Primary objective:

The primary objective of the study was to determine the efficacy of anakinra (compared to placebo) in the treatment of adults with palmoplantar pustulosis. The primary endpoint was change in disease activity at 8 weeks, adjusted for baseline, measured using PP-PASI.

Secondary objectives:

1. Determine the treatment group difference in fresh pustule count, adjusted for baseline.

2. Determine the treatment group difference in total pustule count, adjusted for baseline.

3. Determine the time to response of palmoplantar pustulosis (defined as a 75% reduction in fresh pustule count compared to baseline), and relapse rate (defined as return to baseline fresh pustule count) with anakinra compared to placebo.

4. Determine the proportion of randomised participants who achieved clearance of palmoplantar pustulosis with anakinra compared to placebo by 8 weeks.

5. Determine the treatment effect on the development of a disease flare (>50% deterioration in PP-PASI compared to Baseline) at 8 weeks.

6. Determine any treatment effect of anakinra in pustular psoriasis at non acral sites as measured by change in percentage area of involvement at 8 weeks compared to baseline.

7. Determine any treatment effect of anakinra in plaque type psoriasis (if present) measured using psoriasis area and severity index (PASI) at 8 weeks compared to baseline.

8. Determine the impact of anakinra on patients' symptoms and quality of life compared to placebo at 8 weeks, adjusted for baseline, as assessed using the: Palmoplantar Quality of life instrument (PPQoL), Dermatology life Quality Index (DLQI), Participants Global assessment (PGA) and EQ53-3L.

9. Determine the proportion of randomised participants who found the treatment acceptable or, “worthwhile.”

10. Determine the proportion of randomised participants that adhered to treatment.

11. Determine whether there are any treatment group differences in episodes of serious infections, as defined by any infection leading to death, hospital admission or requiring intra-venous antibiotics

12. Determine whether there are any treatment group differences in neutropenia (neutrophil count of $\leq 1.0 \times 10^9$/l on at least one occasion).

13. Collect data on the adverse event profile and adverse reactions induced by anakinra compared to placebo to evaluate the safety and tolerability of anakinra in the treatment of palmoplantar pustulosis.

Exploratory objectives (mechanistic studies):

1. To validate the hypothesis that abnormal IL-1 signalling is a key driver in the pathogenesis of pustular psoriasis.

2. To determine the genetic status of individuals who responded to treatment as a preliminary step for future pharmaco-genetic studies by comparing the genotypes of responders and non-responders.

3. To characterise the immune phenotype of all subjects entering the trial, to establish whether the disease was associated with alterations in the number or activation status of IL-1 producing cells.

4. To collect mechanistic sample datasets on patients with pustular psoriasis for studies investigating disease pathogenesis (Pustular Psoriasis – elucidating underlying mechanisms [PLUM]).

Open Label Extension (OLE) objectives:

The primary objective of the OLE was to boost recruitment and was introduced part-way through the trial when funding for the required additional anakinra IMP was secured. In addition, we also obtained the following:

1. Observational data on disease activity on anakinra (measured using PP-PASI, fresh pustule count, total pustule count, PPP-IGA and PASI) over an initial 8 week treatment period for individuals originally prescribed placebo who chose to continue into the open label component.

2. Observational data on disease activity on anakinra (measured using PP-PASI, fresh pustule count, total pustule count, PPP-IGA and PASI) over a second 8 week treatment period for individuals originally prescribed anakinra who chose to continue into the open label component.

3. Additional safety data following 8 weeks of anakinra treatment and also at 90 days post last-dose of anakinra for individuals originally prescribed placebo.

4. Longer term safety data on anakinra for individuals originally prescribed anakinra in the double-blind study period.

11. Background and Context

Scientific background:

Psoriasis is a common condition (estimated 2% UK prevalence) that is known to impact on quality of life at a level comparable to other major diseases including chronic heart disease and cancer. Pustular forms of psoriasis are characterised by painful, intensely inflamed, red skin studded by sheets of monomorphic, sterile, neutrophilic pustules. These pustules may be chronic. Pustular psoriasis typically is localised and involves the hands and feet (known as Acral Pustular Psoriasis; APP), though it can also occur more rarely as generalised, episodic and potentially life-threatening (generalised pustular psoriasis; GPP). Some patients may experience both forms throughout their life.

Though pustular psoriasis constitutes less than 10% of all people with psoriasis, it often ranks the highest of all psoriasis phenotypic variants in terms of symptoms (itch, pain, and functional impairment; causing limited mobility and interference with daily living tasks and work). Ultimately, the consequential impact is immense and equivalent to psychiatric illness and other major medical diseases.

Over the past decade significant investment in novel therapies and the advent of biological therapies have revolutionised the treatment and management of plaque-type psoriasis. This has been primarily driven by scientific investigations of underlying genetic and immunological disease pathways. In contrast, the treatment options for pustular psoriasis are currently profoundly limited. Super-potent (topical) corticosteroids, phototherapy, oral treatments (such as acitretin, methotrexate, and ciclosporin), and targeted biologic therapies (notably tumour-necrosis factor antagonists) are all used although evidence for benefit is poor. There is therefore a very significant unmet need in this patient group.

Rationale for study:

Recent evidence indicates that the molecular pathways underlying pustular psoriasis are distinct (from that observed with plaque-type disease) and involve the interleukin IL-36/IL-1 axis. Research has identified functionally relevant *IL36RN* mutations in both Generalised Pustular Psoriasis and

Acral Pustular Psoriasis. *IL36RN* encodes the IL-36 receptor antagonist IL-36Ra (this is an IL-1 family member that antagonises the pro-inflammatory activity of IL-36 cytokines). Disease mutations disrupt the inhibitory function of IL-36Ra causing enhanced production of downstream inflammatory cytokines (including IL-1). Indeed, patients with *IL36RN* mutations have been shown to significantly upregulate IL-1 production in response to IL-36 stimulation. Furthermore, IL-1 is a cytokine that is known to sustain the inflammatory responses initiated by skin keratinocytes.

IL-1 antagonists have previously shown therapeutic benefits in the treatment of IL-1 mediated diseases (many of which feature neutrophilic infiltration of the skin). Furthermore, there has been research that suggests a key pathogenic role for IL-1 in pustular forms of psoriasis.

The model IL-1 antagonist proposed for the study was anakinra. Anakinra is an IL-1 receptor antagonist that is licensed to treat rheumatoid arthritis and, during the timeline of this trial, periodic fever syndromes and Still's disease. Anakinra was selected in preference to other licensed IL-1 antagonists for several reasons. It uniquely blocks the activity of both IL-1a and IL-1ß. Financially, it has the lowest drug acquisition cost (and this is of relevance to the NHS should anakinra show efficacy) and we had access to fully funded trial drug through the manufacturer Swedish Orphan Biovitrum (Sobi™). Anakinra also possesses a rapid onset of action and an established safety profile (with >70,000 patient-years exposure). Furthermore, there is early evidence of therapeutic benefit in patients with pustular psoriasis.

Hypothesis:

We hypothesised that an IL-1 blockade would deliver therapeutic benefits in pustular forms of psoriasis. Therefore, this project aimed to investigate the clinical efficacy of IL-1 blockade in palmoplantar pustulosis (the commonest form of pustular psoriasis) using the model IL-1 antagonist, anakinra, in a randomised, placebo-controlled trial with a two-staged adaptive design, followed by an OLE.

12. Methodology

Study Design:

APRICOT was a phase IV, randomised, double blind, placebo-controlled study with two stages (Stage 1 and Stage 2) and an adaptive element followed by an OLE. Participant data from both stages were included in the main Stage 2 analysis.

Stage 1 compared treatment groups to ensure sufficient efficacy and safety in order to progress to Stage 2. The pre-planned interim analysis for Stage 1 occurred after the randomisation and eight week follow-up of 24 participants. A decision to embark on Stage 2, was made using stop/go efficacy criteria. Fresh pustule counts and PP-PASI scores at eight weeks were compared between treatment groups to assess efficacy. If at the end of Stage 1, the placebo group did as well as, or better than, the treatment group for both of the two outcomes, the study would have stopped. However, because the treatment group did better than the placebo group for at least one outcome, the study proceeded (onto Stage 2).

Furthermore, the primary outcome for Stage 2 was chosen at the end of Stage 1. The two candidate primary outcomes assessed were fresh pustule count (across palms and soles) and the PP-PASI

score. These were recorded at Baseline, and at Weeks: 1, 4, 8 and 12. To determine the efficacy of anakinra for PPP compared to placebo, the primary endpoint for Stage 2 was pre-specified to be the change in disease activity at 8 weeks (adjusted for baseline) measured using fresh pustule count (the default primary outcome) unless PP-PASI was judged more reliable and discriminating.

