APRICOT

Anakinra for Pustular psoriasis: Response In A Controlled Trial

PROTOCOL FULL TITLE:

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

Protocol Short Title/Acronym: APRICOT

[**A**nakinra for **P**ustular psoriasis: **R**esponse in a **Co**ntrolled **T**rial]

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Sponsor:

Name: Guy's and St. Thomas' NHS Foundation Trust

Sponsor Contact: Helen Critchley

Address: King's Health Partners Clinical Trials Office, F16 Tower Wing Guys Hospital, Great Maze Pond, London SE1 9RT

Telephone: 020 7188 5732

Fax: 020 7188 8330

Email: helen.critchley@kcl.ac.uk

Chief Investigator

Name: Professor Catherine Smith

Address: St. John's Institute of Dermatology, 9th Floor Tower Wing, Guy's Hospital, London SE1 9RT

Tel: 0207 188 6277

Fax: 0207 188 8050

Email: catherine.smith@kcl.ac.uk; catherine.smith@gstt.nhs.uk

Name and address of Co-Investigator(s), Statistician, Laboratories etc

Name: Professor Jonathan Barker – (Senior Co-I and contact if CI unavailable)
Address: St. John's Institute of Dermatology, King's College London
Telephone: 020 7188 6412
Fax: 020 7188 8050
Email: jonathan.barker@kcl.ac.uk

Name: Dr Andrew Pink – (Senior Co-I and contact if CI unavailable)
Address: St John's Institute of Dermatology, Counting House, Guy's Hospital
Telephone: 02071886412
Email: andrew.pink@kcl.ac.uk

Name: Dr. Francesca Capon
Address: Division of Genetics and Molecular Medicine, King's College London
Telephone: 020 7188 8079
Fax: 020 7188 8050
Email: francesca.capon@kcl.ac.uk

Name: Dr. Victoria Cornelius
Role: Senior Statistician
Address: Imperial Clinical Trials Unit, School of Public Health, Imperial College London
Telephone: 020 7594 1218
Email: v.cornelius@imperial.ac.uk

Name: Professor Christopher Griffiths
Address: Department of Dermatology, University of Manchester
Telephone: 0161 206 4392
Fax: 0161 206 1095
Email: christopher.griffiths@manchester.ac.uk

Name: Professor Richard Warren
Address: Department of Dermatology, University of Manchester
Telephone: 0161 206 4344
Email: richard.warren@manchester.ac.uk

Name: Professor Nick Reynolds
Address: Department of Dermatology, University of Newcastle
Telephone: 0191 208 5840
Email: nick.reynolds@ncl.ac.uk

Name: Professor David Burden
Address: Department of Dermatology, NHS Greater Glasgow & Clyde
Email: david.burden@glasgow.ac.uk

Name: Ms Helen McAteer
Address: Chief Executive, Psoriasis Association, Northampton
Telephone: 01604 251620
Fax: 01604 251621
Email: helen.mcateer@psoriasis-association.org.uk

Name: Dr Helen Jane Lachmann
Address: National Amyloidosis Centre, University College London
Telephone: 020 7433 2820
Fax: 020 7433 2821
Email: h.lachmann@ucl.ac.uk

1. Study Synopsis

Title of clinical trial	Treatment of Pustular Psoriasis with the IL-1 receptor antagonist anakinra: a randomised, placebo controlled trial and associated mechanistic studies.
Protocol Short Title/Acronym	APRICOT: **A**nakinra for **P**ustular psoriasis: **R**esponse in a **Co**ntrolled **T**rial
Trial Phase if not mentioned in title	Phase IV
Sponsor name	Guy's and St. Thomas' NHS Foundation Trust
Chief Investigator	Professor Catherine Smith
Eudract number	2015-003600-23
ISRCTN number	ISCRTN13127147
REC number	16/LO/0436
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	Clinical: To determine the efficacy of anakinra in treatment of adults with PPP compared to placebo. The primary endpoint is change in disease activity over 8 weeks, adjusted for baseline (visit 1), measured using: 1. Fresh pustule count on palms and soles[1] across 1,4 and 8 weeks, OR 2. Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) across 1,4 and 8 weeks The default primary outcome will be fresh pustule count unless PPPASI is more discriminating (to be reviewed at the end of stage one).
Secondary objective (s)	1. To describe any treatment effect of anakinra in PPP as indicated by change in disease activity over 8 weeks, adjusted for baseline, compared to placebo using the Palmoplantar Pustulosis Psoriasis Area Severity Index. 2. To determine the time to response of PPP (defined as

[1] ie: glabrous skin

	a 75% reduction in fresh pustule count [default primary outcome] compared to baseline), and relapse rate (defined as return to baseline fresh pustule count) with anakinra compared to placebo. 3. To determine the proportion of randomised patients who achieve clearance of PPP with anakinra compared to placebo by 8 weeks. 4. To determine any treatment effect of anakinra in pustular psoriasis at non acral sites (if present) as measured by change in percentage area of involvement at 8 weeks compared to baseline. 5. To 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. 6. To collect data on the adverse event profile and adverse reactions induced by anakinra compared to placebo in order to evaluate the safety and tolerability of anakinra in treatment of PPP. 7. To determine the impact of anakinra on patients' symptoms and quality of life compared to placebo. 8. To determine the proportion of randomised patients who find the treatment acceptable or 'worthwhile'. 9. To determine the proportion of randomised patients that adhere to treatment.
Main Exploratory Objectives (s)	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 respond to treatment as a preliminary step for future pharmaco-genetic studies comparing the genotypes of responders and non-responders. 3. To characterize the immune phenotype of all subjects entering the trial, to establish whether the disease is associated with alterations in the number or activation status of IL-1 producing cells. 4. To collect clinical, DNA, RNA, serum and [optional] tissue (skin and hair pluck) datasets on patients with pustular psoriasis for studies investigating disease pathogenesis (Pustular Psoriasis – elucidating underlying mechanisms [PLUM])
Other Exploratory Objectives (s)	1. Obtain observational data on disease activity on anakinra (measured using PPPASI, 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. Obtain observational data on disease activity on anakinra (measured using PPPASI, 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. Obtain additional safety data on anakinra over a 90 day period for individuals originally prescribed placebo. 4. Obtain longer term safety data on anakinra for individuals originally prescribed anakinra in the double-blind period.
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 determination of the efficacy of anakinra in treatment of adults with PPP compared to placebo, measured by an independent blinded assessor using: 1. Fresh pustule count on palms and soles[2] across 1, 4 and 8 weeks, OR 2. Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) across 1, 4 and 8 weeks The default primary endpoint will be fresh pustule count unless PPPASI is more discriminating (to be reviewed at the end of stage one). **Secondary Endpoints** **Investigator Assessed** 1. Total pustule count on palms and soles[2] 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 [default primary outcome] compared to baseline), and relapse rate (defined as return to baseline fresh pustule

[2] ie: glabrous skin

	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 1.0x10-9/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 0) 3. Dermatology Life Quality Index at 8 weeks compared to baseline (visit 0) 4. EQ5D-3L score at 8 weeks compared to baseline (visit 0) 5. Treatment acceptability (ie: 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
Sample Size	Stage 1: 24 Stage 2. 40 Total sample size: 64 For the mechanistic study: Total sample size: 64
Summary of eligibility criteria	<u>Eligibility criteria (detailed in section 7)</u>: i. Adults (18 years and over) with diagnosis of palmo-plantar pustulosis (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-IGA v. Women of child bearing potential who are on adequate contraception (see Appendix A, contraception guidelines), 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: 17-DEC-2015 Version 1.1: 31-MAR-2016 Version 2: 28-APR-2016 Version 3: 01-SEP-2016 Version 3.1: 05-DEC-2016 Version 4: 03-APR-2017 Version 4.1: 09-JUN-2017 Version 4.2: 01-NOV-2017 Version 5: 01-MAR-2018 Version 5.1: 06-JUN-2018 Version 5.2: 29-AUG-2018 Version 6.0: 15-NOV-2018

2. Disease definitions and Glossary of Terms

2.1 Disease Definitions

The European Rare And Severe Psoriasis Expert Network (ERASPEN http://eraspen.eu/home.html) have recently sought to harmonise phenotypic descriptions of pustular psoriasis, and these criteria will be used in this study as follows:

i. Acrodermatitis Continua of Hallopeau.
   Primary, persistent (> 3 months), sterile, macroscopically visible pustules affecting the nail apparatus
ii. Palmo-plantar Pustulosis.
   Primary, persistent (> 3 months), sterile, macroscopically visible epidermal pustules on palms and/or soles
iii. Generalised Pustular Psoriasis
   Primary, sterile, macroscopically visible epidermal pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques)
   a. With / without plaque psoriasis
   b. With / without systemic inflammation
   c. Relapsing (>1 episode) or persistent (> 3months)
iv. Acral Pustular Psoriasis
   Forms of pustular psoriasis affecting the hands and / or feet

2.2 Glossary of Terms

ACH	Acrodermatitis Continua of Hallopeau
ACH-IGA	Acrodermatitis Continua of Hallopeau - Investigator Global Assessment
AE	Adverse event
APP	Acral Pustular Psoriasis
CAPS	Cryopyrin-Associated Periodic Syndromes
CPP	Chronic Plaque Psoriasis
CXR	Chest X-ray
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
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis

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3. Background & Rationale

3.1 Background

Psoriasis is common (2% UK prevalence) and known to impact on quality of life at a level comparable to other major diseases including chronic heart disease and cancer. Pustular forms of the disease are characterised by painful, intensely inflamed, red skin studded by sheets of monomorphic, sterile, neutrophilic pustules. It may be localised, chronic, and typically, involves the hands and feet (referred to here as Acral Pustular Psoriasis; APP) (1), or, more rarely, generalised, episodic and potentially life-threatening (generalised pustular psoriasis GPP); some patients experience both forms throughout their life. Although pustular psoriasis constitutes less than 10% of all people with psoriasis, it consistently ranks the highest of all psoriasis phenotypic variants in terms of symptoms (pain, itch (2)), and functional impairment (limited mobility, interference with tasks of daily living and work (3)), so that the consequent impact is great, and equivalent to major medical and psychiatric illness (2, 4). Management of plaque-type disease has been revolutionised in the last 10 years with the advent of biological therapies and major investment in new therapies, driven in great part by the scientific discovery of underlying genetic and immunological disease pathways (5). In contrast, treatment options for pustular psoriasis are profoundly limited, and, with the exception of one small, underpowered randomised controlled trial (RCT) in APP involving ustekinumab (n=33) (6), no relevant interventional trials have been performed since 2001 (highlighted in recent NICE guidelines on psoriasis) (7). Topical therapy is useful for a minority of cases with mild disease. There are no published trials in GPP. A recent Cochrane review evaluating interventions for APP (8) identified 23 trials involving 724 people: there was evidence to support only the use of systemic retinoids (improvement rate difference 44%, 95 CI 28 to 59%), a drug with unpleasant dose-limiting muco-cutaneous side effects in most people and of teratogenic potential (extending to 2 years after drug cessation), and oral PUVA (improvement rate difference 44%, 95 CI 26 to 62%), an intervention for short-term use, that necessitates twice weekly attendance for UVA given with oral or topical Psoralen, and carries a risk of skin cancer. Ciclosporin, only to be 'considered' for APP in recent NICE guideline recommendations (7) due to paucity of evidence, should not be used beyond one year due to nephrotoxicity. Tumour necrosis factor (TNF) antagonists, used to great benefit in chronic plaque psoriasis (CPP), are largely ineffective in APP (9) and may precipitate or aggravate the disease (10). There is thus a significant unmet need in this patient group.

3.2 Existing Research

The poor response in pustular psoriasis to therapies used to great effect in plaque type disease may be explained by very recent evidence (2011 onwards) indicating that molecular pathways underlying pustular psoriasis are distinct and involve the interleukin (IL)-36/IL-1 axis.

Several groups, including our own, have identified functionally relevant *IL36RN* mutations in both GPP and APP (11-13). *IL36RN* encodes the IL-36 receptor antagonist (IL-36Ra), an IL-1 family member that antagonizes 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 (12, 13). In keeping with these findings, our group has shown that patients with *IL36RN* mutations significantly upregulate IL-1 production in response to IL-36 stimulation (12). We have also observed that, regardless of *IL36RN* mutation status, the peripheral blood mononuclear cells (PBMCs) of APP patients over-express at least three genes (14, 15) that are consistently up-regulated in IL-1 mediated conditions (unpublished observations). These findings suggest a key pathogenic role for IL-1, a cytokine that is known to sustain the inflammatory responses initiated by skin keratinocytes.

Additionally, we have demonstrated that *IL36RN* alleles do not confer susceptibility to CPP, leading further support to the notion of pathogenic mechanisms distinct from CPP for pustular forms of the disease (16). Underscoring the success of our pustular psoriasis gene identification programme, we have also been able to uncover disease associated mutations in *AP1S3*, a gene that contributes to the regulation of innate immune homeostasis (17). Thus, genetic studies suggest that APP may be caused by abnormal activation of innate immune cells, leading to enhanced IL-1 production. This is consistent with the poor efficacy of therapeutics targeting adaptive immune pathways (e.g. the IL-12/IL-23 antagonist ustekinumab (6)) and indicates that APP is more likely to respond to therapeutics neutralizing the effects of IL-1.

