Evaluating the role of IL-17 as an orchestrator of peripheral-central cross talk in depressive symptoms

ELATE

Running Title	ELATE
Protocol Version	2.1
Protocol Date	20.03.2026
REC Reference Number	25/PR0161
Clinical Trials.org	NCT06786936
Sponsor Protocol Number	GN22MH376
Sponsor	NHS Greater Glasgow and Clyde University of Glasgow
Funder	Medical Research Council
IRAS	345892

AMENDMENT NUMBER	DATE	PROTOCOL VERSION
NS01 (clarification on the use of paper data capture forms)	**28.05.2025**	**1.1**
SA03 (Removal of EEG fMRI coil reference. fMRI completed using Nova MRI coil and subsequently EEG completed outside scanner	**20.10.2025**	**2.0**
NSA 04 Additional PIC site added- NHS Ayrshire & Arran	**20.10.2025**	**2.0**
NSA 05	**20.03.2026**	**2.1**

This study will be performed according to the UK Framework for health and Social care 2017 and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964

CONFIDENTIAL

CHIEF INVESTIGATOR

Professor Jonathan Cavanagh

Professor of Psychiatry

School of Immunology and Infection
Sir Graeme Davies Building
120 University Place
Glasgow
G12 8TA

T: 0141 330 7769

E: Jonathan.cavanagh@glasgow.ac.uk

CO-GRANT HOLDERS

Professor Neil Basu

Professor of Musculoskeletal Medicine & Vasculitis

School of Infection & Immunity

Sir Graeme Davies Building
120 University Place
Glasgow
G12 8TA
T: 0141 330 1718
E: Neil.Basu@glasgow.ac.uk

Professor Stefan Siebert

Professor of Inflammation Medicine and Rheumatology

School of Infection & Immunity
Sir Graeme Davies Building
120 University Place
Glasgow
G12 8TA
T: 0141 330 3375
E: Stefan.Siebert@glasgow.ac.uk

Dr Flippo Queirazza

Clinical Senior Lecturer in Psychiatry

School of Health and Wellbeing

Room 250, Level 2

90 Byres Road

Glasgow

G12 8TB

E: filippo.queirazza@glasgow.ac.uk

Professor Marios Philiastides

Professor of Decision Neuroscience

Centre for Cognitive Neuroimaging

Room 651 Level 6

62 Hillhead street

Glasgow

G12 8QB

E: marios.philiastides@glasgow.ac.uk

CO-GRANT HOLDERS (cont.)

Professor Ian McInnes

Muirhead Professor of Medicine
Vice-Principal and Head of College of MVLS

MVLS College Office
Wolfson Medical School Building
University of Glasgow
Univeristy Place
Glasgow

G12 8QQ

E: Iain.mcinnes@glasgow.ac.uk

Professor Leoni Taams

Professor of Immune Regulation & Inflammation

Centre for Inflammation Biology and Cancer Immunology (CIBCI)
Dept of Inflammation Biology
Kings College
London

E: leonie.taams@kcl.ac.uk

Ms Nicola Greenlaw
Lead Biostatistician

School of Health and Wellbeing
Clarice Pears Building
90 Byres Road
Glasgow
G12 8TB
E: Nicola.greenlaw@glasgow.ac.uk

Dr Areti Makrygeorgou
Associate Specialist Dermatologist

West Ambulatory Care Hospital
Dalnair Street
Glasgow
G3 8SJ

E: areti.makrygeorgou2@nhs.scot

STUDY CO-ORDINATOR

Miss Maxine Arnott

School of Immunology and Infection
Sir Graeme Davies Building
120 University Place
Glasgow
G12 8TA

T: 07890059695
E: Maxine.arnott@glasgow.ac.uk

STUDY STATISTICIAN

Ms Nicola Greenlaw

School of Health and Wellbeing
Clarice Pears Building
90 Byres Road
Glasgow
G12 8TB
T: 0141 330 4744
E: nicola.greenlaw@glasgow.ac.uk

SPONSOR PHARMACY

Jennifer McClintick

Sponsor Pharmacist
NHS Greater Glasgow and Clyde
Clinical Research and Development
Admin Building, Level 2,
Gartnavel Royal Hospital,
1055 Great Western Road, Glasgow,
G12 0XH

T: 0141 314 4019

E:jennifer.mcclintick2@nhs.scot

SPONSOR

Louise Ner

Sponsor Research Co-ordinator
NHS Greater Glasgow and Clyde
Research and Innovation Department
Admin Building, Level 2,
Gartnavel Royal Hospital,
1055 Great Western Road, Glasgow,
G12 0XH

E: louise.ner@nhs.scot

FUNDING BODY

MEDICAL RESEARCH COUNCIL (MRC)

2nd Floor David Phillips Building,
Polaris House,
North Star Avenue,
Swindon,
United Kingdom
SN2 1ET

T: **+**44 (0) 1793 416200

Chief Investigator: **Professor Jonathan Cavanagh**

Professor of Psychiatry
School of Immunology and Infection
Sir Graeme Davies Building
120 University Place
Glasgow
G12 8TA

Signature: 

Date: 20.03.2025

Sponsor Representative: **Louise Ner**

Sponsor Research Co—Ordinator
NHS Greater Glasgow & Clyde
Research & Innovation Department
Admin Building, Level 2
Gartnavel Royal Hospital
1055 Great Western Road
Glasgow
G12 0XH

Signature: 

