Full Title:

A Phase II, Multicentre, Randomised, Double Blind, Placebo Controlled Parallel Group Study, Followed By A 36 Week Active Treatment Phase To Evaluate The Efficacy And Safety Of Secukinumab In Patients With Non-Ocular Behçet's Syndrome

Short Title: Secukinumab in Behçet's

- **This protocol has regard for the HRA guidance and order of content**

Full/Long Title of The Trial	A Phase II, Multicentre, Randomised, Double Blind, Placebo Controlled Parallel Group Study, Followed By A 36 Week Active Treatment Phase To Evaluate The Efficacy And Safety Of Secukinumab In Patients With Non-Ocular Behçet's Syndrome
Short Trial Title / Acronym	**Secukinumab in Behçet's**
Protocol Version Number and Date	Version 1.3_25May2023
Investigational Product	Biological: AIN457/Secukinumab
Phase	Phase 2 Proof of principle
EudraCT Number:	2022-000255-37
ISRCTN Number / Clinical trials.gov Number:	ISRCTN94958652
Sponsor Research Reference Number	SP0422
IRAS Number:	1005007
Sponsor	Liverpool University Hospitals NHS Foundation Trust RGT@liverpoolft.nhs.uk Tel: 0151 706 3702
Chief Investigator	Prof Robert Moots

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.
I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor
I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: Heather Rogers
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.....

Date: 02/06/2023
...../...../.....

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Position: Research Governance Manager
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Chief Investigator:

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Date: 02/06/2023
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.....

(Optional)

Statistician:
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KEY TRIAL CONTACTS

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Study Sites	1. Department of Rheumatology, Aintree University Hospital, Liverpool University Hospitals 2. Department of Rheumatology, Sandwell and West Birmingham NHS Trust 3. Dental Institute, Barts and The London NHS Trust

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ii. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BASDAI	Bath Ankylosing Spondylitis Disease Activity Score
BD	Behcet's Disease
BDCAF	Behçet's Disease Current Activity Form
BDCAI	Behçet's Disease Current Activity Index
BDQoL	Behcet's Disease Quality of Life
BS	Behçet's Syndrome
CA	Competent Authority
CI	Chief Investigator
CR	Complete Response
CRF	Case Report Form
CRP	C-reactive Protein
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
ESR	Erythrocyte Sedimentation Rate

EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of technical requirements for pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IP	Investigational Product
ISF	Investigator Site File (This forms part of the Investigator/Institution TMF)
ISG	International Study Group
ISRCTN	International Standard Randomised Controlled Trials Number
IWRS	Interactive Web Response Systems
LEI	Leeds Enthesitis Index
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PGA	Physician's Global Assessment
PI	Principal Investigator

PIC	Participant Identification Centre
PIS	Participant Information Sheet
OUSS	Oral Ulcer Severity Score
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SpA	Spondyloarthritis
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction TEAEs Treatment Emergent Adverse Events
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
USS	Ulcer Severity Score
VAS	Visual Analogue Scale

iii. TRIAL SUMMARY

Trial Title	A Phase II, Multicentre, Randomised, Double Blind, Placebo Controlled Parallel Group Study, Followed By A 36 Week Active Treatment Phase To Evaluate The Efficacy And Safety Of Secukinumab In Patients With Non-Ocular Behçet's Syndrome	
Internal ref. no. (or short title)	Secukinumab in Behçet's	
Clinical Phase	Phase II Proof of principle	
Trial Design	Randomised, Double Blind, Placebo Controlled Parallel Group Study	
Trial Participants	Male and female patients aged at minimum 18 years at the time of consent, with active non-ocular Behçet's Syndrome (BS) fulfilling 1990 ISG criteria. Patients must have symptoms of active disease with oral or genital ulceration, significant BS related skin rash or arthralgia.	
Planned Sample Size	64 participants (32 each arm)	
Treatment duration	Randomized to placebo or secukinumab for the first 16 weeks, followed by 36 weeks of open label active secukinumab	
Follow up duration	12 weeks after final dosing	
Planned Trial Period	26 months	
	Objectives	Outcome Measures
Primary	1. To evaluate the change in oral ulcer severity score (USS) following 16 weeks of treatment	1. Change from baseline in Behçet's oral ulcer severity score (USS) at 16 weeks. (An improvement of 20% is considered to be clinically meaningful). The USS incorporates six ulcer characteristics: number, size, duration, ulcer-free period, site, and pain. It is scored by the clinician, based on patient reported details. There is a continuous scale between 0 (no problems) to 84 (most severe problems).[1]

Secondary	1. To assess Behçet's Disease Current Activity Form (BDCAF): Behçet's Disease Current Activity Index (BDCAI) at weeks 16 and 52 2. To assess Behçet's Disease Current Activity Form (BDCAF): Patient's Perception of Disease Activity at weeks 16 and 52 3. To assess change in outcome measure Behçet's Disease Current Activity Form (BDCAF): Clinician's Overall Perception of Disease Activity from baseline to weeks 16 and 52 4. Time to Oral Ulcer Resolution (Complete Response) Baseline to week 16	1. Change from baseline in Disease Activity as Measured by (BDCAF) at week 16 and week 52 2. Change from baseline in patient's perception of disease, as measured by BDCAF: patient's perception of disease activity at weeks 16 and 52 3. Change from baseline in Disease Activity as Measured by BDCAF: Clinician's Overall Perception of Disease Activity at Week 16 and 52 4. The time between the first dose date and the date when a complete response was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if no post baseline ulcer assessment. A complete response at Week 16 is defined as the participants who were oral ulcer free at week 16. 5. Comparison of the percentage of participants who were oral ulcer-free between the secukinumab- treated

	5. Percentage of participants Who Experienced an Oral Ulcer Complete Response at Week 16 and week 52	and the placebo-treated groups at Week 16 and at week 52.
	6. Change from baseline in Behçet's Disease Quality of Life (BD Qol) Scores at Week 16 and week 52	6. The Behçet's Disease Quality of Life questionnaire was developed to measure the influence of BD on a participant's life. It comprises 30 self-completed itemised questions that measure disease-related restrictions on the participant's activities and the participant's emotional response to these restrictions. The total score is the sum of all 30 items (each yes scores 1 and each no scores 0), with 0 representing no influence of Behçet's disease on a participant's quality of life and 30 representing the most severe influence. A negative change from baseline indicates improvement.
	7. Change in genital ulcer severity score at week 16 and week 52	7. Change from baseline in Behçet's genital ulcer severity score at week 16 (An improvement of 20% is considered to be clinically meaningful) and week 52
	8. Time to genital ulcer resolution (complete response) baseline to week 16	8. The time between the first dose date and the date when a complete response with respect to genital ulcers was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response of genital ulcers, or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if no postbaseline ulcer assessment. 9. A complete response at Week 16 was defined as the participants who were genital ulcer free at week 16. Comparison of the percentage of participants who were

	9. Percentage of participants who experienced a complete response for genital ulcers at Week 16 and week 52	genital ulcer-free (complete response: free from active genital ulcers) between the secukinumab-treated and the placebo-treated groups at week 16 and week 52.
	10. Time to recurrence of oral ulcers following loss of complete response, who had a complete response (CR) prior to Week 16	10. Defined as the first instance when a participant had a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase. For participants who did not have oral ulcer recurrence or discontinued treatment before any oral ulcer recurrence during the Placebo-controlled Treatment Phase, time to event is censored at the last oral ulcer assessment during Placebo-controlled Treatment Phase; For participants without any oral ulcer assessment following the first complete response, time to event is censored to the first complete response date.
	11.Time to recurrence of genital ulcers Following loss of complete response, who had a complete response Prior to Week 16	11. Defined as the first instance when a participant had a reappearance of genital ulcers following a complete response, during the Placebo-controlled Treatment Phase. For participants who did not have genital ulcer recurrence or discontinued treatment before any genital ulcer recurrence during the Placebo-controlled Treatment Phase, time to event is censored at the last oral ulcer assessment during Placebo- controlled Treatment Phase; For participants without any genital ulcer assessment following the first complete response, time to event is censored to the first complete response date.
		12. Pain of genital ulcers measured using the visual analogue scale (VAS). A 100-mm VAS pain scale for genital ulcers is completed by the participant at

	12. Change from baseline Genital Ulcer Pain as measured by VAS Score at Week 16 and at week 52	timepoints specified in the protocol. The participant was asked to draw a single line perpendicular to the VAS line at the point that represented the severity of their pain during the previous week, with 0 mm (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst pain imaginable. The distance of the perpendicular line from the left-hand end of the scale is measured by ruler and recorded. When responding to a VAS item, participants specify their level of agreement to a statement by indicating a position along a continuous line between two end- points. A negative change from baseline indicates improvement.
	13. Change from baseline in the Total Score of the Static Physician's Global Assessment (PGA) of Skin Lesions of BD at Week 16 and week 52	13. Scoring system for the Static Physician's Global Assessments: Score 0 = clear in severity and described as clear skin Score 1 = mild in severity and described as presence if 1 to 10 lesions (papules, pustules, cysts) at any anatomical site. Score 2 = Moderate; presence of 11 to 20 lesions (papules, pustules, cysts) any anatomical site Score 3 = Severe; presence of >20 lesions (papules, pustules, cysts) any anatomical site
	14. Change in Behçet's related musculoskeletal pain as assessed by the 7 point Likert scale from baseline to week 16 and week 52	14. A change in 20% at week 16 is considered to be clinically meaningful. Assessed between baseline, 16 week and 52 weeks
	15. Change from baseline in Behçet's related musculoskeletal pain as assessed by the Leeds	15. The Leeds Enthesitis Index (LEI) assesses the presence or absence of tenderness on palpation at six keys sites: both lateral epicondyles; medial epicondyles; and Achilles tendons. A change of more

	enthesitis Index (LEI) at week 16 and week 52	than 2 points is considered to be clinically meaningful. Assessed between baseline 16 weeks and 52 weeks
	16. Change in Behçet's related axial musculoskeletal pain as assessed by the Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) at week 16 and week 52	16. Change assessed between baseline, week 16 and week 52
	17. Number of participants with and types of Treatment Emergent Adverse Events (TEAEs) During the placebo- controlled period.	17. Time Frame: From the date of the first dose of IP in the placebo-controlled phase to the date of the first dose of secukinumab in the active treatment phase; median duration of treatment = 16 weeks. Number, nature, incidence, severity, and reversibility of TEAEs, together with number of patients who prematurely discontinue IP due to any AE will be recorded to fully reflect clinical safety.
	18. Number of participants with TEAEs During the secukinumab - Exposure Period	18. Time Frame: From 1st dose of secukinumab (for those randomised to secukinumab at Week 0), and open label follow up of secukinumab (from 16 weeks to 60 weeks. Number, nature, incidence, severity, and reversibility of TEAEs, together with number of patients who prematurely discontinue IP due to any AE will be recorded to fully reflect clinical safety.