Stage 2 commenced with the PP-PASI designated as the primary outcome. Stage 2 included the randomisation of a further 40 participants (64 in total).

Randomisation Procedure:

The randomisation service for the study was provided by the King's Clinical Trials Unit (CTU). Following written consent at the Screening Visit, each participant was registered on the MACRO eCRF system (InferMed Macro) which generated a unique patient identification number (PIN). This unique PIN was then recorded on all source data worksheets and used to identify the participants throughout the study.

At the Baseline Visit, randomisation occurred via a bespoke web based randomisation system hosted at the King's CTU (found at: https://cturandomisation.iop.kcl.ac.uk/APRICOT/Login.aspx?ReturnUrl=%2fAPRICOT). Authorised site staff were allocated a username and password for the randomisation system by the Trial Manager. An authorised staff member (typically the Principal Investigator or Research Nurse) logged into the randomisation system and entered in the patient's details, including the unique study PIN.

Once a participant was randomised, the system automatically generated emails to key staff within the study. For example, an email was sent to the respective local site pharmacy to alert them to a participant's treatment arm (either Treatment 1 or Treatment 2). Additional blinded and unblinded emails were generated from the randomisation system to notify key trial site staff (for example the Chief Investigator and Trial Manager) depending on their role in the study.

The randomisation sequence was generated using blocked randomisation, stratified by centre.

Participant pathway (trial procedures):

The participant pathway consisted of four periods: a screening period, a treatment period, a follow up period and an optional OLE.

The overall study flow is detailed in Figure 1, and the detailed visit schedule is listed in Table 1 (Study procedures for the Clinical Trial), Table 2 (Study procedures for the Open Label Extension) and Table 3 (Exploratory Laboratory Tests).

The screening period between the Screening Visit (Visit 0) and Baseline (Visit 1) was a minimum of 5 days, up to a maximum of 3 months and was used to assess eligibility and to taper off prohibited medicines (as part of the washout period for the study). Patients who failed the screening period had the option to be re-screened if clinically appropriate.

The treatment period (Visits 1-4) was 8 weeks. At the start of the treatment period, eligible participants were randomised to receive the intervention (as described above).

The follow up periods (Visits 5 and 6) at Week 12 and 90 days post last treatment date were used to assess disease relapse off study treatment, follow up any adverse events, and plan for post-treatment management of the participants' condition.

If a participant decided to take part in the optional 8 week OLE, there were two possible pathways:

> For participants who decided to take part in the OLE before or at the Week 12 follow up visit (Visit 5): These participants would begin their 8 week OLE period directly after the 12 week follow up (i.e. their OLE Baseline visit could be on the same day as the Week 12 follow up visit). Their final follow-up visit would take place 90 days after their last dose of anakinra.

> For participants who were beyond the Week 20 follow up visit (Visit 6): These participants may have been on another treatment for their PPP when they decided to take part in the OLE. These participants required an OLE Screening Visit, a possible washout period (as per the study protocol) and an OLE Baseline visit arranged once the required washout period was completed. A final follow up visit was then conducted 90 days after the last dose of anakinra.

To achieve the Exploratory objectives (mechanistic studies), all the participants were invited to provide biological samples for use in exploratory laboratory tests. These were bloods samples taken at Visit 0, and then longitudinal blood samples taken at Visits 1, 2, 4 and 5.

In addition, participants were invited to provide skin microbiopsy samples from the skin on the lateral edge of the base their feet or palms prior to treatment initiation at Baseline (Visit 1) and then at Visit 2 (approximately one week later). These samples were used to understand the underlying pathogenesis of pustular psoriasis, the mechanism by which anakinra may work and to identify potential biomarkers of response.

Participant Withdrawal:

Participants had the right to withdraw from the study at any time for any reason. The Principal Investigator also had the right to withdraw participants from the study drug in the event of: inter-current illness, adverse events, serious adverse events, SUSARs, protocol violations, administrative reasons or other pertinent reasons.

Participants had to discontinue the investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

> Withdrawal of informed consent (if the participant decided to withdraw for any reason).

> Any clinical adverse event, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicated that continued participation in the study was not in the best interest of the participant.

> In the Principal Investigator's opinion, the need to administer concomitant medication not permitted by the trial protocol.

> Pregnancy (followed by immediate notification to the Chief Investigator if a study participant became pregnant).

If a participant decided to withdraw from the trial, all efforts were made to report the reason for withdrawal as thoroughly as possible and participants were encouraged to provide follow-up data for the remaining trial visits but at a minimum were asked for outcome data and safety data (adverse event records) at Week 8 and 90 days post last dose follow up. They were also asked whether they were willing to provide trial specific clinical data (i.e outcome measures) and/or samples for mechanistic study as per the remaining trial schedule. All data and samples collected up to the date of withdrawal were retained.

Safety bloods should have been taken as per the trial schedule for all participants, and/or as considered appropriate by the Principal Investigator.

Blinding:

IMP:

Participants, Investigators, co-investigators, research nurses, clinical trial co-ordinators and clinical trial practitioners were blind to the IMP allocation throughout the duration of the trial.

Each randomised participant was provided with a card detailing code break telephone numbers and emergency contact details.

Emergency Code Break services were provided by ESMS Global; a 24-hour cover service. Emergency unblinding could be performed according to strict criteria to support participant safety.

In the event of an Emergency Code Break, ESMS Global was to notify the King's Health Partners Clinical Trials Office (KHP-CTO) of any code break requests received, irrespective of outcome. The KHP-CTO CRA would then inform the Chief Investigator and respective Principal Investigator of the instance of unblinding. This would then be recorded so that the study statistician could be informed at the analysis stage of the trial.

Skin assessments:

The active trial medication is known to cause injection site reactions in the majority of patients. If present during study skin assessments, this could have led to inadvertent unblinding.

Therefore, primary outcome assessments of fresh pustule count and PP-PASI were carried out by an independent assessor blind to study treatment (a member of the study team trained in the assessment protocol but independent to the rest of the trial). At a study visit, they only had sight of the participants' hands and feet (injection site reactions occur at the site of administration which is generally the abdomen / thighs) and were introduced to the participant by the clinical research team as the independent blinded assessor. The independent blinded assessors were also instructed not to speak to the participant in order to maintain blinding.

Once the relevant outcome measures were assessed, the independent blinded assessor was instructed to leave the consulting room and the treating physician or research nurse could then conduct the rest of the study visit (and protocol-mandated procedures).

A second assessment of the PP-PASI score and PPP-IGA was also conducted by the treating physician or research nurse at each study visit.

Wherever possible, the independent blinded assessor for a particular participant was instructed to remain the same throughout the study.

During Stage 1 fresh pustule counts were also assessed by a central, blinded assessor using photography.

Figure 1 Trial flowchart

Table 1: Study procedures for the clinical trial

	Screening	Treatment Period				Follow up	Safety follow up
Allowed visit window: ± 3 days	**Visit 0**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5[6]**	**Visit 6**
		Baseline	(wk 1)	(wk 4)	(wk 8)	(wk 12)	(wk20)
	Study enrolment	Treatment initiation			Treatment end	Study end	
Informed consent	X						
Randomisation		X					
Medical History	X	X					
Physical Examination	X						
Vital Signs	X	X	X	X	X	X	
Fresh Pustule Count [1]	X	X	X	X	X	X	
Total Pustule Count[1]	X	X	X	X	X	X	
PPPASI [1] (x 2)	X	X	X	X	X	X	
PPP – IGA[1] (x 2)	X	X	X	X	X	X	
PASI (plaque psoriasis only)	X	X		X	X	X	
BSA	X	X	X	X	X	X	
Patient Global Assessment	X	X	X	X	X	X	
Palmoplantar Quality of Life Instrument[1]		X			X	X	
DLQI		X			X	X	
EQ5D-3L		X			X	X	
SMS/Text compliance	X	X	X	X	X	X	
Acceptability Questionnaire						X	
Photography		X	X		X		
CXR	X						
TBSpot.TB[4]	X						
HIV, HBV, HCV	X						
Safety bloods [2,3]	X**	X**	X	X	X	X	
bHCG(blood)[5]	X				X	X	
Exploratory laboratory tests – see Table 3	X	X	X		X	X	
Urine analysis (dipstix)	X	X	X	X	X	X	
Prescribing and dispensing trial IMP		X		X			
Concomitant meds	X	X	X	X	X	X	X
AE monitoring		X	X	X	X	X	X

1 Assessed by Independent blinded Assessor following site training. PPPASI and PPP-IGA also assessed by a second assessor
2 Safety bloods comprise FBC, creatinine, electrolytes, LFTs (including AST, ALT)
3 CRP to be collected at baseline (visit 1) only
4 TSPOT.TB not indicated for those participants known to have been successfully treated for TB (completed the prescribed treatment courses) as screening test is not clinically indicated. If unsure please seek specialist advice
5 bHCG not indicated or applicable for post-menopausal women
6 If patient consents to the OLE, then proceed directly to Visit OLE 1 safety procedures section of Table 2 (Study procedures for the Open Label Extension).