Date: 25.03.2025

TABLE OF CONTENTS

LIST OF ABBREVATIONS

AE	Adverse Event
ALFF	amplitude of low-frequency fluctuations
BBB	Blood-brain barrier
BOLD	Blood-oxygen-level-dependent
CI	Chief Investigator
CNS	Central Nervous System
DAN	Dorsal attention network
DAPSA	Disease activity in Psoriatic Arthritis
DMARD	Disease-Modifying Anti-Rheumatic Drug
DSST	Digit Symbol Substitution Test
eCRF	Electronic case report form
EEG	Electroencephalogram
ELISA	Enzyme-linked immunosorbent assay
EPR	Electronic Patient Record
fMRI	functional Magnetic Resonance Imaging
GAIN	Glasgow Arthritis Involvement Network
IL-17	Interleukin 17
IL17R	Interleukin 17 Receptor
IMID	immune-mediated inflammatory diseases
IVRS	Interactive Voice Response Systems
MRS	magnetic resonance spectroscopy
NAcc	Nucleus accumbens
NICE	National institute for Health and Care Excellence
NMDA	N-methyl-D-aspartic acid
PMBC	peripheral blood mononuclear cell
PASI	Psorisis area and severity Index
PsA	Psoriatic arthritis
PsD	Psoriatic disease (encompassing both PsO and PsA)
PsO	Plaque psoriasis
RACE	Research into Inflammatory Arthritis Centre Versus Arthritis
REC	Research Ethics Committee

RSFA	resting-state fluctuation amplitude
SAE	Serious Adverse Event
SMC	Scottish Medicines Consortium
SPECT	Single-Photon Emission Computerized Tomography
7T	7 Tesla

STUDY SYNOPSIS

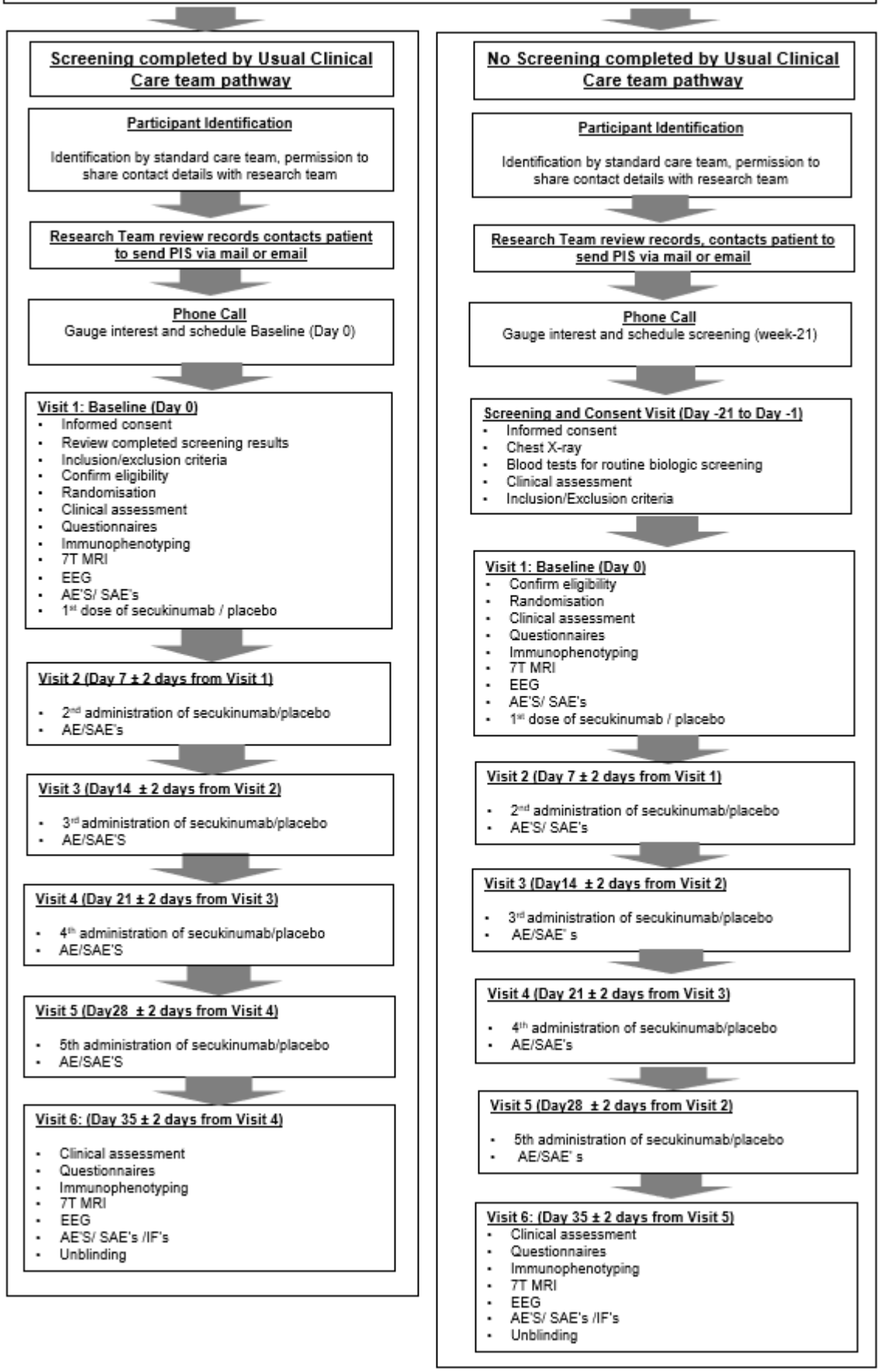
Title of Study	Evaluating the role of IL-17 as an orchestrator of peripheral-central cross talk in depressive symptoms **ELATE Study**
Study Centre	Glasgow
Duration of Study	36 months
Objectives	To determine: 1) The effects of IL-17 antagonism on 7T magnetic resonance spectroscopy (MRS) glutamate concentration in the nucleus accumbens (NAcc). 2) The effects of IL-17 antagonism on the strength of the EEG-informed fMRI coupling between the thalamic and NAcc learning systems and its relationship with depressive symptoms. 3) The relationship between glutamate concentration and depressive symptoms after IL-17 antagonism. 4) The ability of EEG-informed fMRI thalamic-NAcc systems coupling to predict depressive symptoms after IL-17 antagonism. 5) The relationship between resting-state fMRI functional connectivity between the thalamus and the NAcc and depressive symptoms. 6) The ability of resting-state fMRI functional connectivity between the thalamus and the NAcc to predict depressive symptoms after IL-17 antagonism. 7) The correlation between changes in depressive symptoms and peripheral blood immune cell alterations, particularly cells that produce or respond to IL-17.
Primary Objectives	Determine changes in glutamate concentration, as measured by 7T MRS, in the NAcc after IL-17 antagonism in patients with active psoriatic disease (PsD).
Secondary Objective	Determine the EEG-informed fMRI coupling between the thalamic and the NAcc learning systems before and after IL-17 antagonism.
Primary Endpoint	Changes in glutamate concentration in the NAcc as measured by 7T MRS before and after IL-17 antagonism.
Secondary Endpoint	Changes in the EEG-informed fMRI coupling between the thalamic and NAcc learning systems before and after IL-17 antagonism.
Exploratory Endpoint	1) Changes in depressive symptoms following IL-17 antagonism and how this relates to a) glutamate concentration in the NAcc b) EEG-informed fMRI thalamic-NAcc systems coupling c) resting-state fMRI functional connectivity between the thalamus and the NAcc. 2) Changes in peripheral immune biomarkers in patients before and after IL-17.