	19. Change in ESR and CRP at baseline, week 16 and week 52 20. To evaluate the drop out/withdrawal rate due to non-response within the study 21. To evaluate the usage of rescue therapy 22. To evaluate reduction in steroid use	19. Change in CRP and ESR between baseline 16 weeks and 52 weeks 20. Number of patients who discontinue study medication between baseline, 16 weeks and 48 weeks 21. Numbers of patients requiring rescue therapy after week 16. Requirement for rescue therapy with triple mouthwash, parenteral or oral steroid 22. Reduction in oral and or topical steroid therapy between baseline 16 weeks and 60 weeks
Investigational Medicinal Product(s)	AIN457/Secukinumab and matched placebo	
Formulation, Dose, Route of Administration	Dose of 300 milligrams (mg) subcutaneous injection secukinumab or placebo added to participants' existing treatment	

iv. FUNDING AND SUPPORT IN KIND

The trial is funded by Novartis Pharmaceuticals UK Limited. The responsibilities for funding are outlined in the financial agreement between the Sponsor and the funding organisation.

v. ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor is Liverpool University Hospitals NHS Foundation Trust, which is the organisation that is taking legal responsibility for the trial. The Sponsor has entered into an Agreement with PHARMExcel Ltd (CRO), who will be undertaking some trial duties on behalf of the Sponsor. Roles and responsibilities for the trial are listed in an Agreement between both organisations.

vi. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

Trial Management Committees

- Data and Safety Monitoring Board (DSMB)

The DSMB will provide ongoing safety surveillance of the study. A separate DSMB charter will be prepared with additional details. This committee will be responsible for monitoring study conduct and safety data including reported AEs and laboratory values. The DSMB will review the safety experience of each patient and the cumulative occurrences of AEs. Through regularly scheduled and ad hoc meetings or teleconferences, the DSMB will provide ongoing review of safety data to determine whether continued study conduct is justified. Clinical study sites will be notified accordingly when actions in response to safety concerns or protocol modifications occur and should ensure that the REC is notified in a timely manner.

- Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and staff from the CRO. The TMG will be responsible for overseeing the trial and for review of all day to day study activities. A separate TMG charter will be prepared with additional details.

- Contract Research Organisation (CRO)

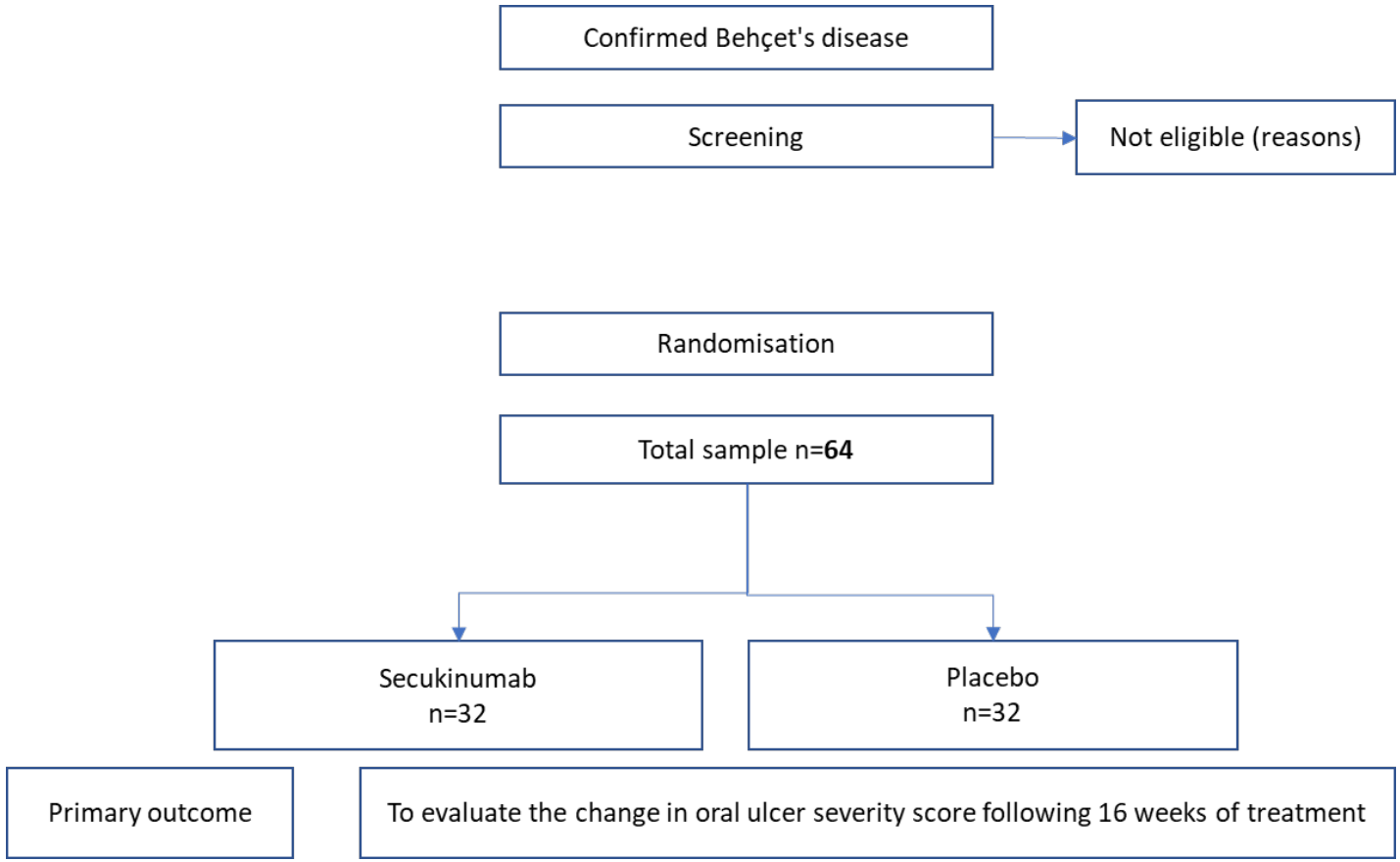
The appointed CRO, (PHARMExcel Ltd.), will be responsible for project management of the trial (on behalf of the Sponsor). The CRO will be responsible for: ethics and regulatory submissions and for the administration of the trial, the review of protocol, investigator's brochure, associated study documents prior to initial submission and prior to any further amendments required,

project management, monitoring, SAE tracking, expedited safety reporting, DSUR submission. The CRO will liaise with the Sponsor and the Chief Investigator for any project management decisions.

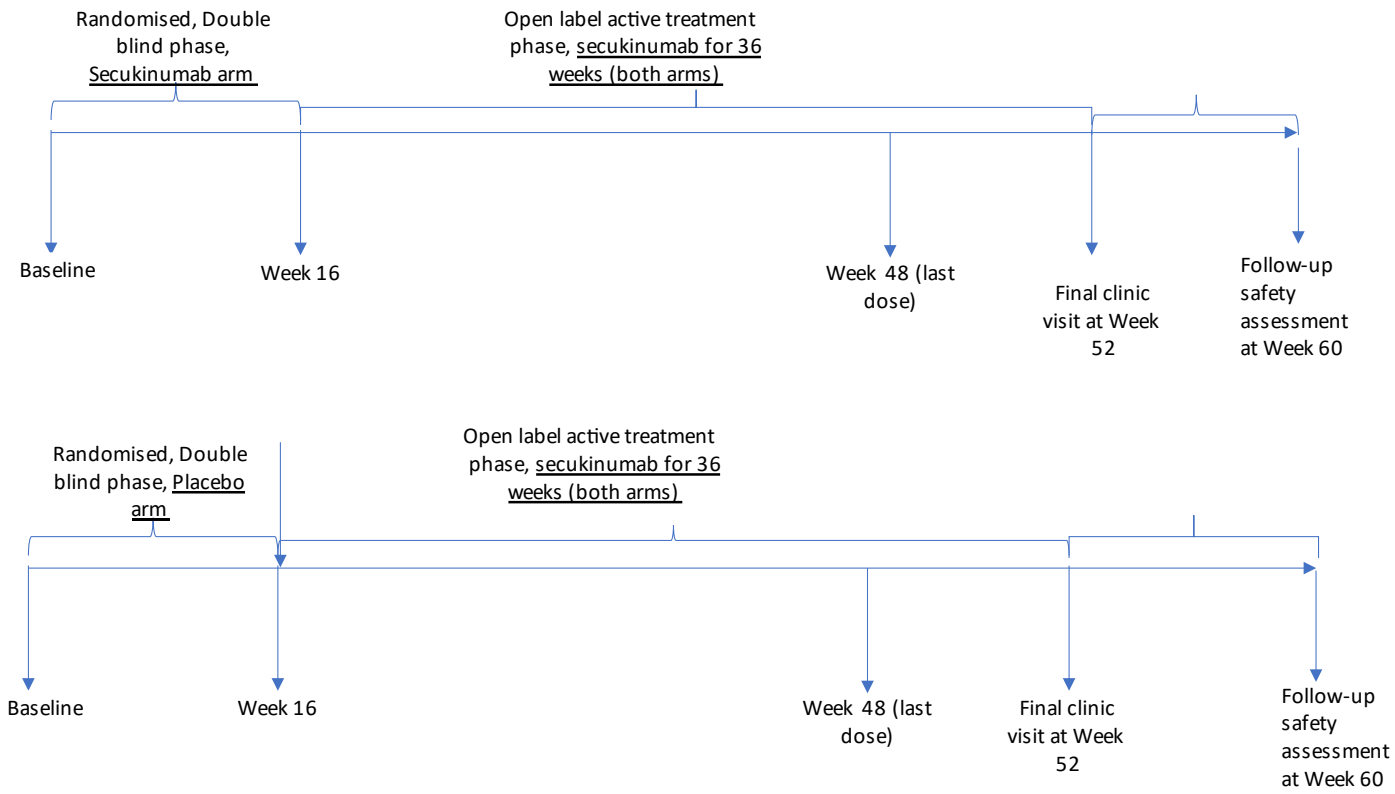
vii. Protocol contributors

The protocol has been developed by the Chief Investigator (Professor Robert Moots) and principal / co-investigators and the PHARMExcel (CRO) trial team.
The protocol will be submitted to the UK HRA/REC and MHRA for regulatory approval.

viii. TRIAL FLOW CHART



Summary of trial design



1 BACKGROUND

Bechet's Syndrome (BS) is a rare chronic, auto-inflammatory, multisystem disorder. The aetiology is currently unknown, but it is presumed to be multifactorial, implicating genetic, infectious and immunologic factors. The disease is characterised by a range of clinical manifestations, typically including recurrent mouth ulcers, genital ulcers, eye inflammation, joint pain and skin lesions, but also with potential CNS or vascular manifestations. In the absence of diagnostic laboratory test, the diagnosis is made based on a combination of clinical symptoms and signs and exclusion of other conditions.

Although the pathogenesis of BS is unclear, studies have shown that immunological aberrations play an important role in the development and progression of this disease. Although BS was once considered to be Th1-mediated, Th17 cells are known to be central in the process of autoimmune diseases. Cytokines such as IL-6, TGF-β, IL-21, and IL-23 promote the differentiation of Th0 cells into Th17 cells by activating signal transducer and activator of transcription (STAT) 3 and various transcription factors. Th17 cells then produce cytokines such as IL-17A, IL-17F, IL-21, IL-22, and IL-23 to regulate inflammation and autoimmunity. The expression levels of Th17 cells and related cytokines are associated with the activity of BD.

2 RATIONALE

The characteristics of peripheral articular involvement in BS closely resemble those of spondylarthritis (SpA). Indeed, BS and SpA share a common immunopathogenic background, with major histocompatibility complex class I (MHC- I) molecules and the IL-17 axis as crucial components.[2-5, 8] The unique attributes of the mucosal and articular phenotype strongly hint at a potential utility for anti- IL-17 drugs.