****Note:** If the time between screening and baseline safety assessment bloods is >4 weeks (i.e for participants washing out for 3 months from biologic therapy) the participant should be asked to attend for additional safety assessment blood tests. If feasible this should be on the same day as the baseline visit (randomisation) allowing for time to clinically review the results before first treatment dose (in which case only one set of baseline safety assessment bloods should be taken), however if not convenient, should be scheduled within 4 weeks of the baseline visit (these may be taken by their GP). If the participant attends an extra visit for these tests then they should also go on to complete the full baseline visit i.e repeat the baseline safety assessment bloods as scheduled.

Table 2: Study procedures for the Open Label Extension

	Screening*	Treatment Period				Safety Follow up
Allowed visit window: ± 3 days	**Visit OLE 0***	**Visit OLE 1**	**Visit OLE 2**	**Visit OLE 3**	**Visit OLE 4**	**Visit OLE 5**
		Baseline	(wk 1)	(wk 4)	(wk 8)	(wk 20)
		Treatment initiation			Treatment end	Study end
Informed consent	X*					
Eligibility review	X*	X				
Physical Examination	X*					
Check washout period	X*	X				
Vital Signs	X*	X	X	X	X	
Fresh Pustule Count		X			X	
Total Pustule Count		X			X	
PPPASI		X			X	
PPP – IGA		X			X	
PASI (plaque psoriasis only)		X			X	
Safety bloods [1,2]	X*#	X#	X	X	X	
TBSpot.TB[4]	X*					
HIV, HBV, HCV	X*					
bHCG(blood) [3]	X*				X	
Urine analysis (dipstix)	X*	X	X	X	X	
Prescribing and dispensing Anakinra		X				
Concomitant meds	X*	X	X	X	X	X
AE monitoring	X*	X	X	X	X	X

*Only required for patients who have already completed entire APRICOT trial before commencing OLE.
1 Safety bloods comprise FBC, creatinine, electrolytes, LFTs (including AST, ALT).
2 CRP to be collected at OLE baseline (visit OLE 1) only.
3 bHCG not indicated or applicable for post-menopausal women.
4 TSPOT.TB not indicated for those participants known to have been successfully treated for TB (completed the prescribed treatment courses) as screening test is not clinically indicated. If unsure please seek specialist advice.

#Note: If the time between the OLE Screening Visit/last clinical trial visit and OLE baseline safety assessment bloods is >4 weeks, the participant should be asked to attend for additional safety assessment blood tests.

If feasible this should be on the same day as the OLE baseline visit allowing for time to clinically review the results before first anakinra dose (in which case only one set of baseline safety assessment bloods should be taken), however if not convenient, should be scheduled within 4 weeks of the OLE baseline visit (these may be taken by their GP).

If the participant attends an extra visit for these tests then they should also go on to complete the full OLE baseline visit i.e repeat the OLE baseline safety assessment bloods as scheduled.

Table 3: Exploratory Laboratory Tests (applies to the randomised control trial aspect of the study)

	Screening	Treatment period				Follow up	Safety follow up
	Visit 0	**Visit 1**	**Visit 2**	**Visit 3**	**Visit4**	**Visit 5**	**Visit 6**
		Baseline	(wk 1)	(wk 4)	(wk 8)	(wk 12)	(wk20)
	Study enrolment	Treatment initiation			Treatment end	Study end	
DNA [1] (1x10ml)	x						
RNA isolation (1x 3ml) [2]	x	x	x		x	x	
Immune phenotyping (1x25ml)[2]		x					
Plasma (1x5ml)[2]	x	x	x		x	x	
Skin microbiopsy (optional)[2'3] unaffected skin		x					
Skin microbiopsy (optional)[2'3] affected skin		x	x				
Hair plucks (optional) [2]	x	x	x		x	x	

1 DNA sample may be taken at any time point throughout the study, whichever is most convenient
2 Designated sites only
3 Participants are invited to donate up to 3x skin microbiopsy samples. All are optional. 2x microbiopsies at baseline (from affected and unaffected skin) and 1x microbiopsy (affected skin) at Week 1.

13. Number of patients (planned and analysed)

13.1 Planned

64 participants (24 to Stage 1 and 40 to Stage 2).

13.2 Analysed

Recruitment took place between October 2016 and January 2020. A total of 64 eligible participants were enrolled, and 33 were randomly allocated to the placebo arm and 31 to the anakinra arm (Table 4: Number of potentially eligible participants identified by site).

Table 4: Number of potentially eligible participants identified by site

Site name	Number of participants identified	Number randomised/ Number identified	Number of participants randomised (%)
Guy's and St Thomas' NHS Foundation Trust	94	22%	21 (33%)
Salford Royal NHS Foundation Trust	51	14%	7 (11%)
Royal Victoria Infirmary	17	24%	4 (6%)
University Hospital of Wales	40	10%	4 (6%)
Ninewells Hospital & Medical School	11	9%	1 (2%)
Liverpool University Hospitals NHS Foundation Trust	22	23%	5 (8%)
Bradford Teaching Hospitals NHS Foundation Trust	22	5%	1 (2%)
Royal Lancaster Infirmary	1	100%	1 (2%)
Russells Hall Hospital	10	10%	1 (2%)
Bristol Royal Infirmary	18	28%	5 (8%)
Addenbrooke's Hospital	9	0%	0 (0%)
Poole Hospital NHS Foundation Trust University Hospitals Dorset	3	67%	2 (3%)
The Princess Alexandra Hospital NHS Trust	4	0%	0 (0%)
Norfolk and Norwich University Hospitals NHS Foundation Trust	27	15%	4 (6%)
University Hospitals of Derby and Burton NHS Foundation Trust	25	8%	2 (3%)
Royal Devon and Exeter NHS Foundation Trust	2	100%	2 (3%)
Nottingham Circle	4	0%	0 (0%)
Broomfield Hospital	8	25%	2 (3%)
West Glasgow Ambulatory Care Hospital	5	40%	2 (3%)
Queen Margaret Hospital and Victoria Hospital	1	0%	0 (0%)
Total	374	17%	64

Screening data is not consistently recorded across sites. Therefore, the reported total number of patients identified for screening is an underestimate of true number of screened patients.

A total of 6 (18%) placebo and 5 (16%) anakinra participants permanently withdrew from the study treatment over the 8 week treatment period (Table 5: Permanent withdrawals from treatment). Temporary treatment discontinuations were reported for 3 (9%) placebo participants and 6 (19%) anakinra participants.

Only three participants (5%) who withdrew from treatment also withdrew entirely from the study. One participant who withdrew from treatment in the placebo group prior to the end of week one did not attend any further follow-up and was withdrawn from the study due to non-compliance with visit schedule. Two further participants who withdrew from treatment early continued in the trial immediately following treatment cessation, but were later withdrawn post Week 4 prior to Week 8 (n=1 placebo due to loss to follow-up) or at the Week 8 visit prior to Week 12 (n=1 anakinra due to a wish to start other therapies).

The primary analysis included data from all participants who provided primary outcome data from at least one follow-up visit (n=63; n=32 placebo and n=31 anakinra). Sensitivity analysis included all 64 participants.

A total of 14 participants entered the OLE (n=9 placebo and n=5 anakinra).

An additional two consenting participants were randomised in error and never received any treatment and are excluded from all analysis.

Table 5: Permanent withdrawals from treatment

Reason for permanent trial treatment discontinuation	Placebo N=33	Anakinra N=31	Total N=64
Adverse event	1[a] (3%)	4[b] (13%)	5 (8%)
Withdrawal of consent	2 (6%)	1 (3%)	3 (5%)
Lack of response	2 (6%)	0 (0%)	2 (3%)
Condition worsening wants other treatment	1 (3%)	0 (0%)	1 (2%)
Total (n=64)	**6 (18%)**	**5 (16%)**	**11 (17%)**

[a] Adverse events in placebo arm resulting in permanent discontinuation was myalia.
[b] In the anakinra arm three participants stopped due to adverse events of injection site reaction and the fourth stopped due to pustular psoriasis. Data shown as n (%).