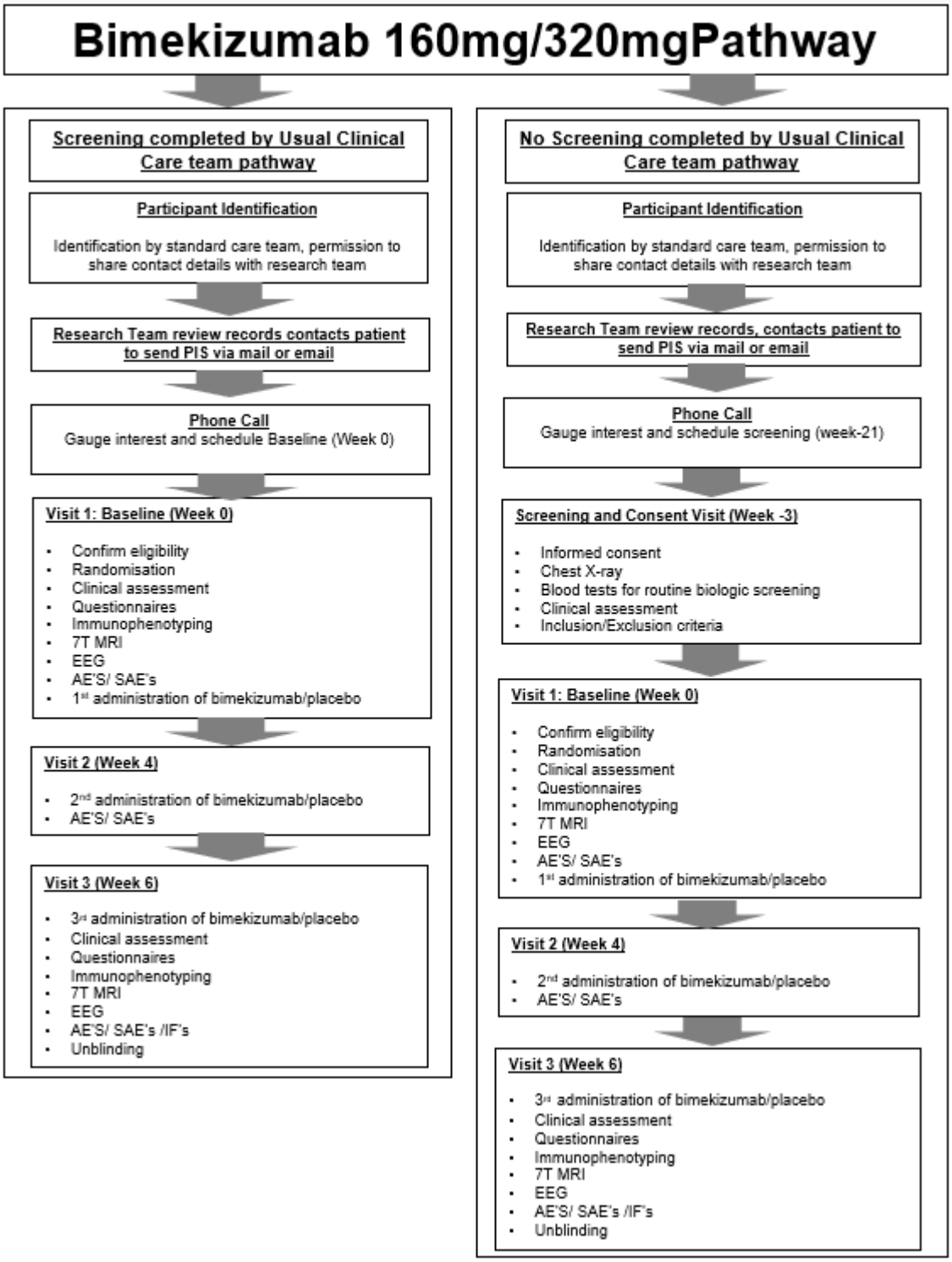
Rationale	Approximately 30-40% of patients with immune-mediated inflammatory diseases (IMIDs), such as Psoriatic disease, experience depression. These symptoms negatively affect clinical outcomes, quality of life and treatment adherence. There is accumulating evidence that peripheral inflammation may contribute to the origins of depression. In particular, a) stimulation of acute phase inflammation results in remitting-relapsing depressive symptoms b) abnormal neural connectivity linked to this depression is correlated with peripheral inflammation and c) biologic therapies targeting specific peripheral inflammation components (cytokines) improve depressive symptoms.
Methodology	Randomised placebo-controlled waiting list experimental medicine study. Participants will be randomised 1:1 to either immediately receive (fast-tracked) IL-17 blockade (secukinumab/ bimekizumab/ Ixekizumab) as per normal dose loading regime or a placebo. The duration of placebo exposure is justified on the basis that it is consistent with current local routine screening and waiting times to start biologics from treatment decision.
Sample Size	50
Screening	Patients with active PsD (who have failed > 1 csDMARD) selected to start Secukinumab, Bimekizumab or Ixekizumab by their dermatology clinical team for PsO or rheumatology clinical team for PsA as part of standard care attending clinics in NHS Greater Glasgow & Clyde, NHS Grampian, NHS Lothian, NHS Tayside, NHS Lanarkshire, NHS Forth Valley.
Randomisation	Randomised 1:1 (IL17 inhibitor or placebo)
Inclusion Criteria	• Adults ≥18 years < 75years • Diagnosis of PsO or PsA, made by a dermatologist or rheumatologist. • Selected to start secukinumab/ bimekizumab/ Ixekizumab as part of their standard clinical care by their usual dermatology team for PsO or rheumatology clinical team for PsA in line with the license for secukinumab/ bimekizumab/ Ixekizumab and NICE/SMC criteria. • No contraindications to MRI (for example metal fragments or implantable devices not compatible with MRI. (no extra x-ray images will be obtained to check placement of metal fragments or clips in situ. Existing images may be used to check for possible contraindications) • Satisfactory completion of standard pre-biologic safety screening (including, but not limited to, exclusion of latent TB infection according to local protocol, chest X-ray, negative HIV screen, negative Hepatitis screen antibody, negative Hepatitis B surface antigen [Hep B sAg] and negative Hepatitis B anti-core antibody [Hep B cAb]) • Recent (but not within 4 weeks prior baseline) use of intra-muscular or intra-articular steroid injections