Given the proven therapeutic effect of IL-1 antagonists in the treatment of IL-1 mediated diseases, many of which feature neutrophilic infiltration of the skin, we hypothesise that IL-1 blockade will deliver therapeutic benefit in pustular forms of psoriasis. Early proof of concept data support this hypothesis: anakinra, a highly effective IL-1Ra produced complete, and rapid resolution of pustules within days in patients with GPP (n=4 (18-20), 3 with and 1 without IL36RN mutations) and APP (n=3 (21, 22), 2 without IL36RN mutations). In two patients with disease relapse on stopping anakinra, pustules cleared on restarting therapy. In contrast, efficacy of anakinra in CPP is limited (23). This project therefore aims to investigate the clinical efficacy of IL-1 blockade in localised forms of the disease using the model IL-1 antagonist, anakinra, in a randomised, placebo-controlled trial with a two-staged adaptive design, followed by an open label extension.

3.3 Rationale for Current Study

We have planned a two staged, adaptive, double blind, randomised, placebo-controlled, trial to test our hypothesis that IL-1 blockade with anakinra will deliver therapeutic benefit in pustular forms of psoriasis. Pustular psoriasis represents a spectrum of disease, with all forms characterised by distinct sterile pustules and the presence of IL36RN mutations in a proportion of cases. Generalised disease is rare, episodic, and potentially life threatening, so inclusion in a trial setting would be difficult, and potentially unethical (given placebo arm). Our study population will therefore be people with palmo-plantar pustulosis (PPP) (a term often used interchangeably with APP), i.e. disease of the hands and/or feet, as the clinical paradigm for all forms, given that it causes very significant disability in its own right, it is the most common form (making recruitment feasible), and features chronic development of pustules, so any treatment effect should be captured within the 8 week treatment period.

Our model IL-1 antagonist will be anakinra, chosen in preference to other licensed IL-1 antagonists because: (i) uniquely, it blocks both IL-1a and ß; (ii) it has the lowest drug acquisition cost (of relevance to the NHS should anakinra show efficacy); (iii) we have access to fully funded trial drug through the manufacturer Swedish Orphan Biovitrum (SOBI); (iv) a rapid onset of action and established safety profile (>70,000 patient-years exposure); (v) early evidence of benefit in pustular psoriasis.

4. Study Objectives

4.1 Primary Objective

To determine the efficacy of anakinra in treatment of adults with PPP compared to placebo. The primary endpoint is change in disease activity over 8 weeks, adjusted for baseline (visit 1), measured

using fresh pustule count, the default primary outcome, unless PPPASI is more discriminating (to be reviewed at the end of stage one).

4.2 Secondary Objectives

1. To describe any treatment effect of anakinra in PPP as indicated by change in disease activity over 8 weeks, adjusted for baseline, compared to placebo using the Palmoplantar Pustulosis Psoriasis Area Severity Index (PPPASI).

2. To determine the time to response of PPP (defined as a 75% reduction in fresh pustule count [default primary outcome] compared to baseline), and relapse rate (defined as return to baseline fresh pustule count) with anakinra compared to placebo.

3. To determine the proportion of randomised patients who achieve clearance of PPP with anakinra compared to placebo by 8 weeks.

4. To 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.

5. To 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.

6. To 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 treatment of PPP.

7. To determine the impact of anakinra on patients' symptoms and quality of life compared to placebo.

8. To determine the proportion of randomised patients who find the treatment acceptable or 'worthwhile'.

9. To determine the proportion of randomised patients that adhere to treatment.

4.3 Exploratory objectives

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 respond to treatment as a preliminary step for future pharmaco-genetic studies comparing the genotypes of responders and non-responders.

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

4. To collect clinical, DNA, RNA, serum and [optional] tissue (skin and hair pluck) datasets on patients with pustular psoriasis for studies investigating disease pathogenesis (Pustular Psoriasis – elucidating underlying mechanisms (PLUM)[2]

4.4 Open Label Extension objectives

The primary purpose of the OLE is to enhance recruitment to the randomised, double blind, placebo-controlled study, so that all participants have the potential opportunity to access Anakinra. To ensure equality of access, all patients who have already participated in, are currently taking part in,

or are considering taking part in APRICOT will be made aware of the 8 week OLE therapy and the criteria for enrolment. In addition we will,

1. Obtain observational data on disease activity on anakinra (measured using PPPASI, 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. Obtain observational data on disease activity on anakinra (measured using PPPASI, 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. Obtain 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. Obtain longer term safety data on anakinra for individuals originally prescribed anakinra in the double-blind period.

5. Trial Design

This will be a phase IV, randomised, double blind, placebo-controlled study with two stages and an adaptive element followed by an open label extension (see study flow chart – figure 1). The interim for Stage 1 will occur after we have recruited 24 patients. A decision to embark on stage 2, involving approx. 25 trial sites and a further 40 patients, powered to determine efficacy, will be made using stop/go efficacy criteria (see below). The choice of primary outcome for stage 2 will be chosen at the end of stage 1.

5.1 Stage 1

Participants with a diagnosis of Palmo-Plantar Pustulosis (n=24) will be randomised (1:1) to receive treatment or placebo for 8 weeks. Every participant will be required to:

1. self administer anakinra or matched placebo subcutaneous injections daily for an 8 weeks
2. return for a follow up visit 4 weeks after treatment (week 12) and 90 days post last dose
3. attend clinic throughout on at least 6 occasions according to the visit schedule (see below).

5.2 STOP/GO Decisions

Outcomes of stage 1 will be measured by:
(i) fresh pustule count and
(ii) PalmoPlantarPustulosis Area and Severity Index (PPPASI) score - a composite measure encompassing area, pustules, redness and scaling. Primary outcome assessments of fresh pustule count and PPPASI will be carried out by an independent blinded assessor blind to study treatment (a member of the study team trained in the assessment protocol but independent to the rest of the trial). Fresh pustule count will also be assessed by a central, blinded assessor using photography (pre-specified views of palms and soles at baseline (visit 1), week 1 (visit 2) and week 8 (visit 5) of treatment). The mean value across follow-up visits will be used to inform decision 1 (below). The distribution for each outcome across follow-up visits, and the agreement between the blinded central outcome assessor and blinded site outcome assessor will be used to inform decision 2 (below).

Decision 1
STOP: placebo group does as well as or better than treatment group for both of the two outcomes (i.e. the mean change in fresh pustule count AND the mean change in PPPASI in the placebo arm

over 1,4 and 8 weeks is the same or less than the treatment arm)
GO: treatment group does better than placebo group for at least one measure (i.e. the mean change in fresh pustule count OR the mean change PPPASI in the treatment arm over 1,4 and 8 weeks is less than the placebo arm).

Decision 2

If 'GO', the choice of primary outcome will by default be fresh pustule count unless PPPASI outcome is judged to be more discriminating and the interrater reliability for pustule count between central assessor and site assessor is inadequate eg: weighted kappa <0.9 between the study sites and central assessors. To maintain blind the Data Monitoring Committee, with contribution from the unblinded trial statistician and EME representation, will be responsible for reviewing the unblinded data and making a recommendation to the Trial Steering Committee and funder (EME) as to whether the trial should continue to stage 2 and choice of primary outcome.

Assuming the GO criteria are achieved, the Data Monitoring Committee will then review all safety data (i.e. from Stage 1, and any new drug safety data available through SOBI or other sources).

5.3 Stage 2

New participants with a diagnosis of Palmo-Plantar Pustulosis (n=40) will be randomised (1:1) to receive treatment or placebo for 8 weeks. Participant experience will be identical to stage 1, and will be required to:

1. Self-administer anakinra or matched placebo subcutaneous injections daily for 8 weeks.
2. Return for a follow up visit 4 weeks after treatment period (week 12).
3. Take part in an optional OLE* after the 12 week follow up visit has been completed.
4. Either attend clinic, or conduct a telephone follow up at 90 days post last dose.
5. Attend clinic throughout on at least 6 occasions (up to 13 visits if patient consents to the OLE) according to the visit schedule (see below).

*The OLE is optional, and will be offered to all patients who complete the 8 week treatment period and the 12 week follow up visit.

Overall the project is expected to last 58 months.

5.4 Open Label Extension

To retain the integrity of the primary randomised, double blind, placebo-controlled study, only patients who have completed the 8 week treatment period schedule, as well as the 12 week follow up visit, can take part in an optional 8 week period of anakinra treatment, as an OLE to the trial. There will be a final follow up visit at 90 days post last dose, measured from the final anakinra dose taken.

Some patients may have completed the entire APRICOT trial before they are invited to the OLE. These Patients will be asked to sign an OLE specific consent form. If these patients are on treatment for their PPP, they will be asked to washout from their current treatment as per the APRICOT protocol prior to commencing anakinra treatment for 8 weeks. Patients will be followed up 90 days post last dose of Anakinra.

The inclusion and exclusion criteria for patients who wish to take part in the OLE are listed in Section ***7. Selection and Withdrawal of patients***.

5.5 Trial Flowchart (Figure 1)

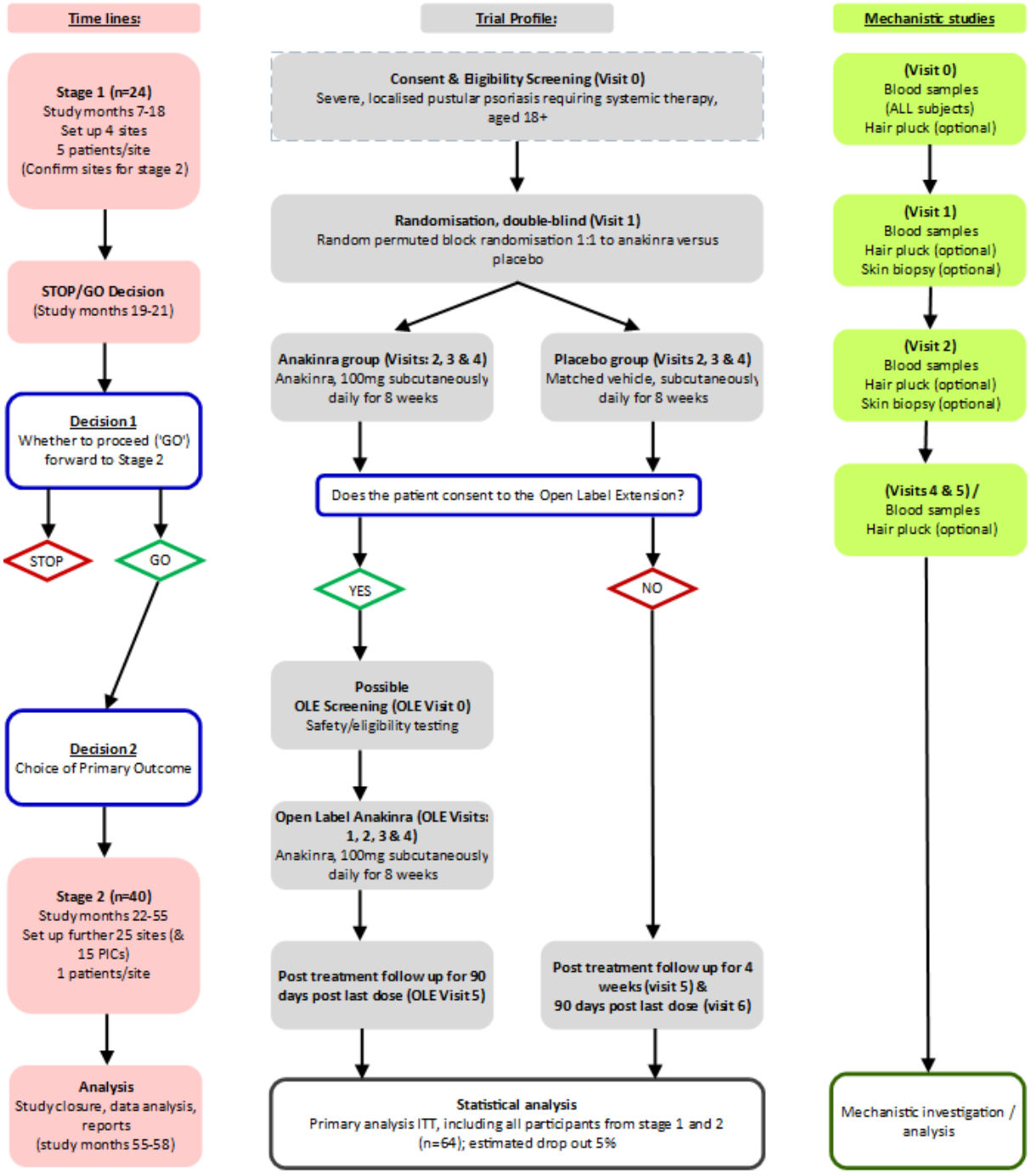

Figure 1 : Notes

1. Decision 1: whether to proceed to stage 2 (ie fully powered study). If the placebo group does as well as or better than the treatment group for both of the two outcomes, PPPASI or fresh pustule count, the study will STOP. If the treatment group does better than the placebo group for at least one outcome, the study will proceed (GO). These decisions will be made on the basis of the mean outcome values for each arm.

2. Decision 2: choice of primary outcome. If the trial continues ('GO'), the choice of primary outcome will by default be the fresh pustule count. If the PPPASI or total pustule count is more discriminating than fresh pustule count, or inadequate agreement is observed between central and site assessors, then the primary outcome will be changed at this point, accordingly

6. Trial Medication

6.1 Investigational Medicinal Product

Definition of Investigational Product: A pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. In this protocol, the investigational product is Anakinra.