14. Diagnosis and main criteria for inclusion

The population designated for the study was patients with palmoplantar pustulosis. This chronic, localised form of pustular psoriasis involves the hands and/or feet, and is associated with significant disability. It is the most common form of pustular psoriasis, making recruitment feasible, and typically features chronic development of pustules so that we would expect to capture any treatment effect within the 8-week treatment period.

All participants were adults (18 years and over) with diagnosis of palmoplantar pustulosis made by a trained dermatologist with disease duration of >6 months and of sufficient impact and severity to require systemic therapy. To be randomised into the study, at the Baseline visit, participants had to exhibit at least moderate disease on the PPP-IGA with evidence of active pustulation on palms and/or soles.

Women who were pregnant, breast feeding or of child bearing age not on adequate contraception or men planning conception were all excluded from taking part in the trial.

The specific inclusion criteria and exclusion criteria for the double-blind, placebo-controlled study and the OLE are detailed below.

Inclusion Criteria for the double-blind, placebo-controlled study:

i. Adults (18 years and over) with diagnosis of PPP made by a trained dermatologist with disease of sufficient impact and severity to require systemic therapy
ii. Disease duration of >6 months, not responding to an adequate trial of topical therapy including very potent corticosteroids
iii. Evidence of active pustulation on palms and /or soles to ensure sufficient baseline disease activity to detect efficacy
iv. At least moderate disease on the PPP Investigator's Global Assessment (PPP-IGA)
v. Women of child bearing potential who are on adequate contraception, who are not pregnant or not breast feeding
vi. Who have given written, informed consent to participate.

Exclusion Criteria for the double-blind, placebo controlled study:

i. Previous treatment with anakinra or other IL-1 antagonists
ii. A history of recurrent bacterial, fungal or viral infections which, in the opinion of the principal investigator, present a risk to the patient
iii. Evidence of active infection or latent TB or who are HIV, Hepatitis B or C sero-positive
iv. A history of malignancy of any organ system (other than treated, localised non-melanoma skin cancer), treated or untreated, within the past 5 years
v. Use of therapies with potential or known efficacy in psoriasis during or within the following specified timeframe before treatment initiation (week 0, visit 1):
    a. very potent topical corticosteroids within 2 weeks
    b. topical treatment that is likely to impact signs and symptoms of psoriasis (e.g. corticosteroids, vitamin D analogues, calcineurin inhibitors, retinoids, keratolytics, tar, urea) within 2 weeks
    c. methotrexate, ciclosporin, acitretin, alitretinoin within 4 weeks
    d. phototherapy or PUVA within 4 weeks
    e. etanercept or adalimumab within 4 weeks
    f. infliximab or ustekinumab or secukinumab within 3 months
    g. other TNF antagonists within 3 months
    h. other immunosuppressive or immunomodulatory therapy within 30 days or 5 half-lives prior to treatment initiation, whichever is longer

i. any other investigational drugs within 30 days (or 3 months for investigational monoclonal antibodies) or 5 half-lives prior to treatment initiation, whichever is longer

vi. With moderate renal impairment [CrCl <50ml/min]

vii. With neutropenia (<1.5x10^9/L)

viii. With thrombocytopenia (<150x10^9/L)

ix. 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.

x. Live vaccinations within 3 months prior to the start of study medication, during the trial, and up to 3 months following the last dose

xi. Women who are pregnant, breast feeding or of child bearing age not on adequate contraception or men planning conception

xii. Poorly controlled diabetes mellitus, cardiovascular disease, asthma, concomitant therapy that may interact with anakinra (for example phenytoin or warfarin) or any condition where, in the opinion of the investigator, anakinra would present risk to the patient.

xiii. Unable to give written, informed consent.

xiv. Unable to comply with the study visit schedule

xv. Diagnosis (or historic diagnosis) of either childhood or adult onset Still's disease.

Inclusion Criteria for the Open Label Extension:

i. Participation in the double-blind placebo controlled study.

ii. Completion past Visit 4 (Week 8) of the double-blind placebo controlled study.

iii. Women of child bearing potential who are on adequate contraception, who are not pregnant or not breast feeding

iv. Who have given written, informed consent to participate.

Exclusion Criteria for the Open Label Extension:

i. A history of recurrent bacterial, fungal or viral infections which, in the opinion of the principal investigator, present a risk to the patient

ii. Evidence of active infection or latent TB or who are HIV, Hepatitis B or C sero-positive (only required for patients who are beyond Visit 5 the double-blind treatment stage, placebo controlled study).

iii. A history of malignancy of any organ system (other than treated, localised non-melanoma skin cancer), treated or untreated, within the past 5 years

iv. Use of therapies with potential or known efficacy in psoriasis during or within the following specified timeframe before treatment initiation (Visit OLE 1):

    a. methotrexate, ciclosporin, acitretin, alitretinoin within 4 weeks

    b. phototherapy or PUVA within 4 weeks

    c. etanercept or adalimumab within 4 weeks

    d. infliximab or ustekinumab or secukinumab within 3 months

    e. other TNF antagonists within 3 months

    f. other immunosuppressive or immunomodulatory therapy within 30 days or 5 half-lives prior to treatment initiation, whichever is longer

    g. any other investigational drugs within 30 days (or 3 months for investigational monoclonal antibodies) or 5 half-lives prior to treatment initiation, whichever is longer

v. With moderate renal impairment [CrCl <50ml/min]

vi. With neutropenia ($<1.5x10^9$/L)

vii. With thrombocytopenia ($<150x10^9$/L)

viii. 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.

ix. Live vaccinations within 3 months prior to the start of study medication, during the trial, and up to 3 months following the last dose

x. Women who are pregnant, breast feeding or of child bearing age not on adequate contraception or men planning conception

xi. Poorly controlled diabetes mellitus, cardiovascular disease, asthma, concomitant therapy that may interact with anakinra (for example phenytoin or warfarin) or any condition where, in the opinion of the investigator, anakinra would present risk to the patient.

xii. Unable to give written, informed consent.

xiii. Unable to comply with the study visit schedule

xiv. Has been previously invited to have the OLE therapy and the patient declined during that instance.

xv. Diagnosis (or historic diagnosis) of either childhood or adult onset Still's disease.

15. Test product, dose and mode of administration and duration of treatment

Interventions:

Participants were randomised (1:1) to receive (100mg/day) either anakinra or placebo for 8 weeks which was administered daily as a self-administered sub-cutaneous injection.

For participants who opted to take part in the OLE, they received a further 8 weeks of anakinra (100mg/day) treatment which was administered daily as a self-administered sub-cutaneous injection. The OLE was optional, and offered to all participants who completed the 8 week treatment period and the 12 week follow up visit.

Topical therapy:

Emollient therapy was permitted throughout the trial.

For injection sites:

To treat the common side effect of injection site reactions the use of topical mild corticosteroid (e.g.: hydrocortisone up to 2.5%) or anti-histamine cream/ointment could be used.

For plaque psoriasis:

Use of emollients was recommended as the first line intervention but mild – moderate topical corticosteroids were permitted as second line for plaques at sites other than the hands and feet at the discretion of the investigator. Gloves should have been worn for application.

For PPP:

Rescue therapy:

During the initial double-blind treatment stage, Investigator-directed "Rescue" medication in the form of potent corticosteroid (eg: mometasone furoate, betamethasone valerate ointment or cream) once daily to affected areas of PPP could be dispensed if necessary, to provide substantial symptomatic relief. Rescue medication could be prescribed as part of normal clinical care, and the volume prescribed recorded at study visits to evaluate any potential confounding effect of topical corticosteroid use. Table 6 (Summary of Concomitant therapy rules for the initial double-blind treatment stage) lists the concomitant medication rules that were used for the initial double-blind treatment element of the study.

Systemic therapy:

Any concomitant treatments for other indications that are not listed in the prohibited medication section should have been at a stable dose for at least 4 weeks before the first study treatment administration. Dose adjustments of these treatments should have been avoided during the study.

Prohibited medication for the initial double-blind treatment stage:

Any therapy likely to have efficacy in PPP or psoriasis or to compound the potential immunosuppressive effects of anakinra was prohibited and stipulated wash out periods should have been adhered to. If treatment with any of the prohibited treatments was essential then the patient should have notified the study team and they should have been withdrawn from the trial.