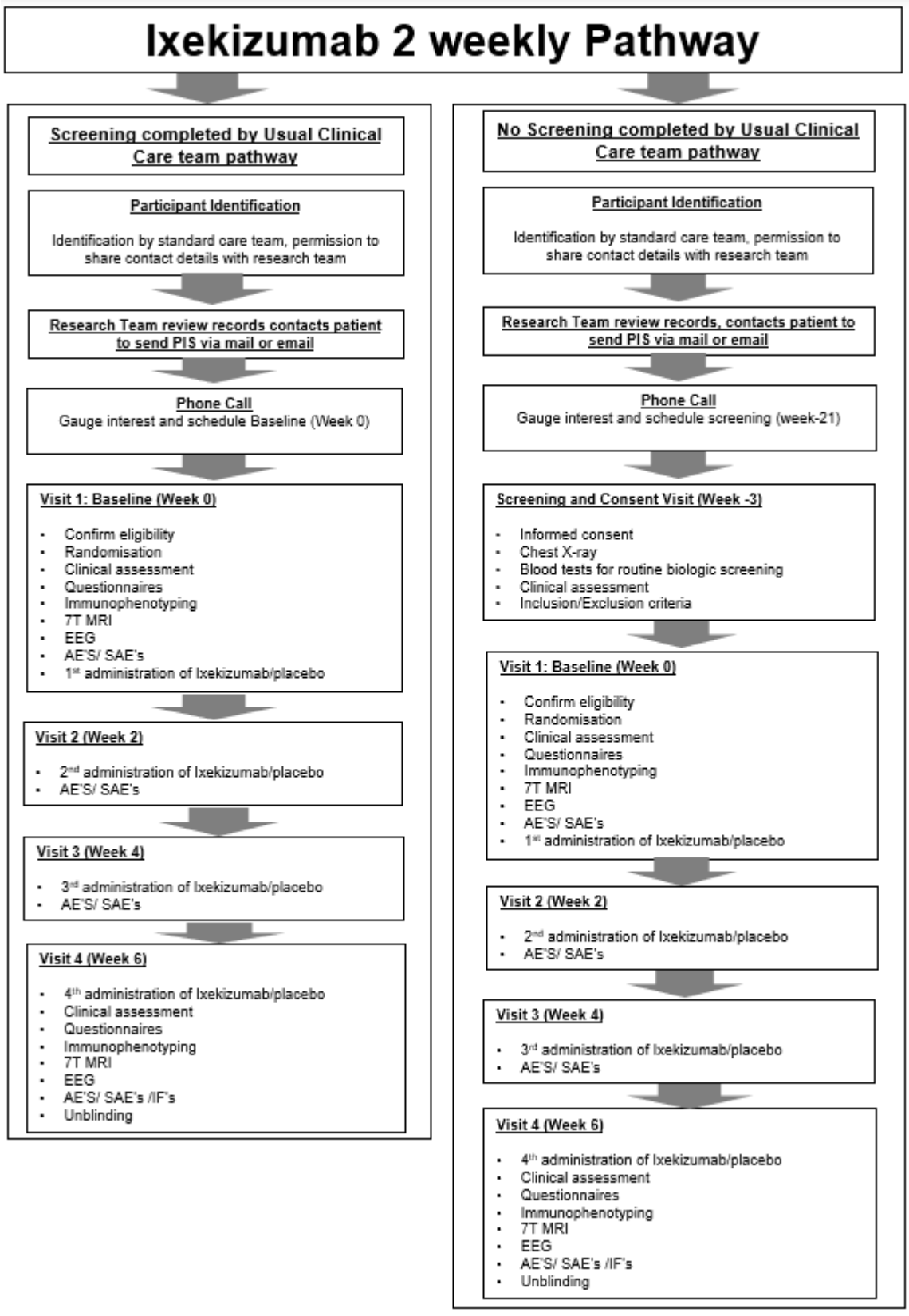
	• Women of Child-Bearing Potential (WoCBP) must be willing to use effective contraception for study duration. Further information is provided in appendix 1. • Willing to participate and give informed consent
Exclusion Criteria	• Inability to provide written informed consent • Severe physical impairment (e.g., blindness, deafness, paraplegia). • Clinically important, active infections e.g. active TB • History of inflammatory bowel disease • Pregnant or breast feeding • Severe claustrophobia precluding MRI • Contraindications to 7T MRI (metal implants in the ears, head or neck, microbladed/ tattooed eyebrows, metal fragments in the eyes) • Confounding neurological disease including MS, Stroke, Traumatic Brain Injury • Previous exposure to IL-17A, IL-17A/F, IL-17R inhibitors or IL-23 p19/p40 inhibitors in the last **6 months** • Hypersensitivity to any of the excipients in secukinumab/ bimekizumab/ ixekizumab. • Any reason which, at the investigator's discretion, would make them unsuitable to take part in the study
Product, Dose, Modes of Administration	Secukinumab 150mg or 300mg subcutaneous per dose loading regime for five weeks, or bimekizumab 160mgs or 320mgs 4 weekly subcutaneous or Ixekizumab 160mg at week 0 then 80mg every two weeks or 4 weeks subcutaneous or placebo that mirrors the dosing regimen of the drug selected by the clinical care team. Participants will be randomised 1:1 to either IL17 inhibitor prescribed and selected by the standard care team or placebo.
Duration of Treatment	6 weeks
Statistical Analysis	Outcomes will be analysed using appropriate generalised linear regression models for the distribution of the data. The difference between the randomised groups for each outcome will be estimated with corresponding 95% confidence intervals. For each randomised group, correlations between continuous outcome measures of interest (e.g., glutamate and depressive symptoms) will be explored. Models may be extended to include other variables of interest.