Definition of Non-Investigational Product: Other medications used in the study as support or escape medication for preventative, diagnostic, or therapeutic reasons as components of a given standard of care.

6.1.1 IMP supplier

Swedish Orphan Biovitrum AB (SOBI) will provide the anakinra and matching placebo for the trial. Guy's and St Thomas' NHS Foundation Trust (GSTT) Pharmacy Manufacturing Unit will package and label the IMP with study specific requirements and distribute IMP to study sites.

6.1.2 Description of the IMP

Anakinra: A pre-filled syringe (27G x 1/2in. Needle) will be supplied by SOBI i.e.: Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe. Each pre-filled syringe contains 100 mg of anakinra* per 0.67 ml (150 mg/ml). It is a clear, colourless-to-white solution for injection that may contain some product-related translucent-to-white amorphous particles.

Placebo: Placebo will be provided in identical, matched syringes, containing 0.67 ml vehicle solution only. Placebo formulation contains 140 mM Sodium Chloride, 10 mM Sodium Citrate, 0.5 mM EDTA, 0.1% (w/w) non-animal derived Polysorbate 80, pH 6.5.

6.1.3 IMP labelling and packaging for study sites

For the double-blind part of the study, IMP will be packaged in boxes containing 4 weeks supply with an additional 7 days to accommodate the +3 day study visit windows (a total of 35 syringes per box). Each box will be labelled with an Annex 13 compliant clinical trial label with an additional tear-off label stating: Treatment 1 or Treatment 2.

For the OLE period, anakinra will be packaged in boxes containing 4 weeks supply (a total of 28 syringes per box). Each box will be labelled with an Annex 13 compliant clinical trial label.

6.1.4 Distribution of IMP to study sites

An unblinded delegated individual will be responsible for the IMP management at sites. The individual will place orders with the GSTT Pharmacy Manufacturing Unit to replenish IMP at sites for the double-blind period and arrange to ship 8 weeks of anakinra to sites for all patients who consent to take part in the OLE treatment. The APRICOT trial manager and all other trial staff are blind to a patient's treatment for the double-blind period.

6.1.5 Dispensing

The IMP will be dispensed by the local pharmacy on receipt of an APRICOT trial specific prescription.

For the double-blind period, the pharmacy trials team will receive notification of the treatment arm to supply via email (i.e. treatment 1 or treatment 2). The tear-off label (Treatment 1 or Treatment 2) will be removed at the point of dispensing and attached to the drug accountability record. Following

randomisation, patients will receive their first box of IMP at baseline and will be resupplied with their second box at week 4, in order to complete their 8 weeks of treatment. Patients will also be supplied with a cool box to transport study medication from the study site to home in addition to information on study medication.

For the OLE period, the pharmacy trials team will dispense an 8 week treatment course (contained in 2 boxes) at Visit OLE 1. Patients will be provided with a cooler box to transport the IMP from the study site to their home.

6.2 Dosing Regimen

6.2.1 Washout of previous treatments prior to entry into the randomised trial

All treatments likely to have efficacy in PPP need to be discontinued prior to treatment initiation in the randomised trial with washout periods as stipulated:

Table 1: Washout periods

Treatment	Wash out period
Topical treatment that is likely to impact signs and symptoms of psoriasis (e.g. corticosteroids, vitamin D analogues, calcineurin inhibitors, retinoids, keratolytics, tar, urea)	2 weeks
Methotrexate, Ciclosporin, Acitretin, Alitretinoin, Fumaric acid esters	4 weeks
Phototherapy or PUVA	4 weeks
Etanercept or Adalimumab	4 weeks
Infliximab or Ustekinumab or Secukinumab	3 months
Other TNF antagonists	3 months
Other investigational monoclonal antibody	3 months
Other investigational drugs	30 days or 5 half lives (whichever is longer)
Other immunosuppressant / immunomodulatory therapy including intra-articular steroids	4 weeks or 5 half lives (whichever is longer)

6.2.2 Washout of previous treatments prior to entry into the Open Label Extension

If a patient is commencing the OLE stage directly after the 12 week follow up visit, no washout is required prior to commencing the OLE, as patients will have been on either anakinra or placebo as part of the study, and will have had sufficient time to washout prior to starting the trial.

If a patient commences the OLE stage once completing the entire APRICOT trial, and are on systemic treatment for their PPP, they will need to washout this treatment in accordance with section 6.2.1, table 1, of this protocol, with the exception of topical therapy. Topical therapy does not need to be washed out and can be continued as clinically indicated.

6.2.3 The treatment

Double-blind study stage: Patients will self-administer a daily, sub-cutaneous injection of IMP (either anakinra or placebo) for 8 weeks.

Open Label Extension therapy: Patients will self-administer a daily, subcutaneous injection of anakinra for a maximum of 8 weeks.

The chosen dose of 100mg/day of anakinra is the licensed dose for rheumatoid arthritis, within the dose range of the recommended dosing for cyropyrin-associated period syndromes (1-2mg/kg) and the dose used in the reported cases of pustular psoriasis.

To alleviate the acute discomfort (stinging, burning) associated with the injection, the syringe should be allowed to come to room temperature (about 15 to 30 minutes). A cold pack can be applied to the injection site 2–3 min before and immediately after the injection. Topical hydrocortisone (up to 2.5%) or anti-histamine cream can be applied to injection site reactions to alleviate symptoms. Oral anti-histamines are also permitted to alleviate symptoms of injection site reactions. Injection sites should be alternated to avoid recall reactions (31) and given according to instructions given in the Study Patient Information Leaflet, and in accordance with guidance in the anakinra (Kineret) SmPC and Patient Information Leaflet.

6.2.4 Follow-up period

All patients will be followed up at the 12 week visit, following the double-blind treatment period.

For patients who decline the OLE, they will be followed 90 days after the last dose.

For patients who opt to take part in the OLE, the 12 week visit will be directly followed by an 8 week treatment period with another follow-up visit 90 days post the last dose of anakinra.

There are no other lifestyle requirements beyond this and attending clinic.

6.3 IMP Risks

Adverse reactions reported with anakinra for its licensed clinical indications Rheumatoid Arthritis (RA), Cyropyrin-Associated Periodic Syndromes (CAPS) and systemic onset juvenile arthritis include injection site reactions (very common), allergic reactions, anaphylaxis (rare), infection, neutropenia and raised liver enzymes. Of these, serious infection presents the most clinically important risk: in a recent systematic review and meta-analysis of 4 trials in RA (33) involving 2771 patients, randomised to receive at least one dose of anakinra (n = 2062) or placebo (n = 729), during 24 weeks the overall pooled OR did not show a significantly increased risk of serious infection. However, the risk may be increased in patients receiving doses greater than 100mg/ daily, co therapy with corticosteroids or with underlying co-morbidities (pulmonary chronic disease, asthma, diabetes, renal impairment, previous malignancy or infection, cardiovascular or central nervous system diseases). For the purposes of this study the anakinra (Kineret) SmPC (as amended from time to time) will be used as the reference document.

Injection site reactions

Injection site reactions are very common, and comprise redness, swelling, bruising or itching at the injection site. These symptoms are generally mild to moderate and are more common at the start of treatment. Patients will be informed about this risk and given advice as to how to manage the reaction (see section 6.7.2). Injection site reactions typically appear within 2 weeks of therapy and disappear within 4 to 6 weeks. The development of injection site reactions in patients who have not previously experienced injection site reactions is uncommon after the first month of therapy.

Allergic reactions

Allergic reactions including anaphylactic reactions, angioedema, urticaria, and pruritus have been reported uncommonly. The majority of these reactions were maculopapular or urticarial rashes.

If a severe allergic reaction occurs, administration of Kineret should be discontinued and appropriate treatment initiated.

Serious infections
In the meta-analysis of RA trials (33) with anakinra, serious infections reported (n=30) included pneumonia, osteomyelitis, cellulitis, bursitis and herpes zoster. No related death or opportunistic infections were described. However, in other clinical studies and during post-marketing use, rare cases of opportunistic infections have been observed. The SPC advises clinicians to exercise caution administering anakinra to patients with recurring infections or with underlying conditions that may predispose them to infections.
For example, for the small number of patients in the meta- analysis RA trials with asthma the incidence of serious infection was higher in anakinra treated patients (4.5%) compared to placebo treated patients (0%). These serious infections were mainly related to the respiratory tract and although absolute incidence number is low (n=8) should be considered relevant and taken into account when screening potential participants.

Neutropenia
In placebo-controlled RA studies with anakinra, treatment was associated with small reductions in the mean values for total white blood count and absolute neutrophil count (ANC). Neutropenia (ANC $< 1.5 \times 10^9$/L) was reported in 2.4% patients receiving anakinra compared with 0.4% of placebo patients. None of these patients had serious infections associated with the neutropenia.
In 43 CAPS patients followed for up to 5 years neutropenia was reported in 2 patients. Both episodes of neutropenia resolved over time with continued anakinra treatment.

Thrombocytopenia
In clinical studies in RA patients, thrombocytopenia has been reported in 1.9% of treated patients compared to 0.3% in the placebo group. The thrombocytopenias have been mild, i.e. platelet counts have been $>75 \times 10^9$/L. Mild thrombocytopenia has also been observed in CAPS patients.
During post-marketing use of Kineret, thrombocytopenia has been reported, including occasional case reports indicating severe thrombocytopenia (i.e. platelet counts $<10 \times 10^9$/L).

Hepatic Events
In clinical studies in RA and CAPS patients, transient elevations of liver enzymes have been seen uncommonly. These elevations have not been associated with signs or symptoms of hepatocellular damage. During post-marketing use isolated case reports indicating non-infectious hepatitis have been received. Hepatic events during post marketing use have mainly been reported in patients that have been treated for systemic onset juvenile arthritis and in patients with predisposing factors, e.g a history of transaminase elevations before start of anakinra treatment.

Cytochrome P450 Substrates
Formation of CYP450 substrates may be normalised during treatment with anakinra and altered drug metabolism cannot be excluded as a cause for a few isolated adverse event case reports from RA trials. This may be clinically relevant for participants prescribed CYP450 substrates with a narrow therapeutic index such as phenytoin or warfarin, where it is advisable to consider additional therapeutic monitoring and dose adjustment for the duration of trial participation.

Further information is provided in the Summary of Product Characteristics at
https://www.medicines.org.uk/emc/medicine/27216

All adverse events will be documented at study visits as outlined in the schedule of safety assessments (see Section 9).

6.4 Drug Accountability

Site pharmacy clinical trial teams must maintain accurate accountability records of IMP including, but not limited to the number of packs received, the number of packs dispensed and to which subject, batch number, expiry date, study drug returns and date of transaction.

An APRICOT drug accountability log (paper version) will be provided by the sponsor, but sites may wish to use in house logs as long as the content is compliant with the requirements above. A copy of the log should be provided to the sponsor.

Participants will be asked to return any un-used syringes and all outer packaging when they attend clinic for scheduled clinic visits as a measure of compliance. Sharps bins will be provided by the research nurse and should be returned to the study team or local GP practice for disposal. Drug accountability will be completed by the dispensing pharmacy at each site.

6.5 Storage of IMP

IMP will always be supplied, stored and distributed at 2°C to 8°C. At study sites, IMP must be stored at 2 °C – 8 °C in a restricted access, temperature monitored storage area, within the hospital pharmacy in its container/packaging to protect from light. Patients will be provided with a cool bag by the research team to transport IMP from the pharmacy to their home where they will be advised to store the IMP in their fridge.

6.6 Subject Compliance

Participants will receive daily text reminder messages to encourage them to comply with the daily dosing schedule and will be asked to respond to the text to confirm that they have taken their medication. Patient consent will be explicitly sought for transfer of their mobile number and study specific ID to the SMS text provider for this study specific use (only). Those patients who are unable to provide a mobile phone number for text reminders or do not wish to, will be asked at each visit for a record of their daily injections.

The dense schedule of clinic visits over the treatment period will allow any compliance (and safety) issues to be identified and addressed quickly.

6.7 Concomitant Medication, Prohibited Medication and Rescue therapy

6.7.1 Permitted medication

All medication must be recorded appropriately on the eCRF.

(i) Topical therapy

Emollient therapy will be 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 can be used.

For plaque psoriasis:

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

For PPP:
Rescue medication as below.

(ii) Rescue therapy

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 can be dispensed if necessary, to provide substantial symptomatic relief. Rescue medication will 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.

(iii) Systemic therapy

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

6.7.2 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 is prohibited and stipulated wash out periods (as described in section 6.2.1) must be adhered to. If treatment with any of these prohibited treatments is essential then the patient must notify the study team and they will be withdrawn from the trial.

Table 2: 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.

6.7.3 Prohibited medication for the Open Label Extension

Stipulated wash out periods (as described in section 6.2.1) must be adhered to. Concomitant topical treatment (only) is allowed only during the OLE stage. If treatment with any of the prohibited systemic treatments (as indicated in Table 2) are essential then the patient must notify the study team and they will be withdrawn from the trial and anakinra will be discontinued.

Table 3: Summary of Concomitant therapy rules for the Open Label Extension

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

7. Selection and Withdrawal of patients

7.1 Inclusion Criteria for the double-blind, placebo controlled study.

i. Adults (18 years and over) with diagnosis of Palmo-Plantar Pustulosis (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 (see Appendix A), contraception guidelines), who are not pregnant or not breast feeding

vi. Who have given written, informed consent to participate

7.2 Exclusion Criteria for the double-blind treatment stage, 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

7.3 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 (see Appendix A), contraception guidelines), who are not pregnant or not breast feeding

iv. Who have given written, informed consent to participate

7.4 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.