Table 6: Summary of Concomitant therapy rules for the initial double-blind treatment stage

Prohibited	Very potent topical corticosteroids (eg: Dermovate) Any topical treatment that is likely to impact signs and symptoms of PPP (e.g. corticosteroids, vitamin D analogues, calcineurin inhibitors, retinoids, keratolytics, tar, urea) Phototherapy or PUVA Methotrexate, Cyclosporine, Acitretin, Alitretinoin, FAE Etanercept or Adalimumab Infliximab or Ustekinumab or Secukinumab Other TNF antagonists Other systemic immunosuppressive therapy Other investigational monoclonal antibody Other investigational drugs
Allowable topical therapy	Emollients. Topical hydrocortisone, antihistamine for injection – site reactions Mild topical corticosteroids for the treatment of psoriasis at sites other than hands and feet, applied with gloves.
Allowable therapy	Oral antihistamine for injection - site reactions
“Rescue” topical therapy	Potent corticosteroid od. To be dispensed only by the study team, at the Investigator’s discretion. Amounts prescribed to be recorded.

Prohibited medication for the OLE:

Stipulated wash out periods should have been adhered to. Concomitant topical treatment (only) was allowed only during the OLE stage. If treatment with any of the prohibited systemic treatments (as indicated in Table 7: Summary of concomitant therapy rules for the OLE) was essential then the patient should have notified the study team and they should have been withdrawn from the trial and anakinra should have been discontinued.

Table 7: Summary of concomitant therapy rules for the OLE

Prohibited	Phototherapy or PUVA Methotrexate, Cyclosporine, Acitretin, Alitretinoin, FAE Etanercept or Adalimumab Infliximab or Ustekinumab or Secukinumab Other TNF antagonists Other systemic immunosuppressive therapy Other investigational monoclonal antibody Other investigational drugs
Allowable topical therapy	Emollients. Topical hydrocortisone, antihistamine for injection – site reactions Mild topical corticosteroids for the treatment of psoriasis at sites other than hands and feet, applied with gloves. Very potent topical corticosteroids (eg: Dermovate) These topical treatments: corticosteroids, vitamin D analogues, calcineurin inhibitors, retinoids, keratolytics, tar, urea.
Allowable therapy	Oral antihistamine for injection - site reactions

16. Criteria for evaluation: Endpoints

16.1 Efficacy

The primary endpoint was change in disease activity at 8 weeks, adjusted for baseline, measured using PP-PASI.

Secondary objectives were to evaluate whether anakinra improves disease severity as assessed by other investigator assessed efficacy outcomes (total pustule counts, PPP-IGA, percentage total body area involvement with pustular psoriasis at non-acral sites), participant-reported measures of efficacy and quality of life and safety measures.

16.2 Safety

Safety measures included monitoring serious infection, neutropenia, serious adverse events and reactions, adverse events and reactions at each visit and throughout the study duration for each participant (up to 90 days after their last dose of trial medication).

Stage 1 compared treatment groups to ensure sufficient efficacy and safety in order to progress to Stage 2. The pre-planned interim analysis for Stage 1 occurred after the randomisation and eight week follow-up of 24 participants. A decision to embark on Stage 2, was made using stop/go efficacy criteria. Fresh pustule counts and PP-PASI scores at eight weeks were compared between treatment groups to assess efficacy.

If at the end of Stage 1, the placebo group did as well as, or better than, the treatment group for both of the two outcomes, the study would have stopped. However, because the treatment group did better than the placebo group for at least one outcome, the study proceeded (onto Stage 2).

17. Statistical Methods

Analysis of Efficacy Variables

The overall sample size was established using a standardised effect size as calculated prior to the completion of Stage 1 of the study when the primary outcome of the main trial analysis was unknown. A large effect size of 0.9 Standard Deviations (SDs) was selected to be the minimum important difference to detect due to the cost of the drug and high patient burden daily self-administered subcutaneous injection treatment. To detect a difference of 0.9 SD with power 90% and 5% significance level, with a conservative allowance for a 15% withdrawal rate, a sample size of 32 per group (N=64 in total) was required. The observed SD for the baseline PP-PASI in APRICOT (n=64) was 10.5; therefore 0.9SD was approximately a change of 9.5 in the PP-PASI.

General statistical principles:

Analysis was conducted subgroup blind (i.e. as group A versus group B) in accordance with the APRICOT statistical analysis plans which were finalized prior to database lock. The main analysis was based on the intention-to-treat (ITT) principle, that is, all participants with at least one follow-up were analysed in the group to which they were randomised regardless of subsequent treatment received. The use of a longitudinal model for the primary analysis means a minimal number of participants would be excluded. Every effort was made to obtain all follow up data for all participants, including those that stopped treatment.

The safety set (SS) population consisted of all participants who received at least one dose of the assigned IMP intervention and was used in the analysis to describe adverse events.

All regression analyses included adjustment for centre, as this was a stratification factor in the randomisation. The inclusion of this adjustment was necessary in the analysis to maintain the correct type I error rate.

Estimates are presented with 95% confidence and p-values. A p-value < 0.05 was interpreted as statistically significant for the primary outcome. All analyses were conducted using Stata version 15.1.

Stage 1 analysis:

At the end of Stage 1, the baseline adjusted mean treatment group difference in the fresh pustule count and PP-PASI score, averaged across follow-up visits, was calculated using a linear regression model. These results informed the decision to progress to Stage 2. The trial continued to Stage 2 if the treatment group did, on average, better than placebo for at least one measure. The primary outcome for Stage 2 was selected based on an assessment of reliability and distributional properties for two candidate outcomes; the fresh pustule count and the PP-PASI. Reliability of the fresh pustule

count was assessed by examining the agreement between the assessments made at site and those assessed centrally based on photographs. Agreement was formally assessed using the method of Bland and Altman and the Intraclass Correlation Coefficient (ICC), calculated using a mixed effect ANOVA with a random intercept for patient and rater. The closer the ICC value is to one the better level of consistency. Reliability of the PP-PASI was assessed by examining the agreement between assessments made at site by two independent assessors using the same methods outlined above. Distribution properties for each candidate outcome was assessed using standardised mean differences, and histograms by treatment group.

Stage 2 analysis:

A Consolidated Standards of Reporting Trials (CONSORT) flow chart was constructed to summarise the participant flow through the study. Baseline characteristics were summarised by randomised arm to examine balance between the arms at Baseline. Treatment adherence, reasons for withdrawal and use of rescue medication, prohibited therapy and other topical were summarised by treatment arm. All primary and secondary outcomes were also summarised by time point and treatment arm. Continuous variables were summarised using mean (SD) where approximately normally distributed and median (IQR) where skewed. Categorical variables were summarised and frequency and percentage.

The primary analysis was based on the ITT principle and estimated the effect of the treatment policy. A linear (Gaussian) mixed effect model including PP-PASI data from Week 1, Week 4, and Week 8 was utilised to obtain an estimate of the mean treatment group difference in PP-PASI at Week 8. The model included random intercepts for participant and centre and fixed effects for study visit, treatment arm, study visit by treatment arm interaction and Baseline PP-PASI. An unstructured covariance matrix was used to model the covariance structure as it allows for all variances and covariances to be distinct, and the model was fitted with REML. The mean difference in the Week 8 PP-PASI, adjusted for baseline, between the two treatment groups formed the focal point of the primary outcome analysis. The main conclusion of the trial was therefore based on this (Week 8) analysis time point. However, treatment effects at Week 1 and Week 4 were also calculated and reported.

In accordance with the ITT principle, all participants who provided data from at least one follow-up visit (at 1, 4 or 8 weeks) were included in the primary analysis model as randomised. All missing response values were assumed to be missing at random (MAR) (i.e. the probability that the response is missing does not depend on the value of the response after allowing for the observed variables).

Pre-planned sensitivity analysis was performed to explore the impact of departures from the main MAR analysis assumption and potential missing not at random (MNAR) mechanisms on the trial results using Multiple Imputation (MI) and a pattern mixture approach.

Four pre-planned supplementary analyses targeted alternative treatment estimands for the trial's primary outcome. These included:

> Supplementary analysis which estimated the treatment effect if rescue therapy was not available: data post initiation of rescue therapy was set missing and MI was used to explore the impact of a worse outcome post initiation on rescue therapy on trial results. The primary analysis model was retained for use in the, following MI.

> Supplementary analysis which estimated the treatment effect if rescue therapy and prohibited therapy was not available: data post initiation of rescue therapy and prohibited medication was set missing and MI was used to explore the impact of a worse outcome post initiation on rescue therapy on trial results. The primary analysis model was retained for use in the analysis, following MI.

> Supplementary analysis which estimated the treatment effect if all topical therapy was not available: data during use of topical therapy was set missing and MI was used to explore the impact of observing on-treatment behaviour (MAR) in the absence on topical therapy on trial results. The primary analysis model was retained for use in the analysis, following MI.