STUDY FLOW CHART

Secukinumab 150mg/300mg Pathway




Bimekizumab 160mg/320mgPathway
Screening completed by Usual Clinical Care team pathway
Participant Identification
Identification by standard care team, permission to share contact details with research team
Research Team review records contacts patient to send PIS via mail or email
Phone Call
Gauge interest and schedule Baseline (Week 0)
Visit 1: Baseline (Week 0)
Confirm eligibility
Randomisation
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's
1st administration of bimekizumab/placebo
Visit 2 (Week 4)
2nd administration of bimekizumab/placebo
AE'S/ SAE's
Visit 3 (Week 6)
3rd administration of bimekizumab/placebo
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's /IF's
Unblinding
No Screening completed by Usual Clinical Care team pathway
Participant Identification
Identification by standard care team, permission to share contact details with research team
Research Team review records, contacts patient to send PIS via mail or email
Phone Call
Gauge interest and schedule screening (week-21)
Screening and Consent Visit (Week -3)
Informed consent
Chest X-ray
Blood tests for routine biologic screening
Clinical assessment
Inclusion/Exclusion criteria
Visit 1: Baseline (Week 0)
Confirm eligibility
Randomisation
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's
1st administration of bimekizumab/placebo
Visit 2 (Week 4)
2nd administration of bimekizumab/placebo
AE'S/ SAE's
Visit 3 (Week 6)
3rd administration of bimekizumab/placebo
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's /IF's
Unblinding