Despite limited randomised controlled trials evidence in many of the manifestations of BS, colchicine and topical treatments (such as steroids) are usually the first- line treatment for mucocutaneous and articular manifestations, before moving on to azathioprine and TNF inhibitor (TNFi), for refractory patients.1 (Also see UK Behçet's Drug Pathway). Roferon, (interferon alpha-2a), is efficacious in BS, but production of this drug has recently ceased, leaving a large gap in the current approach to treatment and a major unmet need for patients.

Secukinumab is a recombinant human monoclonal antibody that selectively binds to cytokine interleukin-17 A (IL-17 A) and inhibits the release of proinflammatory cytokines and chemokines. Preliminary studies suggest that Secukinumab is a safe and effective treatment resulting in improving active mucocutaneous manifestations refractory to previous treatments and inducing articular and

complete response in Behçet's patients[6]. It also suggests a benefit in reducing the use of concomitant immunosuppressive medication in patients with non-infectious uveitis[7].

There is a pressing need for further studies to be conducted in this area. This consortium comprises key opinion leaders and experts in the treatment of patients with Behçet's Syndrome. They are well-known internationally in this field, lead the UK Behçet's Centres of Excellence in Liverpool, Birmingham and London and, having led the first randomised head to head study of biologics in BS (The NIHR UK Research Council-funded BioBehcet's trial) are best placed to deliver on a study to determine the safety, tolerability and clinical effectiveness of Secukinumab in patients with Behçet's Syndrome.

2.1 Assessment and management of risk

This trial is categorised as:

<table>
<tr><td colspan="5">• Type B = Somewhat higher than the risk of standard medical care</td></tr>
<tr><td colspan="5">Justification:

Whilst secukinumab is widely used in conditions such as psoriatic arthritis and psoriasis, it has not formally been evaluated in Behçet's Syndrome, and is not licenced for this condition. It is possible that there are unknown idiosyncratic adverse events in this disease.</td></tr>
<tr><td colspan="2">What are the key risks related to therapeutic interventions you plan to monitor in this trial?</td><td colspan="3">How will these risks be minimised?</td></tr>
<tr><td>IMP/Intervention</td><td>Body system/Hazard</td><td>Activity</td><td>Frequency</td><td>Comments</td></tr>
<tr><td>secukinumab</td><td>Potential for aggravation of uveitis</td><td>Exclusion of patients with active, or recent history of, uveitis</td><td>Check at each clinical assessment, especially in determining inclusion and</td><td>Clinical assessment</td></tr>
</table>

			exclusion criteria	
secukinumab	Potential for aggravation of inflammatory bowel disease	Exclusion of patients with active, or recent history of, inflammatory bowel disease	Check at each clinical assessment, especially in determining inclusion and exclusion criteria	Clinical assessment
secukinumab	Potential for infections and infestations	Compliance with the eligibility criteria, close clinical monitoring	Check at each clinical assessment, especially in determining inclusion and exclusion criteria	Clinical assessment

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

Secukinumab has shown efficacy in several inflammatory diseases, including PsA, AS, and psoriasis. The large safety dataset of secukinumab across indications from 28 clinical trials as well as post-marketing safety surveillance in psoriasis, psoriatic arthritis, and ankylosing spondylitis from 12,637 secukinumab-treated patients did not show unexpected safety issues relative to the known mode of action[10]. Secukinumab was generally safe and well-tolerated. The most frequently reported adverse events (AE) are infections, especially upper respiratory tract with secukinumab relative to placebo. There was an increase in mucosal or cutaneous candidiasis with secukinumab compared to placebo, but the cases were generally mild or moderate in severity, non-serious, and responsive to standard treatment. There was a small increase in mild neutropenia cases with secukinumab compared to placebo. Common Toxicity Criteria (CTC) AE grade 3 neutropenia (<1.0-0.5x109/L) was uncommonly observed with secukinumab, most were transient and reversible without a temporal relationship to serious infections. Hypersensitivity reactions include urticarial and rare event of anaphylactic reaction to secukinumab were also observed in clinical studies. Considering the individual risks as outlined above, the expected risk profile of secukinumab from a mechanism of action perspective is anticipated

to be similar or improved compared to the approved inflammatory cytokine-targeting therapies. Clear information to investigators to avoid such co-morbidities in considering eligibility for trial. The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, close clinical monitoring and withdrawal of IMP if development of uveitis or inflammatory bowel disease, infections or infestations.
Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach. N/A

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

The primary objective is:

1. To evaluate the change in oral ulcer severity score following 16 weeks of treatment

3.2 Secondary objectives

The secondary objectives are:

1. To assess Behçet's Disease Current Activity Form (BDCAF): Behçet's Disease Current Activity Index (BDCAI) at weeks 16 and 52
2. To assess Behçet's Disease Current Activity Form ((BDCAF): Patient's Perception of Disease Activity at weeks 16 and 52
3. To assess change in outcome measure Behçet's Disease Current Activity Form (BDCAF): Clinician's Overall Perception of Disease Activity from baseline to weeks 16 and 52
4. Time to Oral Ulcer Resolution (Complete Response) Baseline to week 16

5. Percentage of participants Who Experienced an Oral Ulcer Complete Response at Week 16 and week 52
6. Change from baseline in Behçet's Disease Quality of Life (BD Qol) Scores at Week 16 and week 52
7. Change in genital ulcer severity score at week 16 and week 52
8. Time to genital ulcer resolution (complete response) baseline to week 16
9. Percentage of participants who experienced a complete response for genital ulcers at Week 16 and week 52
10. Time to recurrence of oral ulcers following loss of complete response, who had a complete response (CR) prior to Week 16
11. Time to recurrence of genital ulcers Following loss of complete response, who had a complete response Prior to Week 16
12. Change from baseline Genital Ulcer Pain as measured by VAS Score at Week 16 and at week 52
13. Change from baseline in the Total Score of the Static Physician's Global Assessment (PGA) of Skin Lesions of BD at Week 16 and week 52
14. Change in Behçet's related musculoskeletal pain as assessed by the 7 point Likert scale from baseline to week 16 and week 52
15. Change from baseline in Behçet's related musculoskeletal pain as assessed by the Leeds enthesitis Index (LEI) at week 16 and week 52
16. Change in Behçet's related axial musculoskeletal pain as assessed by the Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) at week 16 and week 52
17. Number of participants with and types of Treatment Emergent Adverse Events (TEAEs) During the placebo- controlled period
18. Number of participants with TEAEs During the secukinumab -Exposure Period
19. ESR and CRP at baseline, week 16 and week 52
20. To evaluate the drop out/withdrawal rate due to non-response within the study
21. To evaluate the usage of rescue therapy
22. To evaluate reduction in steroid use

3.3 Outcome measures/endpoints

3.3.1 Primary endpoint/outcome

The primary endpoint is:

1. Change from baseline in Behçet's oral ulcer severity score at 16 weeks. (An improvement of 20% is considered to be clinically meaningful). The USS incorporates six ulcer characteristics: number, size, duration, ulcer-free period, site, and

pain. It is scored by the clinician, based on patient reported details. There is a continuous scale between 0 (no problems) to 84 (most severe problems).

3.3.2 Secondary endpoints/outcomes

Secondary endpoints are:

1. Change from baseline in Disease Activity as Measured by (BDCAF) at week 16 and week 52 end of study
2. Change from baseline in patient's perception of disease, as measured by BDCAF: patient's perception of disease activity at weeks 16 and 52
3. Change from baseline in Disease Activity as Measured by BDCAF: Clinician's Overall Perception of Disease Activity at Week 16 and 52
4. The time between the first dose date and the date when a complete response was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if no post baseline ulcer assessment. A complete response at Week 16 is defined as the participants who were oral ulcer free at week 16.
5. Comparison of the percentage of participants who were oral ulcer-free between the secukinumab- treated and the placebo-treated groups at Week 16 and at week 52.
6. The Behçet's Disease Quality of Life questionnaire was developed to measure the influence of BD on a participant's life. It comprises 30 self-completed itemised questions that measure disease-related restrictions on the participant's activities and the participant's emotional response to these restrictions. The total score is the sum of all 30 items (each yes scores 1 and each no scores 0), with 0 representing no influence of Behçet's disease on a participant's quality of life and 30 representing the most severe influence. A negative change from baseline indicates improvement.
7. Change from baseline in Behçet's genital ulcer severity score at week 16 (An improvement of 20% is considered to be clinically meaningful) and week 52
8. The time between the first dose date and the date when a complete response with respect to genital ulcers was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response of genital ulcers, or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if no postbaseline ulcer assessment.

9. A complete response at Week 16 was defined as the participants who were genital ulcer free at week 16. Comparison of the percentage of participants who were genital ulcer-free (complete response: free from active genital ulcers) between the secukinumab-treated and the placebo-treated groups at week 16 and week 52.
10. Defined as the first instance when a participant had a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase. For participants who did not have oral ulcer recurrence or discontinued treatment before any oral ulcer recurrence during the Placebo-controlled Treatment Phase, time to event is censored at the last oral ulcer assessment during Placebo-controlled Treatment Phase; For participants without any oral ulcer assessment following the first complete response, time to event is censored to the first complete response date.
11. Defined as the first instance when a participant had a reappearance of genital ulcers following a complete response, during the Placebo-controlled Treatment Phase. For participants who did not have genital ulcer recurrence or discontinued treatment before any genital ulcer recurrence during the Placebo-controlled Treatment Phase, time to event is censored at the last oral ulcer assessment during Placebo- controlled Treatment Phase; For participants without any genital ulcer assessment following the first complete response, time to event is censored to the first complete response date.
12. Pain of genital ulcers measured using the visual analogue scale (VAS). A 100-mm VAS pain scale for genital ulcers is completed by the participant at timepoints specified in the protocol. The participant was asked to draw a single line perpendicular to the VAS line at the point that represented the severity of their pain during the previous week, with 0 mm (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst pain imaginable. The distance of the perpendicular line from the left-hand end of the scale is measured by ruler and recorded. When responding to a VAS item, participants specify their level of agreement to a statement by indicating a position along a continuous line between two end- points. A negative change from baseline indicates improvement.
13. Scoring system for the Static Physician's Global Assessments:
    Score 0 = clear in severity and described as clear skin
    Score 1 = mild in severity and described as presence if 1 to 10 lesions (papules, pustules, cysts) at any anatomical site.
    Score 2 = Moderate; presence of 11 to 20 lesions (papules, pustules, cysts) any anatomical site
    Score 3 = Severe; presence of >20 lesions (papules, pustules, cysts) any anatomical site
14. A change in 20% at week 16 is considered to be clinically meaningful. Assessed between baseline, 16 week and 52 weeks.
15. The Leeds Enthesitis Index (LEI) assesses the presence or absence of tenderness on palpation at six keys sites: both lateral epicondyles; medial epicondyles; and Achilles tendons. A change of more than 2 points is considered to be clinically meaningful. Assessed between baseline 16 weeks and 52 weeks
16. Change assessed between baseline, week 16 and week 52
17. Time Frame: From the date of the first dose of IP in the placebo-controlled phase to the date of the first dose of secukinumab in the active treatment phase; median duration of treatment = 16 weeks.

Number, nature, incidence, severity, and reversibility of TEAEs, together with number of patients who prematurely discontinue IP due to any AE will be recorded to fully reflect clinical safety.