> Supplementary analysis to estimate the complier average causal effect (CACE): The CACE preserves the benefits of randomisation and compares the average outcome of the compliers in the treatment arm with the average outcome of the comparable group of 'would-be compliers' in the placebo arm. To identify the CACE it is assumed that (i) members of the placebo group have the same probability of noncompliance as members of the intervention group and (ii) being offered the treatment i.e. randomisation itself has no effect on outcome. We estimated the complier average causal effect (CACE) using a two-stage least squares instrumental variable regression for the primary endpoint. Here, we initially defined a 'complier' as those who completed more than 50% of the total planned injections (at any time point). Randomisation was used as an instrumental variable for treatment received, with adjustment for baseline PP-PASI (excluding centre from the analysis). We also calculated the CACE where a complier was alternatively defined as receiving 60-90% of the total planned injections.

Secondary outcome statistical analysis:

Continuous secondary outcomes were analysed using the same modelling approach as specified above for the primary outcome. Binary outcomes were analysed using mixed logistic regression models and ordered categorical outcomes using mixed ordered logistic models. Similar to the primary analysis model, the models for secondary outcomes included participant and centre as a random intercept and fixed effects for time, time-by-treatment group interaction and baseline value of the outcome.

Kaplan Meier curves were plotted for time to response and time to relapse outcomes. As outcomes were observed at a relatively few discrete time intervals (Weeks: 4, 8 and 12) complementary log-log models, were fitted to estimate the treatment effect for the time to event outcomes, as this is an analysis model suitable for discrete survival time data. The time to event models included a fixed effect for treatment arm and a random intercept for centre (stratification variable).

Exploratory analysis:

A longitudinal analysis was undertaken using a linear (Gaussian) mixed model to determine the treatment difference in PP-PASI at 12 weeks. The analysis model was the same as in the primary analysis but included additional data at 12 weeks. The treatment effect for PP-PASI at 12 weeks was estimated and reported with a 95% confidence interval. Since it was hypothesised that palmar disease may respond more quickly to plantar disease pre-planned exploratory analysis separately estimated the efficacy of anakinra on the (i) disease activity at 8 weeks, measured using fresh pustule count on the palms, adjusted for baseline, compared to placebo and (ii) disease activity at 8 weeks, measured using fresh pustule count on the soles, adjusted for baseline, compared to placebo. For each of the palms and soles fresh pustule count a linear mixed effects model was used,

which included fixed effects for treatment group, time (Week 1, Week 4 and Week 8), treatment group by time interaction, and baseline value of the associated outcome. A random intercept for participant and centre was also included in each of the models.

Post-hoc analysis:

The treatment group difference in PPPASI50 and PPPASI75 at Week 8 was assessed using a mixed logistic binary model which included centre as a random intercept and fixed effects for treatment group and Baseline PP-PASI value. We also examined the treatment group difference in the PP-PASI pustule subscale at Week 8, separately for palms and soles, using a mixed ordered logistic model that included participant and centre as a random intercept and fixed effects for time, time-by-treatment group interaction and Baseline PP-PASI pustule subscale. For each participant and region (palm or sole), the maximum severity pustule rating across the left or right component of the region was utilised in analysis.

Mechanistic samples:

Genetic analyses including: whole-exome sequencing, bulk RNA-sequencing, pathway enrichment analyses and upstream regulator analysis, was used on mechanistic samples obtained during the trial to investigate the pathogenic involvement of IL-1 in PPP

OLE analysis:

The number of participants who entered the OLE were summarised by original randomised treatment arm. Baseline characteristics of all participants in the original double-blind period were descriptively compared against those of the participants entering the OLE period.

In the OLE, some participants continued their medication (some following a 4 week break and some with a longer break) and some participants started the medication for the first time. Because of this, it was not possible to undertake a randomised comparison for this extended follow-up period. Therefore, this was treated as an observational intervention period.

For the population of participants that continued into the OLE stage, descriptive statistics were presented for the open label outcomes recorded at the OLE Baseline visit and 8 weeks after OLE treatment initiation (fresh pustule count, total pustule count, PP-PASI, PPP-IGA, clearance on PPP-IGA, and PASI) by original randomised treatment.

The 8-week outcomes of the participants originally randomised to the active arm from the double-blind part of the trial were combined with the 8-week outcomes of participants originally randomised to the placebo arm from the OLE to form a first-time exposure group. Descriptive statistics were presented for the first-time exposure group.

No statistical testing was performed given the open-label study design and how some participants commenced OLE anakinra treatment immediately following the Week 12 visit (of the randomised

double-blind placebo-controlled study), whilst others had previously completed the full double-blind trial schedule.

Analysis of Safety Variables

Data concerning adverse events was collected during study visits from reports from testimony from study participants, clinical observations, clinical examinations and blood tests.

Local clinicians rated the relationship to the study medication (as either: none/unlikely/possible/likely/definite) for each adverse event. From this classification, Adverse Reactions were the subset of non-serious adverse events rated to have a possible/likely/definite relationship with the study medication. Serious Adverse Reactions (SAR) consisted of the subset of serious adverse events (SAE) rated to have either a possible/likely/definite relationship with the study medication. Furthermore, if the event was considered related to the study IMP, then local clinicians would also rate whether the reaction was unexpected.

All Adverse Events were coded using terms referencing the Medical Dictionary for Regulatory Activities (MedDRA) at the, 'Preferred Terms,' level. These were also summarised by MedDRA system organ class and intensity (when subjectively assessed by local clinicians as mild/moderate/severe).

Adverse events were tabulated by treatment group for both the number of events and the number of participants with the type of event. Adverse events were also listed individually by MedDRA preferred term level and intensity (subjectively assessed by local clinical investigators as mild/moderate/severe) and summarised by MedDRA system organ class level. To identify the events with the strongest evidence for between arm differences a volcano plot, which plots the risk difference of the non-serious adverse events and reactions by MedDRA system organ class between the treatment arms against the p-value from a Fishers' exact test, was constructed. To further aid interpretation adverse events were also summarised visually in a Dot plot, which displays the proportions of individuals experiencing each type of event by arm and the relative difference with 95% CI. The number of events related to an infection were also tabulated.

Adverse events were recorded for all participants in the OLE right up until the final follow-up visit.

18. Summary – Conclusions

18.1 Demographic data

Table 8 (Selected Baseline characteristics) summarises the demographics of the study (N=64).

Table 8: Baseline characteristics

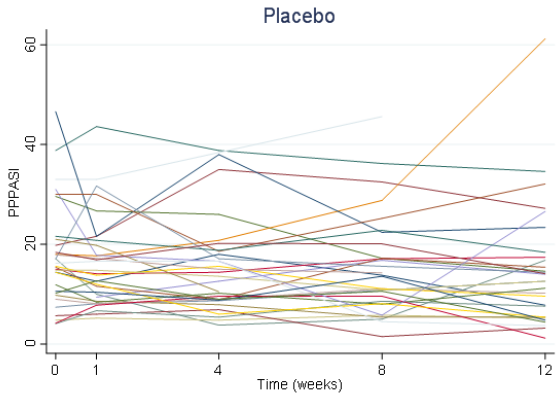
Baseline demographic		Placebo (N=33)		Anakinra (N=31)		Total (N=64)	
Age (years)	Mean, SD	51.7	13.6	49.9	11.9	50.8	12.7
Sex (n, %)	Male	6	18%	4	13%	10	16%
	Female	27	82%	27	87%	54	84%
Ethnicity (n, %)	White	31	94%	28	90%	59	92%
	Asian/Asian British	1	3%	1	3%	2	3%
	Black/Black British	0	0%	1	3%	1	2%
	Chinese/Japanese/ Korean/ Indochinese	0	0%	1	3%	1	2%
	Other	1	3%	0	0%	1	2%
Smoker (n, %)	Current smoker	19	58%	16	52%	35	55%
	Ex-smoker	9	27%	12	39%	21	33%
	Non-smoker	5	15%	3	10%	8	13%

Note: All patients received at least one dose of study treatment.

18.2 Primary outcome

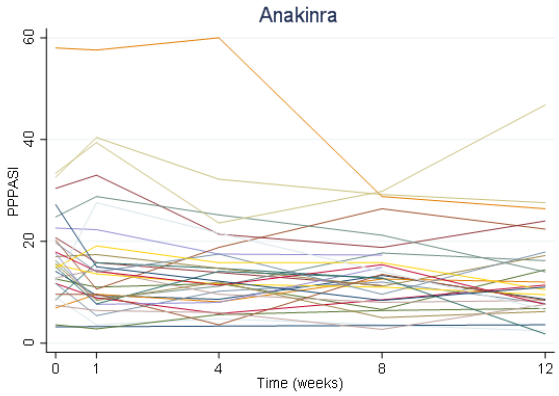
Figure 2 (Placebo participant PP-PASI profiles over time) and Figure 3 (Anakinra participant PP-PASI profiles over time) display the individual participant PP-PASI profiles over time by treatment group. Figure 4 (PP-PASI over 12 week follow-up period) and Table 9 (PP-PASI over time by treatment group) summarises the mean PP-PASI outcome by time point and treatment group, with unadjusted mean treatment group differences. In both treatment groups the mean PP-PASI was lower at Week 8 relative to Baseline indicating improvement. The unadjusted mean difference in PP-PASI between the treatment groups at Week 8 for anakinra versus placebo was -1.4, 95% CI (-6.0, 3.2), where the point estimate was in favour of anakinra.