Ixekizumab 2 weekly Pathway
Screening completed by Usual Clinical Care team pathway
Participant Identification
Identification by standard care team, permission to share contact details with research team
Research Team review records contacts patient to send PIS via mail or email
Phone Call
Gauge interest and schedule Baseline (Week 0)
Visit 1: Baseline (Week 0)
Confirm eligibility
Randomisation
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's
1st administration of Ixekizumab/placebo
Visit 2 (Week 2)
2nd administration of Ixekizumab/placebo
AE'S/ SAE's
Visit 3 (Week 4)
3rd administration of Ixekizumab/placebo
AE'S/ SAE's
Visit 4 (Week 6)
4th administration of Ixekizumab/placebo
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's /IF's
Unblinding
No Screening completed by Usual Clinical Care team pathway
Participant Identification
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Chest X-ray
Blood tests for routine biologic screening
Clinical assessment
Inclusion/Exclusion criteria
Visit 1: Baseline (Week 0)
Confirm eligibility
Randomisation
Clinical assessment
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Immunophenotyping
7T MRI
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AE'S/ SAE's
1st administration of Ixekizumab/placebo
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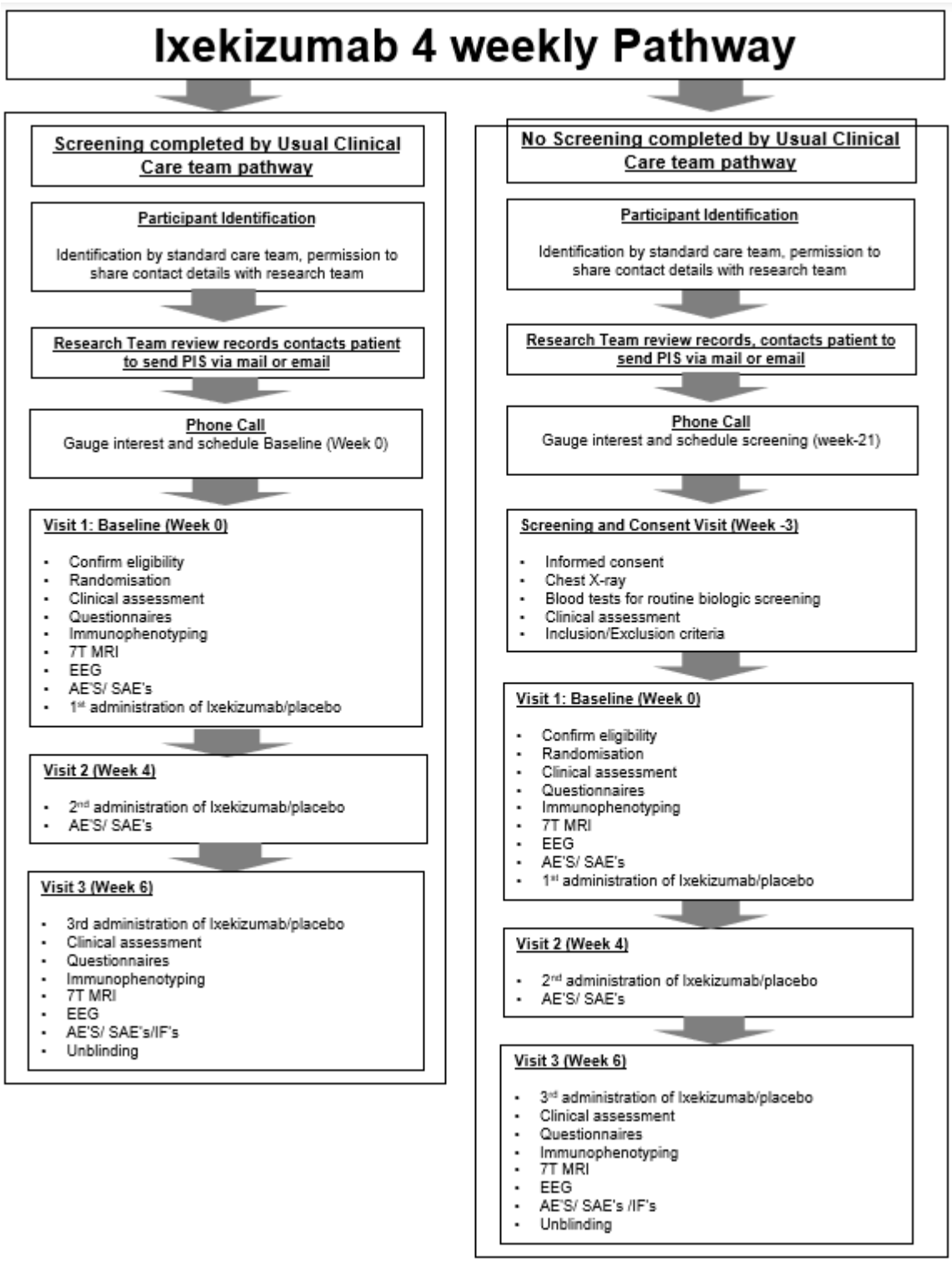
AE'S/ SAE's
Visit 3 (Week 4)
3rd administration of Ixekizumab/placebo
AE'S/ SAE's
Visit 4 (Week 6)
4th administration of Ixekizumab/placebo
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's /IF's
Unblinding


Ixekizumab 4 weekly Pathway
Screening completed by Usual Clinical Care team pathway
Participant Identification
Identification by standard care team, permission to share contact details with research team
Research Team review records contacts patient to send PIS via mail or email
Phone Call
Gauge interest and schedule Baseline (Week 0)
Visit 1: Baseline (Week 0)
Confirm eligibility
Randomisation
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's
1st administration of Ixekizumab/placebo
Visit 2 (Week 4)
2nd administration of Ixekizumab/placebo
AE'S/ SAE's
Visit 3 (Week 6)
3rd administration of Ixekizumab/placebo
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Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's/IF's
Unblinding
No Screening completed by Usual Clinical Care team pathway
Participant Identification
Identification by standard care team, permission to share contact details with research team
Research Team review records, contacts patient to send PIS via mail or email
Phone Call
Gauge interest and schedule screening (week-21)
Screening and Consent Visit (Week -3)
Informed consent
Chest X-ray
Blood tests for routine biologic screening
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2nd administration of Ixekizumab/placebo
AE'S/ SAE's
Visit 3 (Week 6)
3rd administration of Ixekizumab/placebo
Clinical assessment
Questionnaires
Immunophenotyping
7T MRI
EEG
AE'S/ SAE's /IF's
Unblinding