18. Time Frame: From 1st dose of secukinumab (for those randomised to secukinumab at Week 0), and open label follow up of secukinumab (from 16 weeks to 60 weeks).
    Number, nature, incidence, severity, and reversibility of TEAEs, together with number of patients who prematurely discontinue IP due to any AE will be recorded to fully reflect clinical safety.
19. Change in CRP and ESR between baseline 16 weeks and 52 weeks
20. Number of patients who discontinue study medication between baseline, 16 weeks and 52 weeks
21. Numbers of patients requiring rescue therapy after week 16. Requirement for rescue therapy with triple mouthwash, parenteral or oral steroid
22. Reduction in oral and or topical steroid therapy between baseline 16 weeks and 52 weeks

3.7 Table of endpoints/outcomes

	Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary	1. To evaluate the change in oral ulcer severity score following 16 weeks of treatment	1. Change from baseline in Behçet's oral ulcer severity score at 16 weeks. (An improvement of 20% is considered to be clinically meaningful). The USS incorporates six ulcer characteristics: number, size, duration, ulcer-free period, site, and pain. It is scored by the clinician, based on patient reported	Week 16

		details. There is a continuous scale between 0 (no problems) to 84 (most severe problems).	
Secondary	1. To assess Behçet's Disease Current Activity Form (BDCAF): Behçet's Disease Current Activity Index (BDCAI) at weeks 16 and 52	1. Change from baseline in Disease Activity as Measured by (BDCAF) at week 16 and week 52 end of study	Week 16 and week 52
	2. To assess Behçet's Disease Current Activity Form (BDCAF): Patient's Perception of Disease Activity at weeks 16 and 52	2. Change from baseline in patient's perception of disease, as measured by BDCAF: patient's perception of disease activity at weeks 16 and 52	Week 16 and week 52
	3. To assess change in outcome measure Behçet's Disease Current Activity Form (BDCAF): Clinician's Overall Perception of Disease Activity from baseline to weeks 16 and 52	3. Change from baseline in Disease Activity as Measured by BDCAF: Clinician's Overall Perception of Disease Activity at Week 16 and 52	Week 16 and week 52

	4. Time to Oral Ulcer Resolution (Complete Response) Baseline to week 16	4. The time between the first dose date and the date when a complete response was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if no post baseline ulcer assessment. A complete response at Week 16 is defined as the participants who were oral ulcer free at week 16.	Complete response achieved Week 16
	5. Percentage of participants Who Experienced an Oral	5. Comparison of the percentage of participants who were oral ulcer-free between the secukinumab-treated and the placebo-	Week 16 and week 52

	Ulcer Complete Response at Week 16 and week 52	treated groups at Week 16 and at week 52.	
	6. Change from baseline in Behçet's Disease Quality of Life (BD Qol) Scores at Week 16 and week 52	6. The Behçet's Disease Quality of Life questionnaire was developed to measure the influence of BD on a participant's life. It comprises 30 self-completed itemised questions that measure disease-related restrictions on the participant's activities and the participant's emotional response to these restrictions. The total score is the sum of all 30 items (each yes scores 1 and each no scores 0), with 0 representing no influence of Behçet's disease on a participant's quality of life and 30 representing the most severe influence. A negative change from baseline indicates improvement.	Week 16 and week 52
		7. Change from baseline in Behçet's genital ulcer	Week 16 and week 52

	7. Change in genital ulcer severity score at week 16 and week 52	severity score at week 16 (An improvement of 20% is considered to be clinically meaningful) and week 52	
	8. Time to genital ulcer resolution (complete response) baseline to week 16	8. The time between the first dose date and the date when a complete response with respect to genital ulcers was achieved for the first time during the placebo-controlled treatment phase. For participants who did not achieve complete response of genital ulcers, or discontinued treatment before a complete response was achieved during the placebo-controlled treatment phase, time to event was censored at the last oral ulcer assessment date during the placebo-controlled treatment phase or the first dose date if no postbaseline ulcer assessment.	Complete response achieved Week 16

	9. Percentage of participants who experienced a complete response for genital ulcers at Week 16 and week 52	9. A complete response at Week 16 was defined as the participants who were genital ulcer free at week 16. Comparison of the percentage of participants who were genital ulcer-free (complete response: free from active genital ulcers) between the secukinumab-treated and the placebo-treated groups at week 16 and week 52.	Complete response achieved
	10. Time to recurrence of oral ulcers following loss of complete response, who had a complete response (CR) prior to Week 16	10. Defined as the first instance when a participant had a reappearance of oral ulcers following a complete response, during the Placebo-controlled Treatment Phase. For participants who did not have oral ulcer recurrence or discontinued treatment before any oral ulcer recurrence during the Placebo-controlled Treatment Phase, time to event is censored at the last oral ulcer assessment during Placebo-controlled	Time to recurrence of oral ulcers

	11.Time to recurrence of genital ulcers Following loss of complete response, who had a complete response Prior to Week 16	Treatment Phase; For participants without any oral ulcer assessment following the first complete response, time to event is censored to the first complete response date. 11. Defined as the first instance when a participant had a reappearance of genital ulcers following a complete response, during the Placebo-controlled Treatment Phase. For participants who did not have genital ulcer recurrence or discontinued treatment before any genital ulcer recurrence during the Placebo-controlled Treatment Phase, time to event is censored at the last oral ulcer assessment during Placebo- controlled Treatment Phase; For participants without any genital ulcer assessment following the first complete response, time to event is	Time to recurrence of genital ulcers

	12. Change from baseline Genital Ulcer Pain as measured by VAS Score at Week 16 and at week 52	censored to the first complete response date. 12. Pain of genital ulcers measured using the visual analogue scale (VAS). A 100-mm VAS pain scale for genital ulcers is completed by the participant at timepoints specified in the protocol. The participant was asked to draw a single line perpendicular to the VAS line at the point that represented the severity of their pain during the previous week, with 0 mm (the left-hand end of the scale) representing no pain and 100 mm (the right-hand end of the scale) representing the worst pain imaginable. The distance of the perpendicular line from the left-hand end of the scale is measured by ruler and recorded. When responding to a VAS item, participants specify their level of agreement to a statement by indicating a position along a	Week 16 and week 52

		continuous line between two end- points. A negative change from baseline indicates improvement.	
	13. Change from baseline in the Total Score of the Static Physician's Global Assessment (PGA) of Skin Lesions of BD at Week 16 and week 52	13. Scoring system for the Static Physician's Global Assessments: Score 0 = clear in severity and described as clear skin Score 1 = mild in severity and described as presence if 1 to 10 lesions (papules, pustules, cysts) at any anatomical site. Score 2 = Moderate; presence of 11 to 20 lesions (papules, pustules, cysts) any anatomical site Score 3 = Severe; presence of >20 lesions (papules, pustules, cysts) any anatomical site	Week 16 and week 52
	14. Change in Behçet's related musculoskeletal pain as assessed by the 7 point Likert scale from	14. A change in 20% at week 16 is considered to be clinically meaningful. Assessed between baseline, 16 week and 52 weeks	Week 16 and week 52

	baseline to week 16 and week 52		
	15. Change from baseline in Behçet's related musculoskeletal pain as assessed by the Leeds enthesitis Index (LEI) at week 16 and week 52	15. The Leeds Enthesitis Index (LEI) assesses the presence or absence of tenderness on palpation at six keys sites: both lateral epicondyles; medial epicondyles; and Achilles tendons. A change of more than 2 points is considered to be clinically meaningful. Assessed between baseline 16 weeks and 52 weeks	Week 16 and week 52
	16. Change in Behçet's related axial musculoskeletal pain as assessed by the Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) at week 16 and week 52	16. Change assessed between baseline, week 16 and week 52	Week 16 and week 52
	17. Number of participants with and types of		Week 16

	Treatment Emergent Adverse Events (TEAEs) During the placebo-controlled period. 18. Number of participants with TEAEs During the secukinumab -Exposure Period	17. Time Frame: From the date of the first dose of IP in the placebo-controlled phase to the date of the first dose of secukinumab in the active treatment phase; median duration of treatment = 16 weeks. Number, nature, incidence, severity, and reversibility of TEAEs, together with number of patients who prematurely discontinue IP due to any AE will be recorded to fully reflect clinical safety. 18. Time Frame: From 1st dose of secukinumab (for those randomised to secukinumab at Week 0), and open label follow up of secukinumab (from 16 weeks to 60 weeks). Number, nature, incidence, severity, and reversibility of TEAEs, together with number of patients who prematurely discontinue IP due to any AE will be recorded to fully reflect clinical safety.	Week 60 Week 16 and 52

	19.Change in ESR and CRP at baseline, week 16 and week 52	19. Change in CRP and ESR between baseline 16 weeks and 52 weeks	Week 52
	20. To evaluate the drop out/withdrawal rate due to non-response within the study	20. Number of patients who discontinue study medication between baseline, 16 weeks and 52 weeks	Week 16 and 52
	21. To evaluate the usage of rescue therapy	21. Numbers of patients requiring rescue therapy after week 16. Requirement for rescue therapy with triple mouthwash, parenteral or oral steroid	
	22. To evaluate reduction in steroid use	22. Reduction in oral and or topical steroid therapy between baseline 16 weeks and 52 weeks	Week 16 and 52

4 TRIAL DESIGN

This is a traditional double blind randomised placebo controlled study, where a total of 64 patients will be randomised in a 1 :1 ratio (32 per arm) to either placebo or Secukinumab. All patients will switch onto open label secukinumab following 16 weeks assessment, to determine safety and explore the potential for late responders.
Unblinding of the treatment that patients were assigned to during the randomised double blind phase will only occur once all patients have undergone their 52 week assessment, with data base lock, clean and primary end point analysis at week 60.
Open label treatment will continue up to week 48 with last patient last visit at week 60

5 TRIAL SETTING

This is a multicentre, randomised, double blind, placebo controlled trial for the first 16 weeks, followed by a 36 week open label active treatment phase clinical trial conducted at three sites, including Department of Rheumatology at Liverpool University Hospitals, Department of Rheumatology, Sandwell and West Birmingham NHS Trust and Dental Institute, Barts and The London NHS Trust. Patients over the age of 18 years at the time of consent diagnosed with active non-ocular Behçet's Syndrome will be recruited to the study from each site's inpatient population.

6 PARTICIPANT ELIGIBILITY CRITERIA

The study population will comprise the following patients who have passed screening assessments, comply with eligibility criteria and have provided written consent:

6.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfil all of the following criteria:

1. Patient must be able to understand and communicate with the investigator and comply with the requirements of the study and must give a written, signed and dated informed consent before any study assessment is performed
2. Male or non-pregnant, non-lactating female patients at least 18 years of age
3. Diagnosis of Behçet's Syndrome as defined by the 1990 International Study Group (ISG) and who have failed to respond to at least first line treatment with topical steroid (mouth wash or skin cream) and colchicine (≤ 500microg twice/day), azathioprine (≤ 2.5 mg/kg/day), or a single TNFα inhibitor (if due to inefficacy, after a trial of 3 months. If due to intolerance, at any stage).
4. Patients must have either signs of skin manifestations (including papulopustular lesions, erythema nodusum or vasculitis), mucosal ulceration, and/or joint tenderness that the investigator considers to be caused by active BS at randomization.
5. At least one active oral ulcer present at any of the following timepoints:

- Screening visit
- baseline visit
- in between screening and baseline visit as reported by patient

6. Patients taking corticosteroids must be on a stable dose of no more than 5 mg/day prednisone or equivalent for at least 2 weeks before randomization and can continue this during the study
7. Patients taking azathioprine (≤ 2.5 mg/kg/day) are allowed to continue their medication if the dose is stable for at least 4 weeks before randomization.
8. Patients taking topical steroid (as mouth wash or skin cream) can continue with this medication as required.