Figure 2: Placebo participant PP-PASI profiles over time



The raw PP-PASI values for each participant are plotted on the y-axis against the time point on the x-axis.

Figure 3: Anakinra participant PP-PASI profiles over time

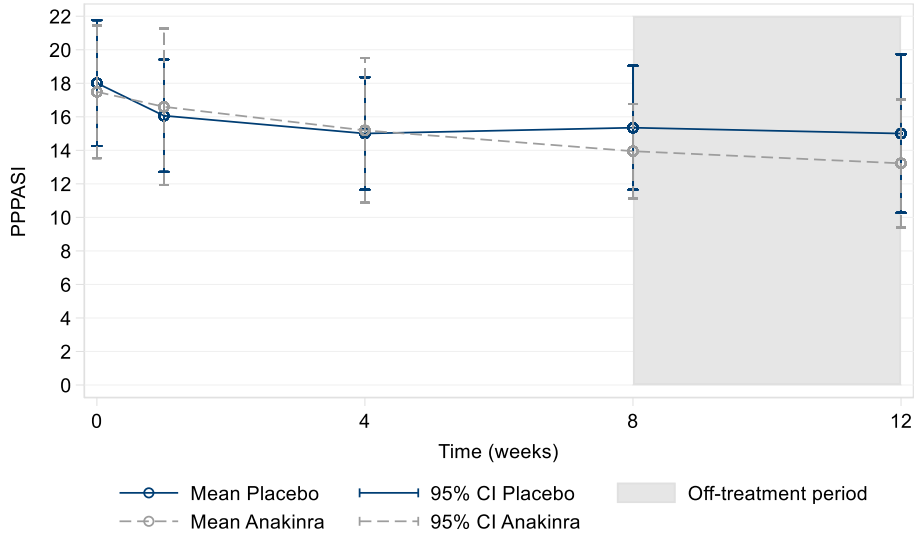


The raw PP-PASI values for each participant are plotted on the y-axis against the time point on the x-axis.

Table 9: PP-PASI over time by treatment group

Time	Treatment Group						Total N	Unadjusted Mean Difference [Anakinra-Placebo] (95% CI)
	Placebo (N=33)			Anakinra (N=31)				
	N	Mean	SD	N	Mean	SD		
Baseline	32	18.0	10.4	31	17.5	10.8	63	-
Week 1	31	16.1	9.1	30	16.6	12.5	61	0.5 (-5.1, 6.1)
Week 4	31	15.0	9.1	28	15.2	11.1	59	0.2 (-5.1, 5.5)
Week 8	31	15.4	10.1	29	13.9	7.4	60	-1.4 (-6.0, 3.2)
Week 12	29	15.0	12.4	27	13.2	9.7	56	-1.8 (-7.8, 4.2)

Figure 4: PP-PASI over 12 week follow-up period



The unadjusted mean PP-PASI is plotted on the y-axis, against the time point on the x-axis for each treatment group. The error bars represent 95% CI's for the unadjusted treatment group means.

18.3 Safety results

Table 10 (Summary of safety events by type and treatment group) summarises the types of adverse events by treatment group during the double-blind, placebo controlled study across all randomised participants (n=64, all received at least one dose of trial treatment). Figure 5 (Adverse events and reactions by MedDRA organ system class) and Figure 6 (Volcano plot of adverse events and Reactions by MedDRA organ system class) summarises the non-serious adverse events by MedDRA system organ class.

Table 10: Summary of safety events by type and treatment group

Event	Treatment Group				Total	
	Placebo		Anakinra			
	Number of Participants	Number of Events	Number of Participants	Number of Events	Number of Participants	Number of Events
Total Non-serious AE	**26**	**84**	**29**	**114**	**55**	**198**
AE	24	52	24	66	48	118
AR	10	30	26	48	36	78
UAR (subset of AR)	2	3‡	2	2¥	4	5
Unclassifiable†	1	2	0	0	1	2
Total Serious AE	**0**	**0**	**0**	**0**	**0**	**0**
SAE	0	0	0	0	0	0
SAR	0	0	0	0	0	0
SUSAR (subset of SAR)	0	0	0	0	0	0
Total	**26**	**84**	**29**	**114**	**55**	**198**

†Relatedness to IMP not available. ‡(i) Cellulitis, (ii) C-reactive protein increased and (iii) Nausea. ¥(i) Injection site reaction, (ii) Nasopharyngitis.

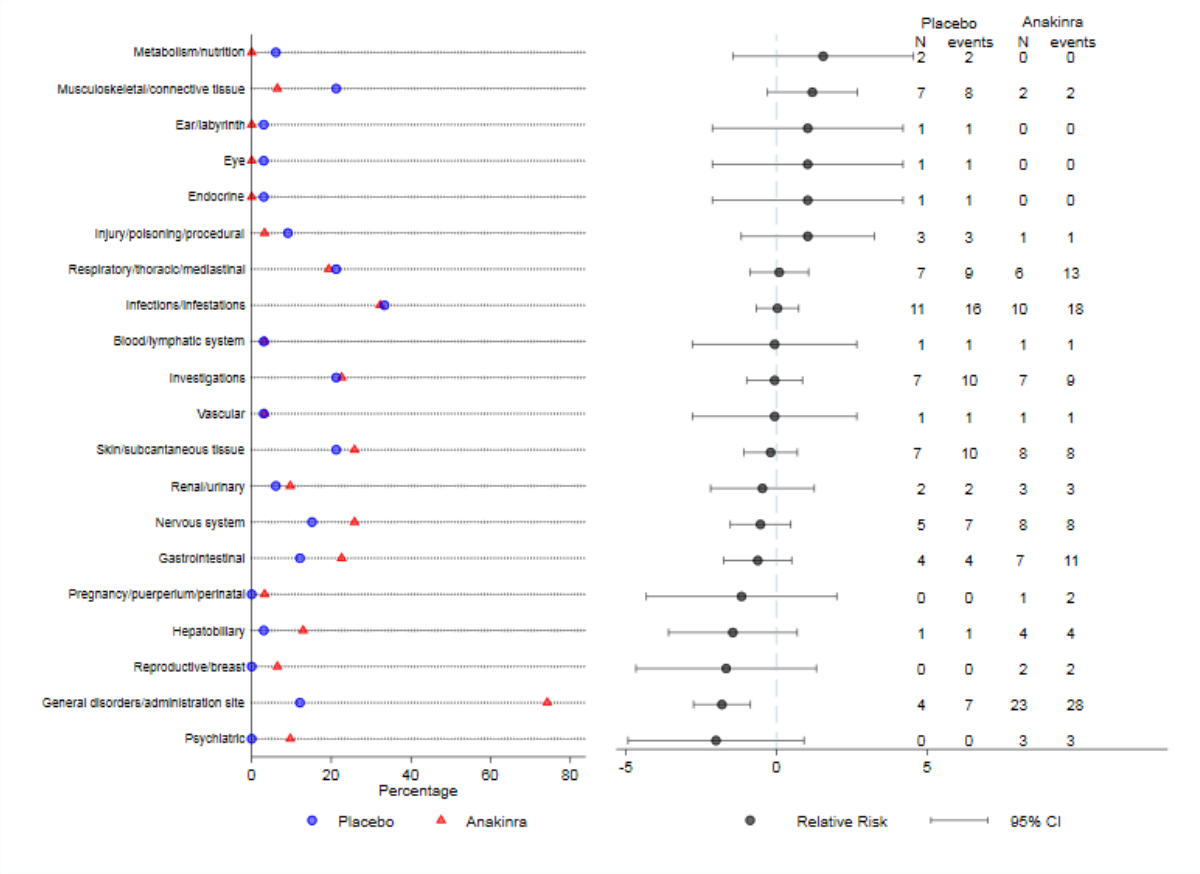
Serious infection and neutropenia
No participants experienced a serious infection, 0/33 (0%) placebo versus 0/31 (0%) anakinra. Similarly, no participants experienced neutropenia (neutrophil count <1.0 x10^9 /L), 0/33 (0%) placebo versus 0/31 (0%) anakinra.