7.5 Identification and Recruitment

Potentially eligible patients will be identified as follows:

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

(ii) Via existing databases
Local study teams will identify 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 may be contacted by their consultant and the research team by letter/email/phone call to invite them to participate and provide them with the patient information leaflet.

(iii) Self-referral
Potential study participants may identify themselves after becoming aware of the trial and in response to various adverts. We plan a multimedia approach with REC approved material via posters in clinic waiting rooms, on the Psoriasis Association website (www.psoriasisassociation.org.uk; CEO Helen McAteer is a co-applicant), other relevant patient organisations, social media (for example a PPP specific Facebook page maintained by a patient) and via the study specific website page. Patients will be invited to register on an interactive web-based patient recruitment questionnaire the results of which will be used by the study team as the first line of eligibility screening.

iv) From Participant Identification Centres
Potential study participants will be identified at participant identification centres (PIC) following review of local clinic and pharmacy lists, electronic patient records, referral lists and letters, research databases and other lists as appropriate. Potential participants identified will be contacted by their direct clinical care team or delegated individual (usually by letter/email/phone call or in person) and invited to self refer on the trial website as above or, with agreement, referred directly to a participating centre for further information regarding participation.

v) GP databases
Potential study participants will be identified via searches of primary care databases, electronic patient records, patient letters and other lists as appropriate. Potential participants identified will be contacted by their direct clinical care team or delegated individual (by letter/email/phone call or in

person) and invited to self refer on the trial website as above or, with agreement, referred directly to a local participating centre for further information regarding participation.

7.6 Randomisation Procedure

Randomisation service will be provided by King's Clinical Trials Unit (CTU). Following written consent, each patient will be registered on the MACRO eCRF system (InferMed Macro) to generate a patient identification number (PIN). This unique PIN will be recorded on all source data worksheets and used to identify the patient throughout the study. Randomisation will be via a bespoke web based randomisation system hosted at the King's CTU. Authorised site staff will be allocated a username and password for the randomisation system by the Trial Manager. An authorised staff member who will typically be the PI or designee will log into the randomisation system (www.ctu.co.uk and click 'randomisation – advanced' and select APRICOT) and enter the patient's details, including the unique PIN.
Once a patient is randomised, the system will automatically generate emails to key staff within the study. E-mails sent to site pharmacies will alert them to a patient's treatment arm (ie: Treatment 1 or Treatment 2). Additional blinded and unblinded emails will be generated from the randomisation system to key trial site staff depending on their role in the study.

7.7 Emergency Code Break

Emergency Code Break and Medical Information will be provided by ESMS Global - a 24-hour cover service.

Unblinding phone number: **020 3282 0458**

This will include enquiry handling throughout stage 1 and 2, full documentation of enquiries and the medical & scientific response provided, and emergency unblinding. There will be peer and medical quality control of all emergency and clinical case enquiries.
Each randomised subject will be provided with a card detailing code break telephone numbers and emergency contact details. Subjects will be requested to carry this card with them at all times whilst participating in the trial and to present this card to their attending healthcare professional.

Information and clinical advice will be provided to health care professions from approved study documentation to support any treatment or management the trial subject may need.
Emergency unblinding can also be performed according to strict criteria to support patient safety.

ESMS Global will notify the KHP-CTO of any code break requests received, irrespective of outcome. KHP-CTO CRA will inform the chief and principal investigator instances of unblinding which will be recorded and the trial statistician informed at the analysis stage of the trial.

7.8 Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study drug in the event of inter-current illness, AEs, SAEs, SUSARs, protocol violations, administrative reasons or other reasons.
It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a participant decide to withdraw from the trial, all efforts will be made to report the reason for withdrawal as thoroughly as possible and they will be encouraged to continue to provide outcome data. All data and samples collected to date will be retained.

Subjects MUST discontinue investigational product (and non-investigational product at the discretion of the investigator) for any of the following reasons:

- Withdrawal of informed consent (subject's decision to withdraw for any reason).
- Any clinical adverse event, laboratory abnormality, or intercurrent illness that, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject.
- In the Principal Investigator's opinion, the need to administer concomitant medication not permitted by the trial protocol
- Pregnancy
    - Instruct women of child bearing potential to contact the investigator or study staff immediately if they suspect they might be pregnant (e.g.: missed or late menstrual period) at any time during study participation. The investigator must immediately notify the Chief Investigator if a study subject becomes pregnant.

Participants who withdraw from trial medication (IMP) will be encouraged to provide follow-up data for the remaining trial visits but at a minimum will be asked for outcome data and safety data (adverse event records) at week 8 and the 90 days post last dose follow up visit. They will be asked to confirm whether they are still willing to provide any/all of the following as per the remaining trial schedule:

- trial specific clinical data (i.e outcome measures)
- samples for mechanistic study

The Principal Investigator should ensure ongoing safety and well-being of the withdrawn participant whether or not trial specific data continues to be collected as per the schedule. Safety bloods should be taken as per the trial schedule for all participants, and/or as considered appropriate by the PI noting that risk of infection is usually deemed to continue up to 90 days post last dose, and reviewed for safety by the PI outside of routine clinical care.

7.9 Expected Duration of Trial

Following informed consent and screening participants will receive study medication for 8 weeks and will be followed up 4 weeks after the double-blind treatment stage. Patients will then be invited to take part in an optional 8 week OLE therapy where all consented patients will receive an 8 week treatment course of anakinra. There will be a final follow up visit 90 days after the last dose of IMP.

The duration of the overall project will depend on whether or not the stop/go criteria are met: stage 1 (24 patients) last patient, last visit is expected to be achieved by June 2017. If the GO criteria are met, a further 40 patients will be recruited.

The APRICOT trial will recruit into Stage 2 until the 30th September 2019, and follow patients up until May 2020, with the entire study to be completed by 31 August 2020.

8. Trial Procedures

8.1 Patient Pathway

The patient pathway consists 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 in tables 4, 5 and 6, by visit below.

The screening period (between screening visit (visit 0) and baseline (visit 1)) is a minimum of 5 days up to a maximum of 3 months and is used to assess eligibility and to taper off prohibited medicines. Patients who fail the screening period may be re-screened if clinically appropriate.

The treatment period (visits 1-4) is 8 weeks. At the start of the treatment period, eligible patients will be randomised, 1:1 to receive either anakinra 100mg/day or placebo, to be administered daily as a self administered sub-cutaneous injection for 8 weeks.

The follow up periods (visits 5&6) at week 12 and 90 days post last treatment date are used to assess disease relapse off study treatment, follow up any adverse events, and plan for post treatment management of their condition.

Should the patients decide to take part in the optional 8 week OLE, there are 2 possible patient pathways:

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

ii) For patients who are beyond the week 12 follow up visit (Visit 5):
These patients may be on treatment for their PPP when they decide to take part in the OLE. These patients would require a screening visit, a possible washout period (as per APRICOT protocol) and a baseline visit arranged once the required washout period has been completed. A final follow up visit would be conducted 90 day after the last dose of anakinra.

To achieve the exploratory (mechanistic) study objectives, all patients will be invited to provide biological samples for use in exploratory laboratory tests (see section 8.3.2). These are bloods samples at visit 0, and then longitudinal blood samples at visits 1, 2, 4 and 5. In addition, patients will be invited to provide skin samples from skin on the lateral edge of the palms prior to treatment initiation (visit 1) and / or hair pluck samples before treatment (visit 1) and then at various time points during treatment (visits 1, 2, 4 and 5). These samples will be used to understand the underlying pathogenesis of pustular psoriasis, the mechanism by which anakinra may work and to identify potential biomarkers of response.

Table 4: 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 6	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 5 (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 5: Study procedures for the Open Label Extension

	Screening*	**Treatment Period**				**Safety Follow up**
Allowed visit window: ± 3 days	**Visit OLE0***	**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*					
Check washout period	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 baseline (visit 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.

Table 6: 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.

8.2 Study Schedule by Visit

8.2.1 Visit 0: Screening (-3 months to -5 days before baseline)

At screening participants with clinically confirmed palmo-plantar pustulosis, with a history of disease of greater than 6 months, who have failed to respond to topical therapy (including topical very potent corticosteroids) will be asked to provide written informed consent.

Consenting patients will undergo the following procedures and evaluations carried out by the research nurse or doctor:

- Assessment of inclusion and exclusion criteria
- Medical history: previous or current diseases and treatments, including risk factors (TB or other infections)

- History of PPP including previous treatments and history of insufficient response to previous topical therapy including cortico-steroids
- Clinical phenotyping of psoriasis
- Disease severity assessments
- Physical examination
- Vital signs
- Patient reported outcome measures
- CXR (unless participant has had a CXR in the previous 12 months for clinical purposes)
- Screening laboratory tests (see table 4)
- Safety assessment bloods (see table 4)
- Mechanistic blood samples (see table 6)
- Hair pluck samples (optional)
- Instructions on washout of any contra-indicated medications for psoriasis

8.2.2 Visits 1-6

All efficacy assessments of PPP (ie: fresh pustule count, total pustule count, PPPASI, percentage area involvement on hands and feet and PPP-IGA) ***will be assessed by an independent blinded assessor*** before all other safety and efficacy assessments. This is to maintain blinding as the active trial medication is likely to cause injection site reactions in approximately a third of patients which may lead to inadvertent unblinding. Where-ever possible, the independent blinded assessor for a particular participant should remain the same throughout the study.

The independent blinded assessor will only have sight of the hands and feet and will be introduced to the patient by the clinical research team as the independent blinded assessor who will therefore not be able to speak to them in order to maintain blinding. The independent blinded assessor may wear headphones to maintain the blind. Once these outcome measures are assessed the independent blinded assessor will leave the consulting room and the treating physician or research nurse will conduct the rest of the study visit. A second assessment of the PP-PASI score and PPP-IGA will also be conducted by the treating physician or research nurse.

Other study safety and efficacy assessments will be conducted by a research nurse or doctor. These consist of vital signs, non-PPP psoriasis skin assessments (i.e Body Surface Area assessment, PASI scoring), concomitant medication review and specific enquiry regarding potential adverse events.

Visit 1: Baseline & Treatment initiation

Research nurse/doctor:

- Confirmation and verification of all inclusion and exclusion criteria
- All blood monitoring investigations will be reviewed and checked to ensure they are normal/negative and/or comply with protocol inclusion criteria
- Completion of PPP efficacy assessments (independent blinded assessor & second assessor)
- Completion of all other efficacy and safety assessments
- Safety assessment bloods (see table 4) – **NB:** if the period between screening and baseline safety assessment bloods is >4 weeks the participant should be asked to attend for additional bloods for safety review prior to randomisation. If at all possible this should be scheduled for the same day as the baseline visit (in which case only one set of baseline bloods need taking), with enough time for clinical review before fist treatment dose, or if not convenient should be scheduled within 4 weeks of the visit (these may be taken by the GP).

If an additional visit is applicable then the participant should also complete the baseline visit in its entirety i.e repeat the baseline safety assessment bloods as scheduled.

- Randomisation
- Mechanistic blood samples (see table 6)
- Hair pluck samples (optional)
- 2mm Skin microbiopsy samples x 2 (affected and unaffected skin) OR x1 sample (unaffected skin) (all optional)

Medical photography (designated sites only)

Pharmacy:
Dispensing of first 4 weeks of study medication and sharps container
Instruction on drug storage

Research nurse:
Support and training in injection technique
Self administration of first injection under supervision
Daily attendance for supervised drug administration to continue until patient is confident

Participant:
Complete all PROMS before any other trial interventions.

- Patient Global Assessment
- Palmo-Plantar Quality of Life Index
- Dermatology Life Quality Index
- EQ5D-3L

Visit 2: Treatment period (week 1)

Research nurse/doctor:

- Completion of PPP efficacy assessments (independent blinded assessor & second assessor)
- Completion of all other efficacy and safety assessments
- Safety assessment bloods (see table 4)
- Medical photography (designated sites only)
- General enquiry including safety assessment
- Safety assessment bloods (see table 4)
- Mechanistic blood samples (see table 6)
- Hair pluck samples (optional)
- 2mm Skin microbiopsy sample (affected skin) (optional)

Participant:
Complete before any other trial interventions.

- Patient Global Assessment

Visit 3: Treatment period (week 4)

Research nurse/doctor:

- Completion of PPP efficacy assessments (independent blinded assessor & second assessor)
- Completion of all other efficacy and safety assessments
- Safety assessment bloods (see table 4)
- Retrieval of empty IMP packaging.

Pharmacy:
Dispensing of second 4 weeks of study medication and sharps container
Instruction on drug storage

Participant:
Complete before any other trial interventions.

- Patient Global Assessment

Visit 4: Treatment end (week 8)

Research nurse/doctor:

- Completion of PPP efficacy assessments (independent blinded assessor & second assessor)
- Completion of all other efficacy and safety assessments as outlined in table 4
- Safety assessment bloods (see table 4)
- Mechanistic blood samples (see table 6)
- Retrieval of empty IMP packaging
- Medical photography (specified sites only)
- Hair pluck samples (optional)

Participant:
Complete all PROMS before any other trial interventions.