SCHEDULE OF ASSESSMENTS for Secukinumab 150mg/300mg

Study Procedure	Visit 0 Screening Day -21 to Day -1	Visit 1 Baseline Day 0	Visit 2 Follow up Day 7	Visit 3 Follow up Day 14	Visit 4 Follow-up Day 21	Visit 5 Follow-up Day 28	Visit 6 Follow up Day 42
Obtain Informed Consent	✓						
Review Inclusion/Exclusion Criteria	✓						
Biologic screening (Blood tests)*	✓						
Biologic screening (Chest Xray)**	✓						
Indices of disease activity***	✓	✓					✓
Medical history	✓						
Concomitant medication review	✓	✓					✓
EEG Checklist	✓	✓					✓
MRI Checklist	✓	✓					✓
Urine pregnancy test****	✓						
Questionnaires *****		✓					✓
Demographics	✓						
Immunophenotyping blood sampling ******		✓					✓
Review of screening tests		✓					
Randomisation		✓					
Alert card issued		✓					
Administration of secukinumab 150mg or 300mg or placebo		✓	✓	✓	✓	✓	
EEG		✓					✓
7T MRI/ MRS/ fMRI		✓					✓
AE/ SAE/ IF check		✓	✓	✓	✓	✓	✓
Unblinding							✓
GP participation letter		✓					
GP completion letter							✓
Participant study exit letter							✓

*Biological blood screening can be completed by study team if not obtained by standard care team (If completed by standard care screening and baseline can be combined)

** Chest x-ray can be requested if not ordered by standard care team (If obtained prior to study entry screening and baseline visits can be combined)

*** Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
Psoriasis participants - Psoriasis Area and Severity Index (PASI) & Dermatology life Quality Index (DLQI), Body surface area (BSA)

**** If applicable (applies only to women of childbearing potential)

***** Questionnaires can be sent via email to be 24 hours prior to visit) Montgomery-Asberg Depression Rating scale (MADRS), Snaith- Hamilton Pleasure Scale (SHAPS), Hospital and Anxiety depression scale (HADS), PROMIS- Depression, anxiety, sleep related impairment, pain interference, fatigue. FACIT-fatigue, Sickness questionnaire, Fibromyalgia degree- 2011 ACR survey criteria, Michigan body map reginal pain, McGill Pain questionnaire Cognitive failures questionnaire.

****** Please refer to section 6 for immunophenotyping blood sampling bottle draw and volume

SCHEDULE OF ASSESSMENTS for Bimekizumab 160mg/320mg				
Study Procedure	**Visit 0 Screening Day -21 to day -1**	**Visit 1 Baseline Day 0**	**Visit 2 Follow up Day 28**	**Visit 3 Follow up Day 42**
Obtain Informed Consent	✓			
Review Inclusion/Exclusion Criteria	✓			
Biologic screening (Blood tests) *	✓			
Biologic screening (Chest Xray)**	✓			
Indices of disease activity***	✓	✓		✓
Medical history	✓			
Concomitant medication review	✓			✓
EEG Checklist	✓			✓
MRI Checklist	✓			✓
Urine pregnancy test****	✓			
Questionnaires *****		✓		✓
Demographics	✓			
Immunophenotyping blood sampling ******	✓			✓
Review Screen test results		✓		
Randomisation		✓		
Alert card issued		✓		
Administration of Bimekizumab 160mg or 320mg or placebo		✓	✓	
EEG		✓		✓
7T MRI/ MRS/ fMRI		✓		✓
AE/ SAE check		✓	✓	✓
Unblinding				✓
GP Participation letter		✓		
GP Completion letter				✓
Participant study exit letter				✓

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***Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint coun

Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)

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SCHEDULE OF ASSESSMENTS for Ixekizumab 2 weekly dosing					
Study Procedure	**Visit 0 Screening Day -21 to Day -0**	**Visit 1 Baseline Day 0**	**Visit 2 Baseline Day 14**	**Visit 3 Follow up Day 28**	**Visit 4 Follow up Day 42**
Obtain Informed Consent	✓				
Review Inclusion/Exclusion Criteria	✓				
Biologic screening (Blood tests)*	✓				
Biologic screening (Chest Xray)**	✓				
Indices of disease activity***	✓	✓			✓
Medical history	✓				
Concomitant medication review	✓				✓
EEG Checklist	✓				✓
MRI Checklist	✓				✓
Urine pregnancy test****	✓				
Questionnaires *****		✓			✓
Demographics	✓				
Immunophenotyping blood sampling ******		✓			✓
Review screening test results		✓			
Randomisation		✓			
Alert card issued		✓			
Administration of Ixekizumab 160mg or 80mg or placebo		✓	✓	✓	✓
EEG		✓			✓
7T MRI/ MRS/ fMRI		✓			✓
AE/ SAE check		✓	✓	✓	✓
Unblinding					✓
GP Participation letter		✓			
GP Completion letter					✓
Participant study exit letter					✓

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***Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count.
Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)

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****** Please refer to section 6 for immunophenotyping blood sampling bottle draw and volume