Pregnancy
There was 1 unplanned pregnancy in a patient who was on the trial (despite following the protocol regarding contraception). They had a positive pregnancy test at their Week 8 visit of the study. The baby was born healthy at full term.

Death
There were no participant deaths during the study.

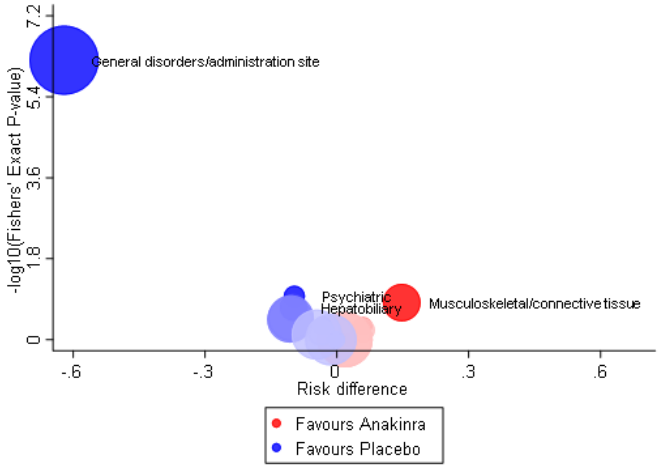
MedDRA dictionary
MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology developed under the auspices of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). MedDRA® trademark is registered by IFPMA on behalf of ICH.

Figure 5: Adverse events and reactions by MedDRA organ system class



This figure plots displays the proportions of individuals experiencing each type of event by treatment arm in the lhs panel, the relative treatment group difference expressed as relative risk with 95% CI in the middle panel and numbers of participants experiencing each event and event totals in rhs panel.

Figure 6: Volcano plot of adverse events and Reactions by MedDRA organ system class



In the volcano plot, the x-axis represents the difference in proportions of patients experiencing each category of adverse event between the treatment arms (placebo– anakinra). Risk difference <0 favour placebo. The y-axis represents the p-value from a Fishers exact test on a negative log scale, smaller p-values are situated higher up the y-axis. The centre of each circle indicates the coordinates for a particular category of adverse events and the size of the circle is proportion to the total number of events for both treatment arms combined. Adverse event categories have been labelled where p<0.2.

Within the per protocol population (n= 64), a total of 198 AEs, including 0 SAE, were identified as treatment-emergent and included in the safety analysis. Summary tables for AEs and SAEs are presented in the appendix of this synopsis.

Overall, 55 patients (86%) patients experienced at least one AE. The proportion that experienced at least one SAE was 0% (n=0).

Incidence of adverse drug reactions (ADRs):

78/198 AEs (40 %) were assessed as related to at least one study drug and 36/64 patients (56%) experienced 78 ADRs.

There were 0 Serious Adverse Reactions (SARs), 0 unexpected SARs and 0 SUSARs.

Open Label Extension (OLE):

A total of 14/64 (22%) participants entered the optional OLE including 9 placebo and 5 anakinra participants.

A total of 26 non-serious adverse events were recorded over the OLE.

18.4 Conclusion

There was no evidence that an eight week treatment policy with anakinra is effective in PPP. For the treatment of PPP IL-1 blockade is not a useful intervention.

21. Date of Report

This is version 1.0 of the Clinical Study Report synopsis, dated 20-SEP-2021.

APPENDICES

i) Summary of treatment-emergent AEs in the per protocol population

Adverse Events listing

Table 11: Adverse events and reactions at preferred term by treatment group.

AE term	Placebo Group N events	Anakinra Group N events	Total N events	Placebo Group N partic.	Anakinra Group N partic.	Total N partic.
Abdominal discomfort	1	0	1	1	0	1
Abdominal pain lower	0	1	1	0	1	1
Arthralgia	2	1	3	2	1	3
Back injury	1	0	1	1	0	1
Biopsy skin	0	1	1	0	1	1
Blood creatinine increased	1	0	1	1	0	1
Blood pressure increased	0	1	1	0	1	1
C-reactive protein increased	1	1	2	1	1	2
Catarrh	1	0	1	1	0	1
Cellulitis	1	0	1	1	0	1
Constipation	0	1	1	0	1	1
Contusion	2	1	3	2	1	3
Cough	2	5	7	2	4	6
Cystitis	1	0	1	1	0	1
DNA antibody positive	1	0	1	1	0	1
Decreased appetite	1	0	1	1	0	1
Depressed mood	0	3	3	0	3	3

Dermatitis	1	0	1	1	0	1
Diabetes mellitus	1	0	1	1	0	1
Diarrhoea	0	5	5	0	5	5
Dizziness	0	1	1	0	1	1
Ear pain	1	0	1	1	0	1
Eosinophilia	0	1	1	0	1	1
Epistaxis	2	0	2	1	0	1
Flushing	1	0	1	1	0	1
Folliculitis	1	2	3	1	1	2
Gestational diabetes	0	1	1	0	1	1
Glomerular filtration rate decreased	1	0	1	1	0	1
Glucose urine present	1	0	1	1	0	1
Haematuria	1	2	3	1	2	3
Head injury	0	1	1	0	1	1
Headache	4	6	10	2	6	8
Hepatitis B antibody positive	0	1	1	0	1	1
Hepatotoxicity	1	4	5	1	4	5
Hyperkalaemia	1	0	1	1	0	1
Hypertension	0	1	1	0	1	1
Influenza	1	0	1	1	0	1
Influenza like illness	1	0	1	1	0	1
Injection site discomfort	0	1	1	0	1	1
Injection site erythema	1	2	3	1	2	3
Injection site pain	0	1	1	0	1	1
Injection site pruritus	1	0	1	1	0	1
Injection site rash	0	1	1	0	1	1
Injection site reaction	1	20	21	1	19	20
Injection site swelling	1	2	3	1	2	3
Lethargy	1	0	1	1	0	1
Lower respiratory tract infection	3	3	6	3	3	6
Lymphadenopathy	1	0	1	1	0	1
Malaise	2	0	2	1	0	1
Mean cell volume increased	1	0	1	1	0	1
Menorrhagia	0	1	1	0	1	1
Metrorrhagia	0	1	1	0	1	1

Migraine	2	0	2	2	0	2
Monocyte count increased	1	0	1	1	0	1
Myalgia	1	0	1	1	0	1
Nasopharyngitis	3	5	8	3	4	7
Nausea	2	2	4	2	2	4
Neuralgia	0	1	1	0	1	1
Neutrophil count increased	0	1	1	0	1	1
Oedema peripheral	0	1	1	0	1	1
Oropharyngeal pain	1	3	4	1	3	4
Osteoporosis	1	0	1	1	0	1
Pain in extremity	1	1	2	1	1	2
Pain of skin	0	1	1	0	1	1
Pharyngeal oedema	1	0	1	1	0	1
Post procedural infection	1	0	1	1	0	1
Pregnancy	0	1	1	0	1	1
Proteinuria	0	1	1	0	1	1
Pruritus	0	1	1	0	1	1
Psoriasis	2	3	5	2	3	5
Psoriatic arthropathy	1	0	1	1	0	1
Pustular psoriasis	2	2	4	2	2	4
Pyuria	0	1	1	0	1	1
Rash macular	1	0	1	1	0	1
Rash papular	1	0	1	1	0	1
Rhinitis	1	1	2	1	1	2
Rhinitis allergic	0	1	1	0	1	1
Rhinorrhoea	0	1	1	0	1	1
Sinusitis	1	2	3	1	2	3
Skin infection	2	1	3	2	1	3
Skin irritation	1	0	1	1	0	1
Skin lesion	1	0	1	1	0	1
Synovial cyst	1	0	1	1	0	1
Synovitis	1	0	1	1	0	1
Tonsillitis	0	1	1	0	1	1
Toothache	1	0	1	1	0	1
Transaminases increased	0	1	1	0	1	1

Upper respiratory tract infection	0	1	1	0	1	1
Urinary tract infection	3	4	7	3	4	7
Urine analysis abnormal	0	1	1	0	1	1
Viral infection	2	0	2	2	0	2
Visual acuity reduced	1	0	1	1	0	1
Vomiting	0	2	2	0	2	2
White blood cell count increased	0	1	1	0	1	1
White blood cells urine positive	2	0	2	2	0	2
Urine analysis abnormal	1	1	2	1	1	2

ii) Summary of treatment-emergent SAEs in the study population

No SAEs occurred.

iii) Summary of treatment-emergent SARs in the study population

No SARs occurred.