- Patient Global Assessment
- Palmo-Plantar Quality of Life Index
- Dermatology Life Quality Index
- EQ5D-3L

Visit 5: Follow-up (week 12)

Research nurse/doctor:

- Completion of PPP efficacy assessments (independent blinded assessor & second assessor)
- Completion of all other efficacy and safety assessments as outlined in table 1
- Safety assessment bloods (see table 4)
- Mechanistic blood samples (see table 6)
- Hair pluck samples (optional)

Participant:
Complete all PROMS before any other trial interventions.

- Patient Global Assessment
- Palmo-Plantar Quality of Life Index
- Dermatology Life Quality Index
- EQ5D-3L
- Acceptability Questionnaire

Visit 6: Safety follow up (90 days post last dose) [Only for patients who do not want to take part in the Open Label Extension]

Every participant should attend a final safety follow up visit 90 days post last trial treatment dose (i.e. at week 20 or earlier depending on the date of last dose). Enquiry should be made into any changes to concomitant medication, intercurrent illness or side effects and general health since the last visit and since last dose. This visit should be in person, but if the participant is not in routine follow up this can be done remotely.

8.2.3 Open Label Extension Visits OLE 0-5

Open Label Extension

After the 12 week follow up, patients will be invited to take part in an optional OLE, where patients will have access to anakinra treatment for an 8 week period.

Visit OLE 0:
This visit is only required for patients who have already completed the entire APRICOT trial before commencing OLE.

All procedures must be carried out following written informed consent from the patient.

Research nurse/doctor:
- Eligibility review
- Vital signs
- Washout period check
- Safety assessment bloods (see table 5)
- Completion of all other efficacy and safety assessments
- Urine analysis
- Pregnancy testing (if applicable)
- Concomitant medication monitoring
- AE monitoring

Visit OLE 1:
Research nurse/doctor:
- Vital signs
- Completion of PPP efficacy assessments (Fresh pustule count, Total pustule count, PPPASI, PPP-IGA, BSA)
- Safety assessment bloods (see table 5)
- Urine analysis
- Prescribe and dispense Anakinra
- Concomitant medication monitoring
- AE monitoring

Pharmacy:
Dispensing of 8 weeks of anakinra and sharps container
Instruction on drug storage

Research nurse:
Support and training in injection technique
Self-administration of first injection under supervision
Daily attendance for supervised drug administration to continue until patient is confident

Visit OLE 2:
Research nurse/doctor:
- Vital signs
- Safety assessment bloods (see table 5)
- Urine analysis
- Concomitant medication monitoring
- AE monitoring

Visit OLE 3:

Research nurse/doctor:

- Vital signs
- Safety assessment bloods (see table 5)
- Urine analysis
- Concomitant medication monitoring
- AE monitoring

Visit OLE 4:

Research nurse/doctor:

- Vital signs
- Completion of PPP efficacy assessments (Fresh pustule count, Total pustule count, PPPASI, PPP-IGA, BSA)
- Safety assessment bloods (see table 5)
- Completion of all other efficacy and safety assessments
- Urine analysis
- Concomitant medication monitoring
- AE monitoring

Visit OLE 5:

- Concomitant medication monitoring
- AE monitoring

Visit OLE 6: Safety follow up (90 days post last dose)

Every participant should attend a final safety follow up visit 90 days post last trial anakinra dose (i.e at week 20 or earlier depending on the date of last dose). Enquiry should be made into any changes to concomitant medication, intercurrent illness or side effects and general health since the last visit and since last dose. This visit should be in person, but if the participant is not in routine follow up this can be done remotely.

8.3 Laboratory Tests

8.3.1 Safety assessment blood tests

Blood samples will be taken for monitoring and safety purposes at every clinic visit. These samples will be handled and stored according to standard clinical protocols at each site, and processed as routine clinic bloods at local laboratory sites.

A set of blood results must be reviewed at baseline prior to randomisation and the administration of the first dose of trial treatment. If the period between screening and baseline safety assessment bloods is > 4 weeks (i.e. due to the 3 month wash out for biologic therapy) then the participant should be asked to attend for additional baseline safety assessment bloods. Ideally, if feasible, these will be one the same day as the baseline visiting allowing for enough time for clinical review before the first treatment dose, however if not convenient should be arranged for another visit within 4 weeks of the baseline visit (visit 1).

8.3.2 Abnormal safety assessment blood tests

Safety blood tests should be reviewed by a clinician at every study visit and an assessment made as to their clinical significance. Abnormal results (trends, Δ, and absolute counts) should be carefully considered in regard to impact on the participant's safe continued participation in the trial, general health, and in line with temporary stopping rules (as detailed in Section 10.2). Of particular importance are neutrophil and thrombocyte counts; a neutrophil count of ≤1.0 x 10^9/L or thrombocyte (platelet) count of <75x10^9/L should trigger a temporary halt in trial medication, although not necessarily a complete withdrawal from the trial (all other data collection should continue); IMP should be permanently discontinued if the neutrophil count ≤0.5 x 10^9/L (see also section 10.2) and must be reported as an Important Medical Event (see section 10.3.2). Any clinically significant changes in neutrophil count or any of the other safety assessment blood tests during the study should also be investigated as directed by the PI. Study teams can contact the Chief Investigator to discuss any major concerns (as detailed in Section 10.2, significant changes in neutrophil count must be raised with the Chief Investigator) and reference should be made to the Summary of Product Characteristics for other information on known risks and contraindications.

8.3.3 Exploratory laboratory tests

All samples (blood, and where applicable, skin and hair plucks) will be taken, processed, stored and then transported to the Francesca Capon lab, King's College, London (see study reference manual for detail on sample preparation, transport and storage). All samples sent to King's College will be curated and stored in line with ICH-GCP and statutory requirements for sample storage and patient confidentiality. The site and/or laboratory performing the mechanistic studies will depend on where the relevant expertise exists. This may be within the lab of Francesca Capon, other laboratories within King's College, London, collaborating partners outside King's College, London, and potential future collaborators that may include industry partnerships.

1. **DNA:** 2 x 6mls of blood will be collected in EDTA vacuette tubes (pink/black top) for DNA extraction (The blood is collected in EDTA coated tubes as this prevents blood from clotting. It is preferable to using heparin as an anticoagulant, as heparin may interfere with subsequent amplification of DNA by PCR).

2. **RNA**: 1 x 3mls of blood into TempusTM tubes (blue top) for RNA isolation.

3. **Plasma:** 1 x 5mls of blood in EDTA vacuette tubes (purple top)

4. **Immune-phenotyping:** 1x25mls of blood in EDTA vacuette tubes (purple top) (central site only)

5. **Hair pluck samples:** At least 6 hairs taken using tweezers. Ideally the temporal part of the head will be sampled. Details of the hair pluck protocol are provided in the APRICOT Laboratory Manual and APRICOT Guidance Notes. (Select sites only)

6. **Skin microbiopsy samples:** up to three (2mm) punch skin microbiopsy samples from consenting participants - two at baseline (affected and unaffected skin) and one at week 1 (affected skin). Preferable microbiopsy sites are the lateral outside edge of the palm. The exact site of the microbiopsy will be recorded. Details of the skin microbiopsy protocol are provided in the APRICOT Laboratory Manual and APRICOT Guidance Notes. (Select sites only)

The following exploratory objectives will be investigated as follows:

(i) **Validating IL-1 signalling as a key pathogenic driver in pustular psoriasis**: At the outset of the study, we will measure the mRNA expression of IL-1 target genes in whole blood, to determine whether IL-1 signalling is up-regulated in patients compared to healthy, (age and sex matched) volunteers. As the expression analysis will be undertaken before treatment is initiated, it will include subjects from both arms of the trial. This will allow us to maximise sample size and statistical power. To validate any differential expression findings, we will also measure transcript levels in skin microbiopsies of the palm (n>12 patients) and in keratinocytes derived from hair plucks (n>12 patients). Control skin biopsies (n≥12) and hair plucks (n>12) will be obtained from age and sex matched healthy volunteers, recruited under the affiliated protocol "Pustular Psoriasis – elucidating underlying mechanisms (PLUM)". We will complement the results of the above experiments by immuno-phenotyping IL-1 producing cells in selected cases and controls. We will isolate PBMCs from whole blood samples and use flow-cytometry to monitor the abundance and activation status of CD14+ monocytes, as well as the induction of IL-1 expression by inflammatory stimuli.

(ii) **Establishing whether response correlates with down regulation of IL-1 transcripts**: In this subsequent stage of the study, we will focus on responders (i.e. subjects recruited in stages 1 and 2, receiving anakinra and displaying a 75% reduction in fresh pustule count from baseline, by 8 weeks) and will investigate whether a positive treatment outcome correlates with a reduction in IL-1 dependent transcripts and whether the individuals who relapse (i.e. return to baseline fresh pustule count on withdrawal of anakinra by week 12) show an up-regulation of IL-1 target genes.

(iii) **Identifying potential genetic biomarkers of response to therapy**. The DNAs of trial participants will be sequenced at known and novel PPP genes to determine whether responders harbour mutations in *IL36RN, AP1S3* or other disease genes uncovered by our parallel exome-sequencing studies. This will enable us to identify potential markers of response.

(iv) **Establishing underlying disease pathogenesis.** All trial participants will be asked to contribute samples (DNA, RNA, plasma) for our companion mechanistic study (PLUM) aimed at understanding the underlying disease pathogenesis.

8.4 Photography

Photography will be completed at select sites only (pre-specified views, assessed independently by a central assessor, blinded to study treatment allocation, using structured assessment tool that will contain the following assessments for each acral site: (i) presence of fresh pustules (present, absent) (ii) fresh and total pustule count (iii) overall disease severity (clear to very severe, 5 point scale). Details of the procedures for photography image acquisition and submission are provided in the APRICOT Guidance Notes.

9. Assessment of Efficacy

9.1 Primary Efficacy Parameters

Fresh pustule count on palms and soles[3] OR Palmoplantar Pustulosis Psoriasis Area and Severity Index (see table 7 below).

(i) Fresh pustule count on palms and soles.

To be included in the count, pustules must be macroscopically visible, white/yellow in colour with no brown colour, and present on the glabrous skin of the palms and / or soles. The size of the majority of pustules will be noted at each site (<1mm, 1-3mm, >3-10mm, confluent lakes of pus).

(ii) Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI)

The PPPASI has been adapted from the PASI by Bhushan et al (25) for a RCT evaluating liazarole in palmo-plantar psoriasis (see below).

Table 7: Palmoplantar pustulosis Psoriasis Area and Severity Index

Score	0	1	2	3	4	5	6
Erythema (E)	None	Slight	Moderate	Severe	Very severe		
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe		
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe		
Area affected (%)[1]	0	>0<10	10<30	30<50	50<70	70<90	90 - 100

PPPASI = [(E+P+D) Area x 0.2 (right palm)] + [(E+P+D) Area x 0.2 (left palm)] + [(E+P+D) Area x 0.3 (right sole)] + [(E+P+D) Area x 0.3 (left sole)]

[1] where area assessed is glabrous skin on the palms/soles

Both fresh pustule count and PPPASI have been used as primary outcome measures in previous trials evaluating interventions in palmo-plantar pustulosis (6,8). The default primary efficacy parameter will be fresh pustule count unless PPPASI is more discriminating (see section 5.2).

[3] ie: glabrous skin

9.2 Secondary Efficacy Parameters

9.2.1 Total pustule count on palms and soles

To be included in the count, pustules must be macroscopically visible, white/yellow/brown in colour, with or without crust, and present on the glabrous skin of the palms and / or soles.

9.2.2 Palmo-plantar Pustulosis (Static) Investigator's Global assessment IGA

clear, almost clear, mild, moderate, severe (see study reference manual for clinical examples).

Score	Wording	Detailed description
0	Clear	No signs of PPP; no scaling or crusts or pustules
1	Almost clear	Slight scaling and/or slight erythema and/or very few new (yellow) and/or old (brown) pustules
2	Mild	Scaling and/or erythema and/or new (yellow) and/or old (brown) pustules of limited number and extent
3	Moderate	Prominent scaling and/or prominent erythema; and prominent new (yellow) and/or old (brown) pustules covering most of the affected site(s)
4	Severe	Severe scaling and/or severe erythema; numerous new (yellow) and/or old (brown) pustules with/without major confluence, covering the entire affected site(s)

9.2.3 Photography

A central assessor will evaluate the following parameters for each hand and foot:

a. Presence of fresh pustules (present, absent)
b. Fresh and total pustule count
c. Overall disease severity

9.2.4 Percentage total body area involvement with pustular psoriasis at non acral sites (not hands or feet)

To be included in the percentage area assessment, primary, sterile, macroscopically visible epidermal pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques) will be estimated using palmar method.

9.2.5 Psoriasis Area And Severity Index (PASI)

An established standard method for the evaluation of plaque psoriasis (32).