9. Patients taking colchicine must be on a stable dose (≤ 500microg twice/day) for at least two weeks before randomization and can continue with this medication.

6.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. History of Behçet's related active central nervous system, peripheral nervous system, vascular disease, gastrointestinal system, or inflammatory ocular disease requiring systemic therapy over the preceding 12 months.
2. If there is chest X-ray or chest MRI with evidence of ongoing infectious or malignant process, obtained within 3 months prior to screening and evaluated by a qualified physician.
3. Patients taking high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)
4. Previous exposure to secukinumab or other biologic drug directly targeting IL-17 or IL-17 receptor
5. Use of any investigational drug and/or devices within 4 weeks before randomization or a period of 5 half-lives of the investigational drug, whichever is longer
6. History of hypersensitivity to the study drug or its excipient or to drugs of similar chemical classes.
7. Any intramuscular or intravenous corticosteroid treatment within 4 weeks before randomization
8. Any therapy by intra-articular injections (e.g. corticosteroid) within 4 weeks before randomization
9. Patients who have previously been treated with more than 3 different TNF-a inhibitors (investigational or approved)
10. Patients who have ever received biologic immunomodulating agents except for those targeting TNFα, investigational or approved
11. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20, investigational agents (e.g., CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
12. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive urine pregnancy test
13. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unwilling to use effective contraception during the study and for 20 weeks after stopping treatment. Effective contraception is defined as either: a. Barrier method: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicide (where available). Spermicides alone are not a barrier method of contraception and should not be used alone

The following methods are considered more effective than the barrier method and are also acceptable:

   a. Total abstinence: When this is in line with the preferred and usual lifestyle of the patient [Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]
   b. Female sterilization: have had a surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

c. Use of established oral, injected or implanted hormonal methods of contraception, intrauterine device (IUD) or intrauterine system (IUS). In case of use of oral contraception women should have been stabile on the same pill for a minimum of 12 weeks before taking study treatment.

NOTE: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile
(e.g. age appropriate, history of vasomotor symptoms) or six months of spontaneous amenorrhea as defined by the Central Lab FSH and/or oestradiol levels

14. Active ongoing inflammatory diseases other than Behçet's syndrome that might confound the evaluation of the benefit of secukinumab therapy
15. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the investigator immunocompromises the patient and/or places the patient at unacceptable risk for participation in an immunomodulatory therapy
16. Significant medical problems or diseases, including but not limited to the following: uncontrolled hypertension (≥160/95 mmHg), congestive heart failure [New York Heart Association status of class Ill or IV], uncontrolled diabetes
17. History of clinically significant liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), alkaline phosphatase, or serum bilirubin. The investigator should be guided by the following criteria:
    a. Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to enrolment/randomization, to rule out lab error
    b. If the total bilirubin concentration is increased above 2 x ULN, total bilirubin should be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin should not exceed the value of 1.6 mg/dl (27 µmol/L)
18. Estimated creatinine clearance less than 30 mL/min
19. Screening total WBC count <3,000/µL, or platelets <100,000/µL or neutrophils <1,500/µL or haemoglobin <8.5 g/dl (85g/L)
20. Active systemic infections during the last two weeks (exception: common cold) prior to randomization
21. History of ongoing, chronic or recurrent infectious disease or evidence of tuberculosis infection as defined by either a positive PPD skin test (the size of induration will be measured after 48-72 hours, and a positive result is defined as an induration of ≥ 5mm or according to local practice/guidelines) or a positive QuantiFERON TB-Gold test as indicated in the assessment schedule Appendix 1. Patients with a positive test may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment according to local country guidelines must have been initiated
22. Known infection with HIV, hepatitis B or hepatitis C at screening or randomization
23. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system within the past 5 years (except for basal cell carcinoma or actinic keratoses that have been treated with no evidence of recurrence in the past 3 months, carcinoma in situ of the cervix or non-invasive malignant colon polyps that have been removed)
24. Current severe progressive or uncontrolled disease which in the judgment of the clinical investigator renders the patient unsuitable for the trial

25. Inability or unwillingness to undergo repeated venepuncture (e.g., because of poor tolerability or lack of access to veins)
26. Any medical or psychiatric condition which, in the investigator's opinion, would preclude the participant from adhering to the protocol or completing the study per protocol
27. Donation or loss of 400 ml or more of blood within 8 weeks before randomization
28. History or evidence of ongoing alcohol or drug abuse, within the last six months before randomization
29. Plans for administration of live vaccines during the study period or within 6 weeks preceding randomization.
30. A diagnosis of current or previous history of inflammatory bowel disease (IBD)

7 TRIAL PROCEDURES

Schedule of procedures and assessments listed in appendix 1.

7.1 Recruitment

Male and female patients with active non-ocular Behçet's Syndrome (BS) aged ≥18 will be considered for inclusion in the study. Potential patients will be identified by an existing member of the patient's clinical care team or will be directed from social media or adverts around clinics to the research team. Participant medical records will be reviewed for consideration of inclusion / exclusion criteria. A delegated investigator will confirm inclusion / exclusion prior to enrolling a patient on the study.

7.1.2 Screening

The investigator or delegate will review the patient's medical history and medical notes for the inclusion and exclusion criteria (section 6.1 and 6.2).
Pregnancy is an exclusion criterion. Non-pregnant status will be confirmed via urine pregnancy test at screening if this has not been carried out as part of standard of care already.
Patients can be re-screened only once, and no re- screening study related procedures should be performed prior to written re-consent by the patient. Mis randomised patients will be withdrawn from the study. If they received dose(s) of study drug they would need to be excluded from efficacy analysis but included in safety analysis for any doses taken.

7.1.3 Payment

No payment will be made to participants other than travel expenses in exceptional circumstances, such as the need to attend additional clinic visits over and above that required for normal clinical care.

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.
The investigator will provide an initial explanation of the aims, required assessments, anticipated benefits and potential hazards of the study as detailed in the Patient Information Sheet (PIS). Patients are given sufficient time (offered a period of 24 hours or more if needed) to consider whether they wish to participate. If the patient decides they would like to participate in the study, written informed consent will be sought prior to any screening activities. Consent will not denote enrolment into trial.
Only patients meeting the eligibility criteria will be enrolled into the study. Participants will be informed that they are under no obligation to enter the trial and that they can withdraw at any time during the trial, without having to give a reason. The PIS and Informed Consent Form (ICF) will be reviewed and updated, if necessary, throughout the trial (e.g. if new safety information becomes available) and participants will be re-consented as appropriate. A copy of the signed ICF will be given to the participant. The original signed ICF will be retained in the Investigator Site File at site and a copy placed in the patient's medical records.

7.3 The randomisation scheme

Consented, participants who meet the inclusion/exclusion criteria will be randomly assigned to one of the treatment groups (secukinumab or placebo) on the basis of 1:1 allocation ratio (32 per arm). patient

This is a double blind placebo controlled randomised study where, following the initial 16 weeks assessment, all patients will switch onto open label secukinumab, to determine safety and explore the potential for late responders.
Unblinding of the treatment that patients were assigned to during the randomised double-blind phase will only occur once all patients have undergone their *52 week* assessment, with data base lock, clean and primary end point analysis at week 60. Open label treatment will continue up to week 48 with last visit at week 60. Patients then will revert to standard of care at the end of the trial at week 60.
Rescue medication will be permitted during the blinded period until at or after week 16, after clinical assessment and will comprise: 1) a course of triple mouthwash provided to patients who report uncontrolled mouth ulcers for up to 3 occasions.

2) Topical therapy with Betnovate ointment provided for uncontrolled genital ulcers, with 1 tube of 30g, with applications recorded. 3) A short course of oral prednisolone (10mg od for 1 week) provided to patients who report uncontrolled Bechet's disease activity in other organ systems (eg joints, skin), for up to 3 occasions.

7.3.1 Method of implementing the randomisation/allocation sequence

Patients will be block randomised on a 1:1 basis to receive secukinumab or placebo. Randomisation will be done using an Advantage eClinical IWRS module. The master randomisation list will be uploaded into eClinical to allow sequential randomisation and automatic output to inform the study team of the intervention allocated.

7.4 Blinding

The study will be conducted according to a double blinded study design during the first 16 weeks of treatment then 36 weeks of open label active treatment. With the exception of the data coordinating centre (Emmes), all participants, study site personnel, the chief investigator, sponsor, and PHARMExcel, will remain blinded to subjects' treatment assignments until first database closure and study unblinding.

7.5 Emergency Unblinding

The randomisation treatment code will only be broken for valid medical or safety reasons e.g. in the case of a serious adverse event where it is necessary for the investigator to know which treatment the patient is receiving before the participant can be treated.

It is essential that any unblinding mechanism does not unblind the whole trial, but only the individual concerned. The actual allocation must NOT be disclosed to the participant and/or other study personnel including other site personnel, monitors, project team members, nor should there be any written or verbal disclosure of the code in any of the corresponding participant documents.

For emergency unblinding a formal request from the site PI (or appropriate designee) to be submitted to the data management company, Emmes. The request to include the participant ID, date of request, who requested the unblinding and the reason for the request as well as the approver's name and date of approval. An Emmes statistician or designee will communicate the treatment assignment for the participant to the site PI or designee verbally after an independent member of the Emmes team verifies the treatment assignment. Emmes will document this in a log and inform study team that the unblinded has occurred (no unblinding information will be provided).

Support will be provided by Emmes 24/7 on unblinding, please find below details:

Name	Role	Email ID	Tel. Contact
Sarah Grace Anderson	BIOSTATISTICIAN MANAGER	sanderson@emmes.com	00 91 7338230461
Sandesh Dattatray Nalawade	PROJECT MANAGER	snalawade@emmes.com	00 91 8512008777

Further details regarding emergency unblinding can be found in the Safety Management Plan.

7.7 Trial assessments

Please see appendix 1 for the details of the schedule of events/assessments.

7.8 IMP education

Full training about the IMP and overall trial will be provided by the research nurses. This includes provision of the drug information sheet (as provided by Versus Arthritis information for patients), explanation and demonstration of injection technique, full explanation about the drug with respect to side-effects, mitigation of infection risk, storage, and the reporting of adverse events. The first dose will be administered at the site, and full training for self-administration at home will be provided, together with provision of contact details for any queries.

7.9 Long term follow-up assessments

This is not directly applicable to this study.

7.10 Qualitative assessments

This is not directly applicable to this study.

7.11 Withdrawal criteria

Subjects may voluntarily discontinue from the study for any reason at any time. They may be considered discontinued if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If premature discontinuation occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's premature discontinuation from the study and record this information on the appropriate Study Phase Completion eCRF. Study treatment must be discontinued if the investigator determines that continuation of study treatment would result in a significant safety risk for a subject.

The following circumstances require study treatment discontinuation:

- Withdrawal of informed consent
- Subject's request to terminate treatment
- Emergence of the following AEs:
- Any severe or serious AE that is not compatible with administration of study medication, including AEs that require treatment with an unacceptable co-medication
- Life-threatening infection
- Severe hypersensitivity reaction or anaphylactic reaction
- Any laboratory abnormalities that in the judgment of the investigator are clinically significant and are deemed to place the subject at a safety risk for continuation in the study
- Pregnancy
- Use of any biologic immunomodulating agent except secukinumab
- Any requirement for intensification of therapy for Behçet's related disease activity prior to week 16, or over and above that permitted at or after week 16, will result in discontinuation from the studyAny protocol deviation that results in a significant risk to the subject's safety.