Table 8: Derivation of the PASI

Body region	Erythema (E)	Thickening (plaque elevation, induration, I)	Scaling (desquamation, D)	Area score (based on true area %, A)*
Head (H)[†]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0<10% 2 = 10<30% 3 = 30<50% 4 = 50<70% 5 = 70<90% 6 = 90-100%
Trunk (T)[‡]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0<10% 2 = 10<30% 3 = 30<50% 4 = 50<70% 5 = 70<90% 6 = 90-100%
Upper limbs (U)	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0<10% 2 = 10<30% 3 = 30<50% 4 = 50<70% 5 = 70<90% 6 = 90-100%
Lower limbs (L)[§]	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0=none 1=slight 2=moderate 3=severe 4=very severe	0 = no involvement 1 = >0<10% 2 = 10<30% 3 = 30<50% 4 = 50<70% 5 = 70<90% 6 = 90-100%

*Percentage (not score) of body region (not whole body) affected will be entered in the eCRF
[†]Neck is assessed as part of the Head (H) body region
[‡]Axillae and groin are assessed as part of the Trunk (T) body region
[§]Buttocks are assessed as part of the Lower limbs (L) body region

9.2.6 Patient reported outcome measures (PROMs).

i. Static Patient's Global Assessment
ii. Palmoplantar Quality of Life Instrument, a PPP-specific measure of impact
iii. Dermatology Life Quality Index, a validated, skin specific, measure impact
iv. EQ5D-3L, a generic measure of health outcome
v. Acceptability of treatment evaluated using a brief questionnaire.
vi. Adherence recorded via text message
vii. Assessment of disease severity/impact via text

9.3 Procedures for Assessing Efficacy Parameters

All efficacy parameters described below will be collected at every study visit for every participant, on the study specific, electronic Case Report Form (CRF). As clinical evaluations and questionnaires these are relatively involved but total visit time is expected to be no longer than 2hrs. Study specific

training on disease severity assessments must be completed before any member of the clinical research team completes study specific efficacy assessments. Clinical assessments should be conducted in a well – lit room. Additional details of the efficacy assessment tools and questionnaires are in the study reference manual.

9.3.1 Efficacy parameters to be completed by the independent blinded assessor

Following introduction with the specified script "I am just assessing your hands and feet. Please don't tell me about or show me anything else" (see also section 8.2.2) the independent blinded assessor will evaluate:

1. Fresh pustule count on palms and soles
2. Total pustule count on palms and soles (ie: yellow and brown pustules)
3. PP-PASI score
4. PPP Investigator's Global assessment

9.3.2 Efficacy parameters to be completed by other members of the study team:

1. A second measurement of the PP-PASI score and the PPP Investigator's Global Assessment
2. Pustular psoriasis at non acral sites (not hands or feet) by assessing the percentage total body area involvement (estimated using palmar method)
3. Psoriasis Area And Severity Index (PASI) to evaluate plaque type psoriasis

A PASI score (Fredriksson and Pettersson 1978), (Weisman et al 2003), (Gottlieb et al 2005) will be derived as indicated in table 8. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region. Further practical details to help with the assessment are provided below:

1. The neck is assessed as part of the head
2. The axillae and groin are assessed as part of the trunk
3. The buttocks are assessed as part of the lower limbs
4. When scoring the severity of erythema, scales should not be removed.

9.3.3 Patient reported outcome measures (PROMs)

All PROMs should be completed before the patient sees the study doctor and independent assessor (investigator or designee). The subject should be given sufficient space and time to complete the questionnaires, and be encouraged to complete any missing responses.

1. Static Patient's Global Assessment (clear, nearly clear, mild, moderate, severe, very severe)
2. Palmoplantar Quality of Life Instrument, a patient-completed 32 item questionnaire capturing symptoms, impact on function and ability to work (score 0-70) (3)
3. Dermatology Life Quality Index, a validated, patient-completed 10 item questionnaire measuring impact of skin disease (score 0-30) (28)
4. EQ5D-3L, a 5 item questionnaire with a Visual analogue scale as a generic measure of health outcome
5. Acceptability of treatment evaluated using a brief questionnaire, administered at study completion with structured items with a response scale of 1-5 and free text box for other issues/expanded responses. Fields will cover acceptability of, and any technical difficulties with, self-administered daily injection, degree of distress and whether the treatment was worthwhile. Results will be tabulated as simple descriptives with illustrative quotes. If the free text boxes elicit a lot of unexpected and/or interesting issues we will undertake a simple content analysis and examination of the dominant (most frequent) categories.
6. Adherence and compliance recorded via text message

10. Assessment of Safety

10.1 Specification, Timing and Recording of Safety Parameters

Throughout the study, Investigator-led evaluation of Safety at each study visit will highlight:
- Adverse events, with special attention to infection
- Severe disease flare
- Treatment withdrawal

During the screening period, in addition to a full history and clinical examination, screening safety investigations will include: CXR, Interferon gamma release assay (TSPOT.TB, Oxford Immunotec), FBC, LFTs (including AST, ALT), creatinine, electrolytes, urine analysis, serology testing for HIV, HBV and HCV.

At visit 1, prior to dispensing drug, all blood monitoring investigations will be reviewed (including CRP count at this visit 1 (baseline) only) and checked to ensure they are normal/negative and/or comply with protocol inclusion criteria.

At each subsequent study visit, specific enquiry will be made about adverse events, intercurrent illness or side effects including formal review of all systems, presence and severity of injection site reactions, any GP or hospital visits, changes to concomitant therapy, or new medications (not necessarily prescription only). Clinical examination will include recording of temperature, blood pressure, general examination and evaluation of disease severity (to identify any potential severe disease flare). Blood monitoring safety assessments at each visit will include FBC, LFTs, creatinine, electrolytes, urine analysis. Results of blood monitoring safety assessments will be checked promptly by the research team.

A final safety visit (can be remote) should be scheduled for each participant 90 days after their last dose of trial medication (i.e. week 20 or earlier depending on last dose date). Specific enquiry must be made regarding adverse events, intercurrent illness or side effects, and concomitant medication and reports must be escalated to the sponsor if applicable.

In the event of adverse events, additional investigations may be arranged as indicated by emergent signs/symptoms by investigators at study sites. All adverse events and side effects will be recorded in the case report form (CRF) throughout the study regardless of their severity or relation to study participation.

10.2 Temporary Treatment Discontinuation

Should blood monitoring safety assessments indicate serious infection, neutropenia (neutrophil count $<1.0 \times 10^9$/L), thrombocytopenia (platelet count $<75 \times 10^9$/L) or in the opinion of the investigator results are clinically significant and continuation on the trial contra-indicated temporary discontinuation of trial treatment is applicable. The local investigator and/or site staff should inform the Trial Manager and Chief Investigator immediately should discontinuation be necessary. The decision to restart should be discussed between the Chief and Principal Investigator and will be assessed on a case by case basis.
N.B: If neutrophil count is $\leq 0.5 \times 10^9$/L IMP should be permanently discontinued.

10.3 Procedures for Recording and Reporting Adverse Events

10.3.1 Eliciting reports

Adverse events will be collected from the time the participant enrols in the study (Visit 0) until the time the event resolves or until 90 days after the participant's last dose of trial medication (i.e. end of week 8 or whenever participant's last dose is given), whichever comes first (this includes the OLE period). Aside from clinical review at study visits, an abnormal value or result from a clinical or laboratory evaluation (e.g. abnormal LFTs) can also indicate an adverse event. If this is the case, then the evaluation that produced the value or result should be repeated until that value or result returns to normal or it can be judged by the Investigator that the participant's safety is not at risk. If an abnormal value or result is determined by the investigator to be clinically significant, it must be recorded as an adverse event on the CRF.

10.3.2 Recording and reporting adverse events

(i) Definitions relevant to safety recording and reporting

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 gives the following definitions:

Adverse Event (AE): Any untoward medical occurrence in a subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR): Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR): An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC) for anakinra.

Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Unexpected Serious Adverse Reaction (USAR): Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that

Results in death;
Is life-threatening;
Required hospitalisation or prolongation of existing hospitalisation;
Results in persistent or significant disability or incapacity;
Consists of a congenital anomaly or birth defect.

Important Medical Events (IME) & Pregnancy

Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious.

Any serious infection, infection requiring intravenous antibiotics, incidence of TB, a neutrophil count of $\leq 0.5 \times 10^9$/L or a platelet count of $< 75 \times 10^9$/L must be reported as an Important Medical Event via the Kings Health Partners Clinical Trials Office SAE reporting pathway. Temporary cessation of treatment should also be considered (discontinuation is essential if neutrophils $\leq 0.5 \times 10^9$/L), and discussion initiated with the CI. Please see Section 8.3.2 and 10.2. Any suspected transmission of an infectious agent via a medicinal product shall also be considered serious.

Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system.

Death as a result of disease progression and other events that are primary or secondary outcome measures are not considered to be SAEs and should be reported in the normal way, on the appropriate CRF.

(ii) Recording adverse events

Safety data will be recorded on a CRF specifically designed for this purpose. All serious adverse events (SAEs) will be reported on an SAE report form as well as on individual CRFs. The current SAE form can be found on the Kings Health Partners Clinical Trials Office website: http://www.khpcto.co.uk/SOP/SAE_Reporting.html. All data will be reviewed periodically by the data monitoring committee (DMC). The DMC has the authority to withdraw any participants and/or terminate the study because of safety findings. The DMC can recommend the termination of the study because of safety findings to the Trial Steering Committee (TSC). The investigator will treat participants experiencing adverse events appropriately and observe them at suitable intervals until their symptoms resolve or their status stabilizes.

Guy's and St Thomas' NHS Foundation Trust, as sponsor, have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the Kings Health Partners Clinical Trials Office (KHP-CTO), London.

(iii) Safety Reporting for local centres

The local PI will report immediately after becoming aware (and no later than 24 hours) all SAEs including Important Medical Events such as serious infection and IV antibiotics, SARs and SUSARs to the KHP-CTO in accordance with the current Pharmacovigilance Policy. Assessment of seriousness, causality, intensity and expectedness for trials involving IMPs must be made by the PI or another authorised doctor. If an authorised doctor from the reporting site is unavailable, initial reports without causality and expectedness assessment should be submitted to the Sponsor by a healthcare professional within 24hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter. The Chief Investigator must confirm the seriousness, causality, intensity and expectedness of any SAE, SAR and SUSAR by signing and dating the report form received from the local site, then send a copy of the signed report to the KHP-CTO and back to the local site. In his/her assessment, the Chief Investigator can agree with or upgrade a safety report, but not downgrade it. Sites should not request emergency unblinding when reporting any SUSAR unless the information is needed to make immediate medical decision (see also section 10.3).

(iv) Safety reporting for the coordinating centre

All SAEs, SARs and SUSARs will be reported immediately (and no later than 24hours) by the CI to the KHP-CTO in accordance with the current PV policy.

The KHP-CTO will report SARs and SUSARs to the Medicines and Healthcare products Regulatory Agency (MHRA). Reporting timelines are as follows: SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days. SUSARs that are not fatal or life threatening must be reported within 15 days of the sponsor first becoming aware of the reaction. The CI will provide an annual report of all SARs (expected and unexpected), and SAEs which will be distributed to the Sponsor (KHP-CTO), MHRA and the Research Ethics Committee (REC). Serious adverse events will be reported to the respective REC as mandated by them. The DMC will be provided listings of all SAEs on an ongoing basis.

10.3.3 Adverse events that do not require reporting

All AEs which occur within the trial period (12 weeks) and during the OLE period (for applicable patients) will be recorded on the trial CRFs. AEs occurring after the trial period and up to 90 days post last dose of trial medication must also be reported if necessary escalated to the sponsor and/or DMC.

10.4 Trial Stopping Rules

Enrolment or participation in the trial may stop at any time if there are significant safety concerns. The trial may be prematurely discontinued by Trial Steering Committee at any time.

If the trial is prematurely discontinued, active participants will be informed and no further participant data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

All serious life threatening adverse events will be reported to the DMC within 24 hours of the investigator team being informed of the event. The trial will be suspended pending review in the event of death in any participant where death is attributed in any way to study therapy, or of serious adverse event(s) if, in the opinion of the DMC, this is warranted.

Study unblinding will be invoked for any study participant experiencing a clinical adverse event when, in the opinion of the healthcare professional in charge of their clinical care, knowledge about whether or not a patient is receiving active study drug would materially change clinical management and/or benefit the patient's safety and wellbeing (e.g.: suspected sepsis).
The emergency code break, along with all study documentation and medical support will be available 24 hours a day to all authorised users (all healthcare professionals responsible for the care of study subjects, Clinical Trial investigators and pharmacists) via the King's Health Partners' approved independent provider, ESMS Global, and in accordance with standard operating procedures (http://www.khpcto.co.uk/index.html). Each randomised subject will be provided with a card detailing code break telephone numbers and emergency contact details. Subjects will be requested to carry this card with them at all times whilst participating in the trial.

11. Study Variables

11.1 Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (age, weight, height, ethnicity), disease phenotype as described in by the European Rare And Severe Psoriasis Expert Network, medical and medication history.

11.2 Primary endpoints

The determination of the efficacy of anakinra in treatment of adults with PPP compared to placebo, measured by an independent blinded assessor using:

Fresh pustule count on palms and soles[4] across 1,4 and 8 weeks, adjusted for baseline (visit 1), OR

Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) across 1,4 and 8 weeks, adjusted for baseline (visit 1)

[4] ie: glabrous skin

The default primary endpoint will be fresh pustule count unless PPPASI is more discriminating (to be reviewed at the end of stage one).

The Stage 1 review occurred on 22nd January 2018. As a result of this review the DMC recommended the primary outcome to be PPPASI and this was passed by the TSC. Fresh pustule count will be a secondary outcome.

11.3 Secondary endpoints

11.3.1 Investigator assessed

Total pustule count on palms and soles[4] across weeks 1, 4, 8, adjusted for baseline (visit 1)

PPP - Investigator's Global assessment (PPP-IGA) at weeks 1, 4 and 8 compared to baseline (visit 1)

Time to response of PPP (defined as a 75% reduction in fresh pustule count [default primary outcome] compared to baseline), and relapse rate (defined as return to baseline fresh pustule count)

Achievement of 'clear' on PPP-IGA by 8 weeks

Development of a disease flare (ie: $\geq$50% deterioration in PPPASI compared to baseline, visit 1)

Pustular psoriasis at non acral sites (not hands and feet) as measured by change in percentage area of involvement at 8 weeks compared to baseline (visit 1)

Plaque type psoriasis (if present) measured using Psoriasis Area and Severity Index (PASI) at 8 weeks compared to baseline (visit 1)

Serious infection as defined by any infection leading to death, hospital admission or requiring IV antibiotics

Neutropenia (ie: neutrophil count of $1.0x10^{-9}$/l on at least one occasion)

11.3.2 Patient reported outcome measures (PROMS)

Patient's Global Assessment (clear, nearly clear, mild, moderate, severe, very severe) across 1, 4, 8 weeks compared to baseline (visit 1)

Palmoplantar Quality of Life Instrument score in randomised patients at 8 weeks compared to baseline (visit 0)

Dermatology Life Quality Index at 8 weeks compared to baseline (visit 0)

EQ5D-3L score at 8 weeks compared to baseline (visit 0)

Treatment acceptability (ie: whether the treatment is 'worthwhile') evaluated using a brief questionnaire with a response scale of 1-5 at study end

Adherence to treatment measured by responses to daily text message over 8 weeks of treatment

11.4 Exploratory (mechanistic) endpoints

Expression levels of IL-1 related transcripts in blood, skin and keratinocytes derived from hair plucks

Disease-associated mutations

Patient immune phenotypes

Complete clinical, DNA, RNA, serum datasets (with optional tissue samples [skin and hair pluck]) on patients with pustular psoriasis

11.5 Open Label Extension endpoints

11.5.1 Investigator assessed

Palmoplantar Pustulosis Psoriasis Area and Severity Index (PPPASI) at Visit OLE 4.

Fresh pustule count at Visit OLE 4.

Total pustule count at Visit OLE 4.

PPP-IGA at Visit OLE 4.

Achievement of 'clear' on PPP-IGA at Visit OLE 4.

Plaque type psoriasis (if present) measured using Psoriasis Area and Severity Index (PASI) at Visit OLE 4.

Serious infection as defined by any infection leading to death, hospital admission or requiring IV antibiotics.

Neutropenia (i.e.: neutrophil count of $1.0x10^{-9}$/l on at least one occasion).

11.5.2 Patient reported outcome measures (PROMS)

Adherence to treatment measured by responses to daily text message over 8 weeks of treatment

12. Statistics

12.1 Sample Size

12.1.1 Clinical Trial

Stage 1. The sample size for stage 1 is based on correct ordering of group means. We want a high probability of continuing ('GO') if there is a true difference in means between the groups of 0.5 standard deviations (SDs), in favour of the treatment group. This size of difference is conservative, i.e.: larger differences have been reported. With 20 patients assuming a real difference of 0.5 standard deviations, the probability that the means for treatment arms will be correctly ordered (i.e. treatment > placebo) is 0.85. If two outcomes are assessed, each with an expected difference of 0.5 SDs, then the overall probability of failing to GO is $(1-0.85)^2 = 0.0225$ i.e. less than 3 in 100. There is thus a minimal chance of failing to continue if the treatment really is beneficial. If there is no treatment benefit, the probability of not progressing to the next stage is 0.25. Whilst this seems low, the balance of errors has been selected to allow optimal identification of treatment benefit and at most could only be 0.5 under this design. Stage 1 does not involve statistical tests or estimation and

so none of the 'p' is spent in this first stage. To ensure that 10 participants contribute to each arm the interim for Stage 1 will occur after 24 participants have been randomised and followed up

Stage 2. We anticipate the average number of fresh pustules at baseline will be 20 and that the placebo arm will see minimal reduction over time (25). As there are two potential primary outcomes the sample size has been calculated using a standardised effect size. A large effect size of 0.9 SD has been assumed. This was chosen with consideration to the cost of the drug and motivation for patients to adhere to treatment given the requirement for daily self-administered subcutaneous injections. In addition large effect sizes have been reported with oral retinoids (8, 26), a recommended systemic intervention for pustular psoriasis To detect a difference of 0.9 SD with power 90% and 5% significance level a sample size of 27 per arm would be required, RCTs involving placebo arms (8, 25), observed a withdrawal rate less than 5%. We aim to recruit 32 participants per arm (N=64 in total) which will allow for an approximate 15% withdrawal rate.

12.1.2 Mechanistic Study

To determine whether IL-1 target genes are up-regulated in patient blood, we will compare the levels of >80 transcripts in 96 cases (all 64 trial participants + 32 affected individual recruited through our companion mechanistic study[5]) vs. healthy, age and sex matched volunteers (n = 48, recruited through our companion mechanistic study[6]). Our power calculations indicate that this sample would have adequate power (>80%) to detect two-fold differences in gene expression, at a significance level ($P < 0.0001$) that would withstand robust corrections for multiple testing. To determine whether any differentially expressed gene is regulated by anakinra, we will examine transcript levels in responders (n =14, blinding of the clinical study team will be maintained) and in patients receiving placebo (n=14, negative control group), at visits 0, 1, 2, 4 and 5. To enable a more robust assessment of baseline gene expression levels, we will take two independent measurements, using samples obtained at visits 0 and 1.

To validate the IL-1 signature observed in blood, we will also analyse the differentially expressed genes in skin and in keratinocytes obtained from hair plucks. As we will also be taking samples from the patients enrolled in our affiliated mechanistic study[6], we anticipate that we will be able to analyse 12 skin biopsies and 12 sets of hair plucks, which we will compare to control samples (n≥12 for both datasets), obtained from volunteers entering the mechanistic study[6]. Our calculations indicate that both the responder cohort, the hair pluck and the skin biopsy dataset would have sufficient power to document two-fold differences in gene expression, at a significance level ($P < 0.005$) that would withstand the modest corrections for multiple testing built in a targeted follow-up experiment.

Importantly, the proposed sample size for this experiment is comparable to that described in recent transcriptomic studies, which successfully detected an IL-1 down-regulation signature in patients treated with anakinra (14, 15). To determine whether IL-1 producing cells are more abundant or abnormally activated in patients, we will be immune-phenotyping PBMCs obtained from trial participants and unaffected controls (n =20, recruited as part of the companion mechanistic study[6]) Our calculations show that this dataset would have sufficient power to demonstrate 2-fold differences in cell numbers/activation read-outs, at a significance level ($P < 0.005$) that would withstand the modest corrections for multiple testing built in a targeted experiment

To determine the mutation status of study participants we will analyse a cohort (n=64) that has >80% power to detect low-frequency disease alleles, accounting for as little as 2% of patient chromosomes.

12.2 Randomisation

[5] Pustular Psoriasis – elucidating underlying mechanisms (PLUM)

Participants will be randomised using an online randomisation system by the King's Clinical Trial Unit to ensure allocation concealment. Participants will be allocated to treatment arms using blocked randomisation stratified by centre. Randomisation will be based only on unique identification numbers (not participant personal details).

12.3 Analysis

12.3.1 Clinical Trial

The primary analysis will follow the intention to treat principle and include all participants in the treatment arms to which they were allocated to regardless of treatment subsequently received. At stage 1 the mean of fresh pustule count and PPPASI will be calculated by treatment arm and the distribution of the outcomes assessed. These results will form part of the decision to progress to stage 2. The pre-specified criteria for this decision have been listed above. If the mean pustule count OR PPPASI is lower in the treatment arm compared to the control arm then the efficacy based recommendation will be to proceed to stage 2 (to be considered with other criteria such as harms and feasibility aspects). Stage 1 analysis will be performed after 24 participants have been recruited and completed 8 weeks of follow-up after start of treatment.

At the end of stage 2, the primary analysis model will be a linear (Gaussian) mixed effect model, using data (fresh pustule count or PPPASI) from 1, 4, and 8 week follow up assessments, with random subject effects and fixed effects for study visit, treatment arm and study visit by treatment arm interaction. Centres will be included in the model either as a fixed of random effect depending on the total number of centres recruiting to the study and with consideration to the average number of participants recruited from each centre. The estimated treatment effect at 8 weeks will be reported with 95% confidence intervals and corresponding p value. The main conclusion of the trial will be based on this analysis time point. We will also report the treatment effect at weeks 1 and 4. Model assumptions, including the normality of residuals and random effects distributions will be assessed in addition to a diagnostic assessment of influential observations. If any assumptions are poorly met then an appropriate transformation of the outcome (e.g. log transformation) will be considered.

A sensitivity analysis will then be undertaken for the primary analysis with adjustment for use of rescue medication. The proportion of participants using rescue medication and the amount used will be summarised by treatment arm. The primary analysis will be repeated including 12 week follow up data. All treatment effect estimates will be reported with 95% confidence intervals and 5% significance level will be used.

Every effort will be made to obtain all follow up data for all participants including those that have stopped treatment. The analysis methods above employ maximum likelihood estimation and thus are efficient for handing missing outcome data under a missing at random (MAR) assumption. We will undertake a sensitivity analysis in which we will impute values for missing outcome data to examine the potential impact of missing values using the strategy laid out in White et al (29).

Continuous secondary outcomes will be analysed using the same modelling approach as specified above. Binary outcome data will be analysed using logistic regression models which include adjustment for centre (stratification variable). To visualise the raw data Kaplan Meier curves will be plotted for time to response and time to relapse. Since outcomes are observed at relatively few discrete time intervals (week 1, 4, 8 and 12) an analysis model suitable for discrete survival time data, such as a complementary log-log model, will be fitted to estimate the treatment effect for the time to event outcomes. The time to event models will include a treatment arm and covariate and adjustment for centre (stratification variable). If the proportional hazard assumption is not met an

alternative parameterisation (e.g. including a treatment by time varying effect), restricting the observation time or suitable time-to-event model will be sought.

Adverse events will be tabulated by treatment group. Where useful Poisson regression models will be used to estimate relative risks, risk differences and incidence rate ratios for adverse events. Where suitable the timing of adverse events (using hazard plots) by treatment arm will be examined. No hypothesis testing will be undertaken for adverse event outcomes but approaches to assess signal for ADRs will be explored.

A detailed statistical analysis plan for stage 1 will be drawn up and agreed by the TSC prior to data being extraction from the Kings CTU database. For stage 2, a detailed statistical analysis plan will be drawn up and agreed by the TSC once the primary outcome has been confirmed and prior to any unblinded data extraction by the sub-group blind statistician for the final analysis. All analyses will be undertaken by sub-group blind study statisticians. The DMC will be responsible for assessing safety with judgments made at their discretion, as no formal statistical stopping rules will be employed.

12.3.2 Open Label Extension

The number of participants entering the OLE will be summarised overall and by original randomised treatment arm. Baseline characteristics of all participants in the original double blind period will be descriptively compared against those of the participants entering the OLE period. In the OLE some participants will be continuing their medication (some following a 4 week break and some with a longer break) and some participants will be starting the medication for the first time. As a result it is not possible to undertake a randomised comparison for this extended follow-up period and we will instead treat this as an observational intervention period. A summary of the total time on-treatment will be presented for individuals originally assigned to the active treatment arm who enter the OLE, in addition to the time-off treatment in between the double-blind an open label component.

For the population of participants continuing into the OLE phase, descriptive statistics will be 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, PPPASI, PPP-IGA, clearance on PPP-IGA, and PASI) by original randomised treatment. Any occurrences of serious infection or neutropenia will be summarised by original randomised treatment arm. We will also combine the 8 week outcomes of the participants originally randomised to the active arm from the double blind portion of the trial 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 will be presented for the first time exposure group.

Adverse events will be tabulated for the exposed patients at a selected number of follow-up times (8, 12, 16, 20, +) from the time the drug was first started until their longest follow-up time. For AEs of special interest that have > 5-10 events we will plot the hazard rate overtime for the exposed. No statistical testing will be performed given the open-label study design and how some participants will commence OLE treatment immediately following the 12 week visit, whilst others will have previously completed the full double-blind trial schedule.

12.3.3 Mechanistic study

Gene expression levels at week 0 will be compared in cases vs. controls using an unpaired t-test. Transcripts that show a change in expression of at least two-fold and yield *P* values < 0.05 after correction for multiple testing will be selected for follow-up. In the second stage of the study, the genes that are differentially expressed in patients will be examined in 14 responders receiving anakinra and 14 patients receiving placebo. Transcript levels measured at weeks 0, 1, 8 and 12 (visits

1, 2, 4 and 5) will be compared within each group using One Way ANOVA with a Bonferroni post-test. *P* values < 0.05 after correction for multiple testing will be considered statistically significant. Those genes that are differentially expressed in responders, but not in patients receiving placebo, will be defined as therapeutic targets regulated by anakinra.
Genes that are differentially expressed in patient blood will also be followed up in skin and in keratinocytes obtained from hair plucks. For both datasets transcript levels will be compared in cases (n≥12) vs. controls (n≥12), using an unpaired t-test. Upon completion of flow-cytometry experiments, monocyte numbers, activation marker expression levels and IL-1 induction will also be compared in cases vs. controls. *P* values <0.05 after correction for multiple testing will be considered statistically significant.