In addition to these requirements for study treatment discontinuation, the investigator should discontinue study treatment for a given subject if there is a lack of improvement or worsening of their symptoms, or if on balance, he/she thinks that continuation would be detrimental to the subject's well-being.

Subjects who discontinue study treatment should not be considered withdrawn from the study. A Study Treatment Discontinuation form should be completed, giving the date and primary reason for stopping study treatment. For subjects remaining in the trial, all visit 52 assessments must be performed on the day of study treatment discontinuation (or as early as possible after study treatment discontinuation); then all subsequent visits will be performed according to the assessment schedule.

7.12 Storage and analysis of clinical samples

The taking of blood samples and equipment will be supplied by the sites and all analyses conducted by in accordance with the sites' local protocols. Details are provided in the sites' laboratory/pathology manual for all blood tests. No samples will be stored and following the required testing of the blood samples, all samples will be destroyed in accordance with the sites' internal regulations.
The schedule of sample collections is contained in section Appendix 1 Trial Procedures and Assessments. All samples taken will be appropriately labelled in accordance with procedures to comply with the General Data Protection Regulations (GDPR) and Data Protection Act 2018 and will be identified by normal clinical practice at the sites.

All Biological samples collected from participants as part of this trial will be transported, stored, accessed and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

7.13 End of trial

The expected duration of the trial is 26 months from recruitment of the first participant. The end of trial is the date of the last visit of the last participant and MHRA and REC will be informed.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product

Secukinumab: is a human IgG1κ monoclonal antibody that binds to the protein interleukin (IL) – 17A. It is marketed by Novartis for the treatment of psoriasis, ankylosing spondylitis and psoriatic arthritis and delivered by subcutaneous injection. This drug is widely used in the three participating centres for the licenced indications. The IMP (active drug and matched placebo are being provided by Novartis as clinical trial supplies (i.e. not provided as marketed commercial packs). However, as per the Reference Safety Information section (RSI – below), the Cosentyx® SmPC is being used as RSI. Secukinumab is supplied as AIN457 300mg in liquid in pre-filled syringe 2mL. Matched placebo is supplied as AIN457 0mg in liquid in pre-filled syringe 2mL

8.2 Regulatory status of the drug

MHRA and EMA approval for treatment of psoriasis, ankylosing spondylitis and psoriatic arthritis. Secukinumab is not licensed for use in Behçet's syndrome.

8.3 Product Characteristics

The Cosentyx Summary of Product Characteristics (SmPC) submitted and accepted by MHRA in the clinical trial authorisation will be used as Reference Safety Information (RSI) for this study. A copy of initial and updates to RSI will be provided to participating sites.

8.4 Drug storage and supply

Secukinumab and placebo to be stored at 2-8^{0}C (do not freeze and protect from light). A pharmacy manual will be provided.

8.5 Preparation and labelling of Investigational Medicinal Product

Novartis AG, Basle will provide unlabelled primary packaged clinical trial supplies of secukinumab (AIN457, 300mg) in pre-filled syringes and matched placebo (AIN457, 0mg). Clinical Trial labelling will be arranged by MODEPHARMA (on behalf of the Sponsor) in accordance with the approved Clinical Trial Authorisation. Clinical Trial labelled supplies will be distributed to participating sites by MODEPHARMA.

8.6 Dosage schedules

Blinded 300mg sc of secukinumab or matched placebo will be self-administered by patients once a week for four weeks (weeks 0, 1, 2, 3, 4), then once every four weeks at week 8 and 12. Then open label secukinumab 300mg sc every 4 weeks from week 16 up to and including week 48.

8.7 Dosage modifications

Dosage modification will not be permitted, except temporary suspension of therapy in clinical situations such as infection (as for normal clinical use)

8.8 Known drug reactions and interaction with other therapies

Commonly reported drug reactions include immunosuppression, diarrhoea, fatigue, headache, increased risk of infection, nausea, rhinorrhoea. Uncommon drug reactions include Conjunctivitis, inflammatory bowel disease, neutropenia (usually mild and reversible) and skin reactions. Theoretical interactions may occur with live vaccines (eg BCG), JAK inhibitors such as filgotinib and other cytokine inhibitors, none of which are permitted in this study.

8.9 Concomitant medication

Concomitant medications taken at enrolment and through the end of the study will be recorded in the eCRF and will be available in the patients' medical records. No routine concomitant medications will be withheld as a result of participation in this study.

8.10 Trial restrictions

There will be no trial restrictions.

8.11 Assessment of compliance with treatment

By direct questioning from clinical teams at each assessment and documenting in medical records

9 PHARMACOVIGILANCE

9.1 Definitions

The following definitions have been adapted from Directive 2001/20/EC and ICH-GCP E6:

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

Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be

	due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within it's licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

NB: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

9.2 Operational definitions for (S)AEs

AEs, SAEs and SUSARs will be recorded and reported according to applicable trial regulations. However certain episodes such as elective procedures or admissions do not need to be reported as SAEs through the expedited system. These events should however, be recorded in the eCRF with grading of severity and details on cause for later analysis.
Any episode subsequently determined by the CI as possibly, probably or certainly causally linked to the IMP and fulfilling the criteria in the table above will be retrospectively re-graded as a SAE or SUSAR and reported as appropriate.

All SAEs (as per definitions) must be recorded and reported to the **Sponsor (Heather Rogers: RGT@liverpoolft.nhs.uk**) and **CRO (safety@pharmexcel-cro.com)** immediately/within 24hrs of the site becoming aware of the event.

Any change of condition or other follow-up information should be sent to the Sponsor and CRO as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

9.3 Recording and reporting of AEs

All adverse events that occur between informed consent and until the end of the patient participation in the trial (i.e., end of data collection for each trial participation at week 60). must be recorded in the patient notes and in the trial eCRFs. Pre-existing conditions (as recorded at screening visit) do not qualify as adverse events unless, in the opinion of the treating clinician, have worsened since baseline. Information regarding dates of event onset and resolution, outcome, severity and causality for the trial treatment must be recorded.

Those AEs meeting the definition of Serious (SAE) must also be reported to the Sponsor and the CRO as per section 9.2.
All AEs will be recorded in the participant's medical records, recorded in the CRF and reported to the Sponsor at the time frame agreed. Each adverse event will be assessed for seriousness, causality, severity and expectedness as described below.

The Sponsor (or their authorised delegate) shall forward to Novartis any SAEs, reports of drug exposure during pregnancy and reports of Study Drug misuse or abuse, including initial and follow up reports, arising from the Study in patients exposed to the Study Drug, as soon as it becomes available, but in any event within fifteen (15) calendar days of becoming aware of such information.

9.3.1 Assessment of Severity

The PI or delegated clinician must perform an assessment of severity for each AE based on CTCAE v5.0 according to the following categories.

Severity category	Definition of severity category
Mild (Grade 1)	AE that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with everyday activities
Moderate (Grade 2)	AE that is sufficiently discomforting to interfere with normal everyday activities

Severe (Grade 3)	AE that prevents normal everyday activities
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE

9.3.2 Assessment of Seriousness

Those AEs meeting the definition of Serious (SAE) as per section 9.1 will be recorded as SAE. Seriousness assessment is made by the PI or authorised study clinician.
Each SAE must be reported to the Sponsor as per section 9.2 and 9.4.

9.3.3 Assessment of Causality

The PI or delegated clinician must perform an evaluation of causality for each adverse event. The investigator will use clinical judgement to determine relationship to IMP. Each AE must also be assessed for Causality regardless of whether the event is serious or not.

Causality Category	**Causality category definition**
Definitely	Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.
Probably	Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause
Possibly	Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.

Unlikely	Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
Not Related	Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.

9.3.4 Assessment of Expectedness

Only SAEs that are deemed to have a causal relationship (definitely, probably, possibly) to the IMP-treatment (compromising secukinumab and matched placebo) will undergo an expectedness assessment against the RSI approved by the MHRA (please see section 8.3 for further information) . The expectedness assessment is performed by the Sponsor or their authorised representative

9.3.5 IMP reporting pathway – SUSAR Reporting

The CRO, on behalf of the sponsor, will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales (15 days for all SUSARs, unless resulting in death or is life threatening in which case 7 days, with a final report within a further 8 days (total 15)). Unblinding will occur prior to reporting.

The Sponsor will also inform all Investigators concerned of relevant blinded information about SUSARs that could adversely affect the safety of participants.

9.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness and causality to event/reaction
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

3. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
4. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether an event/reaction was anticipated or expectedness in line with the Reference Safety Information.
4. Immediate review of all SUSARs (delegated to independent physician).
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol section 9 as detailed in the Trial Safety Management Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR) – delegated to independent physician.
8. Ensuring changes to RSI are submitted to the MHRA for clinical trial authorisation
9. The CI will delegate a senior independent unblinded study physician to review SUSARs and prepare & sign off DSUR

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database – oversight, delegated to CRO
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Safety Management Plan.- delegated to CRO
3. Reporting safety information to the independent oversight committees identified for the trial (DSMB) according to the Trial Safety Management Plan – delegated to CRO
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines. – oversight, delegated to CRO

5. Notifying Investigators of SUSARs that occur within the trial – delegated to CRO. 'Blinded' SUSARs will be reported to the investigators so that study blind is maintained
6. The unblinding of a participant for the purpose of expedited SUSAR reporting – delegated to an unblinded study doctor and CRO, who will send the report to MHRA and REC. The SUSAR is unblinded for MHRA & REC reporting purposes only, but the participant and study team remains blinded in the study.
7. Checking for (monthly) changes to the SmPC and assessing if change of RSI required. Submitting initial and updated RSI to MHRA for clinical trial authorisation. Providing PIs with initial and updates to the RSI for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC. – providing safety data, QC check and submission delegated to CRO.

CRO
The appointed CRO, PHARMExcel Ltd., will be responsible for project management of the trial (on behalf of the Sponsor). The CRO will be responsible for review of study documents to be submitted for ethics/regulatory approvals, tracking the progress of the study and timelines, SAE tracking and management, expedited safety reporting (SUSARs), submission of DSUR and ethics progress reports, site initiation visit and site activation, study monitoring.

Data Safety Monitoring Board (DSMB):
In accordance with the Trial Terms of Reference for the DSMB, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

All deaths will be reported to the Sponsor irrespective of whether the death is related to disease progression, the IMP or an unrelated event. All deaths occurring during the study will be reported to the Sponsor by the investigator by emailing. The CRO will be copied in the correspondence. For all deaths, available autopsy reports and relevant medical reports will be made available for reporting to the relevant authorities. These will be pseudo anonymised with study ID number before submitting outside the site (i.e. they will not contain any patient identifiers that identify patient)

9.6 Pregnancy reporting

Should a pregnancy occur, it must be reported and recorded on the trial's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital

abnormality) must be followed up and documented even if the patient was discontinued from the study. All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.
All reports of drug exposure during pregnancy will be reported to the Sponsor by the investigator by emailing **Heather Rogers: RGT@liverpoolft.nhs.uk**. The CRO will be copied in the correspondence.

Pregnancy outcomes will not be collected for the female partners of male patient participating in the trial as secukinumab is not considered a significant risk in this population.