13. Trial Management Group

The Trial Management Group (TMG) consists of the Co-Applicants to the trial grant and is responsible for decisions on the day to day running of the trial and provides the mechanism though which co-applicant opinion can be sought on matters arising by the central trial team at Guy's Hospital. The TMG has a responsibility to report to the Trial Steering Committee and will meet by teleconference at least once a month and in person approximately every three months.

14. Trial Steering Committee

The Trial Steering Committee (TSC) will include an independent Chair (E O'Toole, Professor of Molecular Dermatology, Barts and the London School of Medicine, Queen Mary University of London), two independent members (H Bachelez, Professor of Dermatology, Saint-Louis Hospital, Paris and S Kelly, Consultant Rheumatologist, Barts Health NHS Trust), independent patient representative, C Smith (CI) and V Cornelius (Trial Statistician).. The TSC will meet as required with invited observers from EME programme, and is responsible to the EME programme board. The TSC is the main decision making body. It has overall responsibility for scientific strategy and direction and has ultimate responsibility for ensuring the project's aims are delivered on time and within budget. Specific roles, meeting frequency and timelines will be detailed in the Trial Steering Committee Terms of Reference according to the MRC guidelines for Good Clinical Practice in Clinical Trials 1998 and will be:

1. to make decisions necessary to ensure successful delivery of the study
2. to evaluate progress against the agreed timetable and deliverables
3. to administer the budget and monitor spending
4. to develop and implement successful communication between study staff and external stakeholders
5. to consider and act, as appropriate, upon the recommendations of the Data Monitoring and Ethics Committee and the Patient and Lay members group
6. development, implementation and evaluation of appropriate policies and procedures to facilitate the protection of knowledge and exploitation of results
7. development, implementation and evaluation of appropriate policies and procedures to ensure the effective dissemination of results to appropriate stakeholders

15. Data Monitoring Committee

The Data Monitoring Committee (DMC) will be chaired by an independent Chair (Chair D Symmons, Professor of Rheumatology and Musculoskeletal Epidemiology, University of Manchester) and will be responsible for monitoring evidence for treatment harm and review all decisions made in relation to the safety aspects of the study. The DMC will meet on initiation of the project, and agree the type, frequency and format of data reports. A DMC Charter will be constructed and agreed prior to first review of study data. Meeting time points, subject to agreement by members of DMC are:

1. when approximately the first 10 patients (5 in each group) have completed 8 weeks of treatment
2. at completion of stage 1 (after 24 participants have been recruited and completed 8 weeks of treatment)
3. when required during stage 2 (e.g.: when 15, and 30 patients have been recruited)
4. at end of study
5. extraordinary meetings may be convened to discuss severe adverse events

The DMC chair will be notified within 24 hours of any SAE/SAR/SUSAR. The DMC reports to the TSC and (via the TSC) to the EME programme.

16. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the Sponsor(s), Regulators and REC direct access to source data and other documents (e.g. patients' case sheets, blood test reports, X-ray reports, histology reports etc.).

17. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of GCP and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to London Dulwich Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor), the REC and the MHRA within the timelines defined in the Regulations

18. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

18.1 General monitoring

The trial will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and standard operating procedures. Regular monitoring will be performed according to ICH GCP. The investigator sites will provide direct access to all trial related source data/documents and reports for the purpose of monitoring and auditing by the sponsor and inspection by local and regulatory authorities. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements

18.2 Audit & Inspection

The Quality Assurance manager will conduct internal audits to check that the trial is being conducted, data recorded, analysed and accurately reported according to the protocol and in compliance with ICH GCP, meeting the requirements of the MHRA. The audits will also include laboratory activities according to an agreed audit schedule taking into consideration the 2009 MHRA guidelines for GCP in the laboratory.

18.3 Serious breaches

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.
A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree a) the safety or physical or mental integrity of the subjects of the trial; or (b) the scientific value of the trial”. In the event that a serious breach is suspected, the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and the NHS host organisation within seven calendar days.

18.4 Site Training

Trial specific training for participating centres will be provided by the central study team. This will include a comprehensive site initiation visit where all involved local staff will be trained on the protocol and trial procedures. Guidance throughout the trial will be available from the central study team on request and contact details will be provided.

19. Data Handling

The Chief Investigator will act as custodian for the trial data.

Data will be managed using the InferMed MACRO database system. An electronic Case Report Form (eCRF) will be created using the InferMed Macro system. This system is regulatory compliant (GCP, 21CRF11, EC Clinical Trial Directive). The eCRF will be created in collaboration with the trial statisticians and the CI and maintained by the King’s Clinical Trials Unit. It will be hosted on a dedicated secure server within KCL.

Source data will be entered by authorised staff onto the eCRF with a full audit trail. Study sites will aim to enter eCRFs within 7 days of data collection.

Data relating to samples will be entered on a secure, web based database, hosted on secure servers by Guy’s and St Thomas’ NHS Foundation Trust. Photographs will be transferred to the central trial team via secure nhs.net email accounts and will be saved onto a separate secure database.

Over the course of the trial, the Trial Manager and/or the Trial monitor will conduct on-site/central monitoring. The Data Manager/Statistician may identify data fields that should be checked against the source data during site monitoring visits, the specifics will be outlined in a Trial Monitoring Plan. Where there are data queries raised the recruiting centre staff will be responsible for resolving the queries. The Trial Manager will review responses before closing queries.

20. Data Management

Trial data:
(i) Database Website Address
Go to www.ctu.co.uk and click the link to MACRO EDC V4 on the lower right hand side of the screen.

(ii) Database passwords:
Database access will be strictly restricted through passwords to the authorised research team. The CI or delegate will request usernames and passwords from the KCTU. It is a legal requirement that passwords to the eCRF are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a personalised username and password should be requested via the CI or delegate (e.g Trial Manger) from the KCTU administrator.

(iii) Data Handling & Confidentiality/Format of Records
Data will be handled, computerised and stored in accordance with the Data Protection Act, 1998.

Participants will be identified on the study database using a unique code and initials. The investigator will maintain accurate patient records/results detailing observations on each patient enrolled.

(iv) Identifiable Data
All participant contact information data will be stored on spreadsheets within the recruiting site, which will have restricted access from password protected computers. Accrual data uploaded to the UKCRN portfolio database will be anonymised and collated by the CI or delegate to the CLRN. No identifiable data will be entered on the eCRF or transferred to the KCTU.

(v) Main Database
SAE data will be collected on paper SAE report forms and faxed or emailed to the KHP CTO. Summary details of SAEs will be transcribed to adverse event section of the eCRF.

For all other data collected, source data worksheets will be prepared for each patient and data will be entered onto the eCRF database. Source data worksheets will be reconciled at the end of the trial with the patient's medical notes in the recruiting centre. During the trial, critical clinical information will be written in the medical notes and/or the electronic patient record (depending on arrangements within local participating sites for routine medical record keeping) to ensure informed medical decisions can be made in the absence of the study team. Trial related clinical letters will be copied to the medical notes during the trial. The Principal Investigator will provide an electronic signature for each patient Case Record Form once all queries are resolved and immediately prior to database lock.

At the end of the study, essential documentation will be archived in accordance with sponsor and local requirements. The retention of study data will be the responsibility of the Chief Investigator.

(vi) Assessments/Data Collection:
Written informed consent must be obtained prior to screening and any other study specific procedures taking place.

(vii) Database lock
The final checking of data and data cleaning will be undertaken by the trial manager, in collaboration with the investigators and trial statistician. After completion of all follow-ups and prompt entry of data, the Trial Manager will review the data and issue queries as necessary. The study site must then answer these queries before the participant's data is locked within the database. After that time, changes will not be made to the database by the research site unless specifically requested by the coordinating site in response to statistician data checks.

At the end of the trial, the site PI will review all the data for each participant and provide electronic sign-off to verify that all the data are complete and correct. At this point, all data will be formally locked for analysis. At the end of the trial, each centre will be supplied with a CD-ROM containing the eCRF data for their centre. This will be filed locally for any future audit.

Sample related data:
Data relating to samples will be entered directly onto a secure research database. The database will be password protected and access restricted to named study individuals only. The database used may be one purpose built, developed and maintained by the NIHR Biomedical Research Centre at

Guy's and St Thomas's NHS Foundation Trust (GSTT) and King's College London (KCL)known as CAPTURE (ChArting PaTient outcomes Using an online REsource).

CAPTURE is a web-based forms system used to record clinical research data for use in research studies and clinical trials. CAPTURE sits on the GSTT servers behind the NHS firewall and data stored within CAPTURE is afforded the same security controls as any clinical data held within the GSTT servers. CAPTURE will be used by GSTT and KCL staff members onsite as well as third-party collaborators. External staff will access the system via the public internet, secured with industry standard SSL and SafeNet 2-factor authentication. Further details of the architecture of CAPTURE and additional CAPTURE specific security measures can be found in the CAPTURE Information Governance Policy.

Identifiable information held on the database will only be accessible by the Chief Investigator and approved delegated members of the study team.

Photographs:
Photographs taken at participating centres (four hub sites only) will be transferred and stored at the central site. Images will be anonymised but will be saved on the secure NHS database using initials and possibly date of birth.

21. Publication Policy

The main outputs from this research comprise:
- precise delineation of clinical efficacy of anakinra in Palmo-Plantar Pustulosis, PPP
- identification of potential biomarkers of response to anakinra
- optimised trial methodology for investigating interventions in pustular psoriasis
- augmented biobank of samples for future research

The strong clinical, academic and industry collaboration that has been forged to successfully deliver this project will be used to ensure wide dissemination and uptake of research findings. We have immediate access to facilitate this through clinical and academic networks nationally (eg: UK Translational Research Network in Dermatology, British Association of Dermatologist's Biologics Interventions Registry, UK Dermatology Clinical Trials Network, PSORT) and internationally (European Rare And Severe Psoriasis Expert Network, International Psoriasis Council); Lachmann (Co-app) will disseminate findings to relevant audiences beyond dermatology.

Methods used will include presentations and published abstracts at relevant scientific meetings, publication of full papers in high impact scientific journals, and a full and complete account of the trial and related mechanistic research will be published in the NIHR Programme specific journal (as per NIHR guidance).

People with pustular psoriasis will be informed of results in formats reviewed and approved by our Patient and Lay-members Group, via the Psoriasis Association website (40,000 hits/month) and meetings, PPI groups, planned information exchange events and related social media. The Psoriasis Association will also ensure information is disseminated internationally to patient groups.

Information will also be disseminated to the pharmaceutical industry (inc. ABPI), particularly, those developing agents for IL-1 mediated diseases as our studies have the potential for providing key information for further drug development.

We also plan (and have costed) a formal event at the end of the project to disseminate research

findings with components tailored to the individual needs of the academic, patient, public and industry communities.

22. Insurance / Indemnity

Insurance for this trial is provided by Guy's and St Thomas' NHS Foundation Trustunder the Clinical Negligence Scheme for Trials (CNST).

Circle health limited (Nottingham) is a non-NHS APRICOT site, and is a member of the Clinical Negligence Scheme for Trusts (CNST). NHA resolution have provided indemnity cover to Circle Health Limited for clinical negligence liability.

23. Financial Aspects

Funding to conduct the trial is provided by the MRC NIHR EME programme. IMP (anakinra and placebo) is provided by SOBI.

As this is a non-commercial research study eligible for inclusion in the National Institute for Health Research (NIHR) Clinical Research Network Portfolio database, NHS Support Costs, including the additional patient-related costs associated with the research, (costs which would end once the R&D activity in question has stopped) for example extra patient tests, extra in-patient days, and extra nursing attention, may be met by NHS R&D Support Funding (Clinical Local Research Network (CLRN) funding). Further information is provided in the Department of Health's AcoRD (Attributing the costs of health and social care Research and Development) document, which can be downloaded at: http://www.ccf.nihr.ac.uk/RfPB/Documents/dh_4125282.pdf.

24. Signatures

_____	_____
Principal Investigator	Date
_____	_____
Chief Investigator *Professor Catherine Smith*	Date
_____	_____
Statistician *Victoria Cornelius*	Date

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26. Appendix A: Contraception Guidelines

Women of Child-Bearing Potential (WOCBP) are eligible to participate in the study following confirmation:

(i) agreement to remain abstinent during the period of IMP dosing and for at least 4 weeks after the last dose. Abstinence is acceptable if it is in line with the preferred and usual lifestyle of the patient or

(ii) use single or combined contraceptive methods that result in failure rate <1% per year during the IMP dosing and for at least 4 weeks after the last dose of study treatment.

Examples of contraceptive methods with a failure rate of <1% per year include tubal ligation, male sterilisation, hormonal implants, combined contraceptives (oral/injection), certain IUDs. Alternatively two methods (eg: two barrier methods such as condom and a cervical cap) may be used to achieve a failure rate of <1%. Barrier methods must always be supplemented with use of spermicide.

For men: it is not known if the study medicine will affect sperm or semen. Therefore it is recommended that you should not father a child while taking study medication. Male subjects will need to use adequate contraception during the period of IMP dosing and for up to 10 weeks after the last dose of study drug. If your partner might become pregnant you must use reliable forms of contraception e.g. oral contraceptive and condom, intra-uterine device (IUD) and condom, diaphragm with spermicide and condom. If your partner becomes pregnant while you are taking study medication, or within 6 months of stopping treatment, you should inform your study doctor immediately. As the risk to your partner and baby is unknown, it is desirable for your partner to agree to medical supervision during her pregnancy and for the baby after it is born.