9.7 Overdose

The definition of an overdose for this study is the misuse and abuse of an IMP, other medication errors and uses outside of what is foreseen in the protocol (irrespective if a clinical event has occurred) in relation to the dosing schedule displayed in section 8.6. All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor. The CRO will be copied in the correspondence. If an SAE is associated with the overdose it will be fully described in the SAE report form by the investigator or delegate. An overdose will be recorded as a protocol deviation and recorded on the protocol deviation log.

9.8 Reporting urgent safety measures

An Urgent Safety Measure (USM) is a procedure which is not defined by the protocol that can be put in place with immediate effect without needing to gain prior authorisation by the MHRA and REC, in order to protect clinical trial participants from any immediate hazard to their health and safety.
If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures. Should a PI need to implement an USM, both the CI and Sponsor will need to be informed immediately.

9.9 The type and duration of the follow-up of participants after adverse reactions.

Patients that experience an adverse reaction as a result of trial treatment will be followed up until resolution of the event. If additional follow up is required for safety reasons the investigator will discuss this with the participant and make appropriate arrangements. Adverse events will be recorded and reported for the duration of the patient's participation in the study. Any SUSAR will need to be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred until resolved.

9.10 Development safety update reports

The delegated unblinded study doctor and Sponsor will be responsible for Development Safety Update Report (DSUR) content with input from CRO for safety data and QC check. CRO will be responsible for submission to the competent authority and ethics committee on the anniversary of the first approval date from the MHRA of the protocol.

10 STATISTICS AND DATA ANALYSIS

The following section provides an overview of the statistical methodology and the proposed analyses for the randomised, double blind, placebo controlled study. A full Statistical Analysis Plan (SAP) is to be produced separately.

Descriptive statistical methods will be used to summarise the data from this study with hypothesis testing performed for the primary and other efficacy endpoints. Unless stated otherwise, the term "descriptive statistics" refers to number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous data, and frequencies and percentages for categorical data. The term "treatment group" refers to a group of subjects that have received Secukinumab or placebo.

All data collected during the study will be reported/analysed to the greatest extent possible. Unless specified otherwise, all statistical testing will be two-sided and performed using a significance (alpha) level of 0.05. All statistical analyses will be conducted using SAS v9.4 or greater.

A formal SAP will be utilised to analyse the data. This document will provide a more technical and detailed description of the proposed data analysis methods and procedures. Any deviation from the analyses outlined in the Protocol will be described in the most current version of the SAP.

10.1 Sample size calculation

Recurrent aphthous stomatitis (RAS) is considered a major criteria in the diagnosis of Behçet's disease (BD). In a study of 35 participants with BD, 13 (37%) had major, 21 (60%) had minor, and 1 (3%) had herpetiform RAS.

In another study evaluating OUSS (oral ulcer severity score) as a clinical assessment of disease severity in RAS3, the mean (standard deviation [SD]) score for major, minor and herpetiform RAS was 29.2 (5.3) (N=136), 39.9 (6.1) (N=72) and 36.6 (8.4)

(N=15), respectively. Therefore, the mean and SD of OUSS in the placebo group was assumed to be between 25-40 and SD 5.0-6.5 (due to the relatively fewer number of participants in the herpetiform RAS group, the higher SD observed in this group was not considered), respectively. Further, a 20% improvement in OUSS was considered clinically significant.

Therefore, assuming a mean (SD) OUSS of 30 (6.0) in the placebo group, considering a 20% decrease in OUSS in the secukinumab group is clinically meaningful and assuming equal variance in both groups, a total of 64 participants (32 per randomised group) would be required to achieve 90% power at a one-sided type I error rate of 2.5% after accounting for 20% dropouts using Mann Whitney U test.

10.2 Planned recruitment rate

The planned recruitment rate is to recruit 64 randomised and treated patients in a 12 month period from the recruitment of the first patient.

The accrual pattern across time periods is uniform (all periods equal). A screening failure rate of about 20% and post-randomization drop out rate of 20% is expected, therefore approximately 77 patients will need to be screened in order to achieve 64 randomised and treated patients.

A conditional rate of recruitment has been adopted to allow for variations in recruitment numbers, time taken to recruit and consent eligible patients.

The three hospitals currently treat over 60 patients per month. There are no other potential competing studies taking place in these sites.

10.3 Statistical analysis plan

Standard statistical summaries (e.g. means and standard deviations) and graphical plots showing relational data will be presented for the primary and secondary outcome measures. Baseline data will be summarised to check comparability between the treatment groups, and to highlight differences between those individuals in the study, those ineligible, and those eligible but withholding consent.

A two treatment group design has been chosen to ensure that each treatment group can be reviewed independently and comparatively.

10.3.1 Summary of baseline data and flow of patients

The following is the list of variables to be used to assess baseline comparability of the randomised groups: age, sex, race/ethnicity, BMI, and medical history.

The proposed consort flow diagram (http://www.consort-statement.org/) in Figure 1 of this protocol allows for attrition rates, in order to ensure that we achieve a total of 32 participants in each treatment group.

10.3.2 Primary outcome analysis

The primary endpoint of this study is to evaluate the change from baseline in oral ulcer severity score at 16 weeks between the two treatment groups, Secukinumab and placebo. A two-sided type I error rate of 0.05 is assumed.

A *t*-test or Mann Whitney U test will be used to assess the primary efficacy outcome of the oral ulcer severity score at 16 weeks. The *t*-test will be used if all assumptions are met. The mean difference in the oral ulcer severity score and a 95% confidence interval will be constructed. If the assumptions are not met for the *t*-test, Mann Whitney U will be used to calculate the *p*-value between the two treatment distributions and the Hodges-Lehmann estimation will be used to calculate a 95% confidence interval of the location shift between the two treatment groups.

10.3.3 Secondary outcome analysis

Continuous secondary outcome measures will be analysed using the same methods as the primary efficacy outcome if they are measured only at baseline and the visit at which they should be assessed (i,e. week 16 or 52) . If the continuous secondary outcome is assessment as multiple visits until the visit at which they should be evaluated (i.e. week 16 or 52), then a repeated measures model will be used. The continuous secondary outcome objectives are:

- To assess Behçet's Disease Current Activity Form (BDCAF): Behçet's Disease Current Activity Index (BDCAI) at weeks 16 and 52
- To assess Behçet's Disease Current Activity Form (BDCAF): Patient's Perception of Disease Activity at weeks 16 and 52
- To assess change in outcome measure Behçet's Disease Current Activity Form (BDCAF): Clinician's Overall Perception of Disease Activity from baseline to weeks 16 and 52
- Change from baseline in Behçet's Disease Quality of Life (BD Qol) Scores at Week 16 and week 52
- Change in genital ulcer severity score at week 16 and week 52

- Change from baseline Genital Ulcer Pain as measured by VAS Score at Week 16 and at week 52
- Change from baseline in the Total Score of the Static Physician's Global Assessment (PGA) of Skin Lesions of BD at Week 16 and week 52
- Change from baseline Genital Ulcer Pain as measured by VAS Score at Week 16 and at week 52
- Change from baseline in the Total Score of the Static Physician's Global Assessment (PGA) of Skin Lesions of BD at Week 16 and week 52
- Change in Behçet's related musculoskeletal pain as assessed by the 7 point Likert scale from baseline to week 16 and week 52
- Change from baseline in Behçet's related musculoskeletal pain as assessed by the Leeds enthesitis Index (LEI) at week 16 and week 52
- Change in Behçet's related axial musculoskeletal pain as assessed by the Bath Ankylosing Spondylitis Disease Activity Score (BASDAI) at week 16 and week 52
- ESR and CRP at baseline, week 16 and week 52

Categorical secondary outcome measures will be summarized descriptively by treatment group and by visits, as applicable. McNemar's test will be used to compare the number of patients with at least one event between Secukinumab and the placebo group. Repeated measures model may be used if the outcome is assessed at multiple visits until the visit at which they should be evaluated (i.e. week 16 or 52). Categorical secondary outcome measures are:

- Percentage of participants Who Experienced an Oral Ulcer Complete Response at Week 16 and week 52
- Percentage of participants who experienced a complete response for genital ulcers at Week 16 and week 52
- Number of participants with and types of Treatment Emergent Adverse Events (TEAEs) During the placebo-controlled period
- Number of participants with TEAEs During the Secukinumab-Exposure Period
- To evaluate the drop out/withdrawal rate due to non-response within the study
- To evaluate the usage of rescue therapy
- To evaluate reduction in steroid use

Time to event outcome measures will be summarized using Cox proportional hazards model. A hazard ratio and a 95% confidence interval will be constructed to compare Secukinumab to the placebo group to detect differences. Time to event secondary outcome measures are:

- Time to Oral Time to genital ulcer resolution (complete response) baseline to week 16

- Time to genital ulcer resolution (complete response) baseline to week 16
- Time to recurrence of oral ulcers following loss of complete response, who had a complete response (CR) prior to Week 16
- Time to recurrence of genital ulcers Following loss of complete response, who had a complete response Prior to Week 16

The analysis of all secondary outcomes will be considered exploratory. Therefore, no multiplicity adjustments will be used.

10.4 Subgroup analyses

No analysis is planned for other subgroups as any such analyses are likely to be underpowered.

10.5 Adjusted analysis

The Statistical Plan will address the need for any adjusted analysis.

10.6 Interim analysis and criteria for the premature termination of the trial

No formal interim analysis will be conducted.
The occurrence of unexpected serious AEs, severe AEs (i.e, Grade 3 or higher), or unexpectedly frequent but less severe AEs among study subjects may result in the Sponsor's decision to terminate the study. A decision to terminate may also be made by health authorities, regulatory bodies, or an ethics committee (EC).

10.7 Participant population

The populations defined for analysis will include the intent-to-treat (ITT), per protocol (PP), and safety population.

- Intent-To-Treat Population: The ITT population (primary and secondary analysis) will be all subjects who have been randomised regardless of treatments applied.
- Per Protocol Population: The PP population for the 52-week study will comprise all the subjects in the ITT population with no major protocol violations, and in which for both groups complete data are available for all primary and secondary endpoints at 52 weeks.
- Safety Population: the safety population will be all subjects who have received at least one treatment.

Additional analysis populations may be defined to evaluate study results. Any additional analysis populations will be defined in the SAP.

10.8 Procedure(s) to account for missing or spurious data

Every effort will be made to obtain required data at each scheduled visit from all subjects who have been enrolled. In situations in which it is not possible to obtain all data, it may be necessary to impute missing data (for endpoints pertaining to the 12-week study). Subjects who are lost to follow-up will be included in the ITT analysis of primary and secondary endpoints using Last Observation Carried Forward principles to impute missing data. Data will also be imputed using algorithms for maximum likelihood for primary endpoint analysis (unadjusted and adjusted analyses) if feasible.

10.9 Other statistical considerations.

There is a requirement for an economic analysis plan, and this may be considered be outsourced to York Health Economics Consortium.

10.10 Economic evaluation

As this treatment is a novel treatment for Behçet's Disease, an economic evaluation may be undertaken by the York Health Economics Consortium who will compare the cost of treatment to patient outcomes.

11 DATA MANAGEMENT

11.1 Data collection tools and source document identification

The data management, collection tools and the management of the EDC will be controlled by Emmes India (Emmes). This will include development of a data management plan, development, build and validation of the clinical trial database and coding of and reconciliation of data. At the end of the study and with Sponsor approval, the database will be locked and export of data to the statistician will be undertaken. All Data Management activities will be undertaken in accordance with Emmes' SOPs.
Patients will provide informed consent for their data to be transferred (in a pseudo-anonymised format) outside of the UK for the purposes of the study

Source Data is defined by the ICH E6 section 1.51, defines source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)."

Case Report Forms [CRFs]

CRFs will be captured in an electronic database 'Advantage eClinical', managed by Emmes in order to ensure regulatory and statutory compliance.
Only the data required by the protocol will be captured in the eCRF. All source documents will be managed and maintained by the CI/PI at each site with oversight of all study documentation by the CRO.
Data collection will be via electronic data capture in Emmes Advantage eClinical, and a source data agreement will be in place to confirm what is defined as source at each site.
Trial staff at site will complete the eCRFs. The data can be viewed or checked remotely in Emmes Advantage eClinical by the Monitor/Data Manager from the CRO.

11.2 Data handling and record keeping

The data management will be outsourced to Emmes to ensure rigorous GCP data compliance and safeguarding the quality and integrity of the data handling and record keeping.
Emmes will manage Advantage eClinical – a web-based, electronic database (eCRF) - including maintenance of the SOPs for the use of the system, maintain a security system to protect against unauthorised access, maintain a list of the individuals authorised to use the system and their access rights, maintain adequate backup of the data, and provide the electronic data for

archiving. Advantage eClinical has an audit trail and electronic signatures. Advantage eClinical, provides web-based access, query management and resolution, and customisable reports and is 21CFR Part 11, EU GMP Annex 11, GDPR and HIPAA adherent.
All iterations of data will be clearly identified ensuring that it is possible to compare the original data and observations with the processed data. An unambiguous participant identification code that allows identification of all the data reported for each participant will be used. The Sponsor's Trial Master File (TMF) (paper) will be maintained by the CRO, with oversight from the Sponsor, and the CI/PI will maintain the Investigator Site File (ISF) at each site. Both files will be kept in secure locations with restricted access to authorised personnel.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections, - in line with participant consent. The funder or their authorised representatives may also be granted access to audit the study and study data if required.

11.4 Archiving

Archiving of the trial documentation at the end of the trial will be authorised by the Sponsor following the submission of the end of trial report.
During the trial phase all trial documents oversight will be managed by the CRO with each site being responsible for the location, retention and archiving of all trial documents, including all essential documentation and the trial database.
All essential documents will be archived for 25 years after completion of the trial and any destruction of essential documents will require authorisation from the Sponsor.

12 MONITORING, AUDIT & INSPECTION

Monitoring will be conducted by the CRO following the CRO SOPs. Written reports will be provided to the Sponsor following on-site monitoring visits, and regular updates provided in terms of recruitment, data capture, safety reporting and any other trial-related issues. Any reportable protocol deviations or violations as defined in the Monitoring Plan, will be discussed with the CI and notified to the Sponsor, and reporting of serious breaches will occur if such events are identified.
Auditing activities will be the responsibility of the Sponsor.

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Research Ethics Committee (REC) review & reports

Before the commencement of the trial, approval will be sought from a REC for the trial protocol, together with the informed consent forms and other relevant documents including the participant information and GP information letters.

All correspondence with the REC and the MHRA is retained in the Trial Master File.
An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the End of Trial is declaration is submitted. The Chief Investigator and Sponsor is responsible for the production of the annual reports as required and CRO will be responsible for submission.

The CRO will notify the REC and MHRA of the end of the trial in accordance with section 7.12
Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts, to the REC.
The CSR will also be submitted to the MHRA in accordance with MHRA guidelines.

13.2 Peer review

In order to provide high quality peer review that was independent, proportionate and with input from experts, the peer review process has been robust and this protocol has been reviewed.

13.3 Public and Patient Involvement

The involvement of patients and members of public in clinical research is deemed fundamental to good research and the CI and Sponsor have obtained input from patients and members of the public in ensuring not only the relevance of the design of the research but their input has been fundamental in devising the patient information about the trial. Specifically, input from Behçet's UK, the national patient group for Behçet's syndrome has been provided.

13.4 Regulatory Compliance

The trial will not commence until a Clinical Trial Authorisation (CTA) is obtained from the MHRA and Favourable REC opinion.
The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and any relevant amendments and will follow the Principles of GCP.

The CRO will ensure that appropriate approvals from participating organisations are in place.
For any amendment to the study, the CRO, in agreement with the CI and Sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The CRO will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

13.5 Protocol compliance

The Investigator agrees to comply with the requirements of the Protocol and Good Clinical Practice.
Protocol compliance will be overseen by the CRO, and any deviations or violations documented and reported to the CI, Sponsor and Trial Steering Committee.
Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials except for urgent safety measures as described in section above and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Should accidental protocol deviations occur, they must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately. Any consistent and reoccurring deviations from the protocol are not acceptable and will be discussed with the PI and corrective and preventative actions identified. If protocol non-compliance continues, this will require escalation to the Sponsor and review, and could potentially be classified as a serious breach.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is defined as a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or

(b) the scientific value of the trial

Should there be any breach of the protocol and/or GCP, the Sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase and the Sponsor of a clinical trial will notify the licensing authority, in writing, of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or

(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach.

The Sponsor will notify the MHRA GCP Inspectorate using the following email address: GCP.SeriousBreaches@mhra.gov.uk and the REC in writing.

13.7 Data protection and patient confidentiality

Patient confidentiality is a fundamental principle of the study and will be maintained at all times. The TMG, CI and Sponsor will ensure that the trial is compliant with the requirements of the General Data Protection Regulations (GDPR) and Data Protection Act 2018

All investigators and trial site staff must comply with the requirements of the GDPR and Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles.

All personal information that is collected, will be kept securely, and maintained. In general, this involves:

- The creation of coded, depersonalised data where the participant's identifying information is replaced by an unrelated sequence of characters.
- Secure maintenance of the data and the linking code in separate locations using encrypted digital files within password protected folders and storage media.
- Limiting access to the minimum number of individuals necessary for quality control, audit, and analysis

Confidentiality of data will be preserved when the data are transmitted to sponsors and co-investigators by ensuring all data is anonymised.

13.8 Financial and other competing interests for the chief investigator

Novartis are providing funding support and IMP (secukinumab and placebo) for the study. The CI has received prior research grant funding and has received fees for presentation of scientific work at meetings sponsored by Novartis.

13.9 Indemnity

The NHS Clinical Negligence Scheme will apply for this study.

13.10 Amendments

All amendments will be assessed and documented by the Sponsor to confirm if the amendment should be processed as a non-substantial or substantial amendment. All required approvals will be sought for any amendments required to the protocol.

Process for making amendments to the Trial Protocols

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial.
If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor must inform the CRO who will submit a valid notice of amendment to the licensing authority (MHRA) for consideration.
If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must inform the CRO who will submit a valid notice of amendment to the REC for consideration. The MHRA and/or the REC will provide a response regarding the amendment within 35 days of receipt of the notice.

It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

Amendments need to be notified to NHS R&D departments of participating sites to assess whether the amendment affects the capacity and capability for that site. All amendments must be notified to the HRA and CRN for categorisation. Implementation will be based upon the amendment category assigned.

Version control will be maintained for any amendments made. Substantial Amendments (SAs) will be identified by a whole number change (i.e. v1.0, v2.0) and non-substantial amendments (NSAs) identified by a decimal change (i.e. v1.1, v1.2).All amendments will be logged at each site and a central copy maintained in the TMF.

Guidance on the categorisation of amendments can be found on the HRA website http://www.hra.nhs.uk/resources/after-you-apply/amendments/

13.11 Post trial care

No interventions or benefit related to the study will be provided to participants once the study has completed. Patients will follow routine clinical care once their participation in the study has ended.

13.12 Access to the final trial dataset

The CI and Sponsor will have jurisdiction over the release of the final trial dataset and site investigators will have access to the full dataset if a formal request describing their plans is approved by the CI and Sponsor.

14 DISSEMINIATION POLICY

14.1 Dissemination policy

The study and study results will be published on ISRCTN.

On completion of the study a final check on the data will be performed and any missing data collected or otherwise accounted for.
Data will be tabulated and analysed as described in the statistical plan. A final study report will be prepared by the CI with input from the Sponsor and the CRO, for submission to the REC, MHRA, Sponsor and R&D.

The time period from the completion of follow-up of the last trial patient and submission of the report will follow regulatory guidelines.
All publications relating to the study will follow Consort Guidelines.

It is anticipated that the study will be prepared for submission to meetings and for publication. Any publication must have the approval of the CI/PI. There will be no time limit for the production of any publication.

Participants in the study will be informed of the final results if appropriate to do so. Participants will be informed following the preparation of the final report and may be provided with a lay person's summary of the conclusions. Behçet's UK will help in dissemination of the results, through social media and publication on their website.

14.2 Authorship eligibility guidelines and any intended use of professional writers

The list of authors will consist of those individuals who, at the discretion of the CI, have contributed to the creation of the study itself, to the recruitment and care of patients, to the collection and analysis of the data, to the preparation of any reports, abstracts and commentary and final publication of the study.

15 REFERENCES

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16. APPENDICIES

16.1 Appendix 1 – Schedule of Procedures

Procedures and assessments	**Visits**																		
	Screening	**Base line, Wk 0**	**Treatment Phase**																
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	Wk 60
Visit window	**-28days**	**0**	**+/- 2 days**				**+/- 3 days**			**+/- 5 days**									
Informed consent	X																		
Inclusion/exclusion criteria check	X	X																	
Demographics	X																		
Medical history	X																		
Physical examination	X																		
Symptom directed physical examination		X							X		X				X				
Vital signs (BP, Temp, HR, RR)	X	X							X		X				X				
Height	X																		
Weight	X																		
HIV, Hep, TB	X																		
Biochemistry, FBC, LFTs, U&Es, CRP, ESR	X								X		X				X			X	
Concomitant medications	X	X	X			X	X		X	X	X		X		X	X		X	X
Adverse events assessments		X	X			X	X		X	X	X		X		X	X		X	X

Procedures and assessments	**Screening**	**Base line, Wk 0**	**Treatment Phase**															
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	
Visit window	**-28days**	**0**	**+/- 2 days**				**+/- 3 days**			**+/- 5 days**									
Randomisation		X																	
Dispensing of IMP		X							X		X				X				
Telephone Only consultation			X			X	X			X			X			X			X
Clinic Visit	X	X							X		X				X			X	
IMP education		X																	
IMP/placebo administration		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Unblinding																		X	
Compliance		X	X			X	X		X	X	X		X		X	X		X	
Oral Ulcer assessment – severity score		X							X		X				X			X	
Genital ulcer assessment		X							X		X				X			X	
Urine pregnancy test		X							X										
Washout		X																	
Previous therapies including steroids for Behcets	X	X																	
VAS		X							X		X				X			X	
BDQoL		X							X		X				X			X	

BDCAF		X							X		X				X			X	
BSAS		X							X		X				X			X	
BASDAI		X							X		X				X			X	
LEI		X							X		X				X			X	

16.2 Appendix 2– Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
1	1.2	15Sep2022	Brigitta Sarosi	Minor changes to inclusion criteria
2	1.3	25May2023	Brigitta Sarosi	Addition of social media advertising or advertising via posters in clinics.

Secukinumab in Behcet protocol 1.3_25May2023_clean

Final Audit Report 2023-06-02

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