SCHEDULE OF ASSESSMENTS for Ixekizumab 4 weekly				
Study Procedure	**Visit 0 Screening Day -21 to day -1**	**Visit 1 Baseline Day 0**	**Visit 2 Follow up Day 28**	**Visit 3 Follow up Day 42**
Obtain Informed Consent	✓			
Review Inclusion/Exclusion Criteria	✓			
Biologic screening (Blood tests) *	✓			
Biologic screening (Chest Xray)**	✓			
Indices of disease activity***	✓	✓		✓
Medical history	✓			
Concomitant medication review	✓			✓
EEG Checklist	✓			✓
MRI Checklist	✓			✓
Urine pregnancy test****	✓			
Questionnaires *****		✓		✓
Demographics	✓			
Immunophenotyping blood sampling ******		✓		✓
Review Screen test results		✓		
Randomisation		✓		
Alert card issued		✓		
Administration of Ixekizumab 160mg or 80mg or placebo		✓	✓	
EEG f		✓		✓
7T MRI/ MRS/ fMRI		✓		✓
AE/ SAE check		✓	✓	✓
Unblinding				✓
GP Participation letter		✓		
GP Completion letter				✓
Participant study exit letter				✓

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** Chest x-ray can be requested if not ordered by standard care team (If obtained prior to study entry screening and baseline visits can be combined)

***Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count

Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)

****If applicable (applies only to women of childbearing potential)

- ***** Questionnaires can be sent via email to be 24 hours prior to visit) Montgomery-Asberg Depression Rating scale (MADRS), Snaith- Hamilton Pleasure Scale (SHAPS), Hospital and Anxiety depression scale (HADS),PROMIS- Depression, anxiety, sleep related impairment, pain interference, fatigue. FACIT-fatigue, Sickness questionnaire, Fibromyalgia degree- 2011 ACR survey criteria, Michigan body map reginal pain, McGill Pain questionnaire, Cognitive failures questionnaire

****** Please refer to section 6 for immunophenotyping blood sampling bottle draw and volume

1.0 INTRODUCTION

1.1. BACKGROUND

Approximately 30-40% of patients with immune-mediated inflammatory diseases (IMIDs), such as psoriatic disease, experience depression. These symptoms negatively affect clinical outcomes, quality of life and treatment adherence. There is accumulating evidence that peripheral inflammation may contribute to the origins of depression. In particular, a) stimulation of active phase inflammation results in remitting-relapsing depressive symptoms b) abnormal neural connectivity linked to this depression is correlated with peripheral inflammation and c) biologic therapies targeting specific peripheral inflammation components (cytokines) improve depressive symptoms.
In this proposal, psoriatic disease (PsD), encompassing both psoriasis and PsA, will be our IMID exemplar. In this condition, the IL-23/IL-17 cytokine axis is central to pathogenesis, as proven by successful application of inhibitors to this pathway. Moreover, this axis has also recently been implicated in the neurobiology of depression in both preclinical and clinical studies.

We aim to uncover the mechanisms that underlie depression in the context of IMIDs, delivered by a focused immune intervention study examining brain circuitry using state of the art imaging in the context of exquisitely specific therapeutic immune interception in human immune disease.

1.2. RATIONALE

The rationale for this study is to use this specific therapeutic immune intervention to leverage mechanistic understanding of brain changes that drive depressive symptoms. Prior animal studies have clearly demonstrated the deleterious effects of proinflammatory cytokines on neural functioning. We will integrate current therapy with innovative neuroimaging technologies to obtain data for the first time in humans that have hitherto only been possible in animal studies.

1.3. DOSE SELECTION

The intervention tools proposed herein (secukinumab, bimekizumab or Ixekizumab) are IL-17 inhibitors licensed for treatment of active PsO and PsA. Secukinumab, bimekizumab and Ixekizumab are widely used in clinical practice globally and across the UK as a first/second-line biologic disease modifying antirheumatic drug (DMARD), in line with national/international NICE (TA350, TA445, TA723, TA916, TA442, TA537) treatment recommendations. Secukinumab is given by self-administered subcutaneous injection weekly for the first five weeks of treatment and thereafter by monthly maintenance injections. Bimekizumab is given by self-administered subcutaneous injection 4 weekly, Ixekizumab is given by self -administered subcutaneous injection either 2 or 4 weekly. Typically, depressive symptoms are attenuated within weeks of therapeutic initiation. Prior study data indicate a beneficial effect of IL17 antagonism on depressive symptoms, but the mechanism of action has not yet been explored.

1.4. STUDY HYPOTHESIS

We seek clinically actionable understanding of the mechanisms that underlie depression in the context of immune mediated inflammatory diseases (IMIDs), delivered by a focused immune intervention study examining brain circuitry using state of the art imaging in the context of exquisitely specific therapeutic immune interception in human immune disease.

Glutamate concentration in the NAcc will be positively correlated with the magnitude of the inflammatory response and will be attenuated by IL-17A inhibition. Ultimately, this will be associated with an improvement in depressive symptoms.

The strength of coupling between early (e.g. thalamus) and late (e.g. NAcc) systems will be attenuated in the context of IL-17A-driven inflammation and will be correlated with less frequent switching behaviour in a learning task following negative outcomes and ultimately depressive symptoms. This coupling will be re-established following IL-17 antagonism.

Patients whose depressive symptoms benefit most from IL-17A antagonism will exhibit greatest resting-state and task-specific functional connectivity between thalamus-NAcc.

2.0 STUDY OBJECTIVES

To determine:

- The effects of IL-17 antagonism on 7T magnetic resonance spectroscopy (MRS) glutamate concentration in the NAcc.
- The effects of IL-17 antagonism on the strength of the EEG-informed fMRI coupling between the thalamic and NAcc learning systems and its relationship with depressive symptoms.
- The relationship between glutamate concentration and depressive symptoms after IL-17 antagonism.
- The ability of EEG-informed fMRI thalamic-NAcc systems coupling to predict depressive symptoms after IL-17 antagonism.
- The relationship between resting-state fMRI functional connectivity between the thalamus and the NAcc and depressive symptoms.
- The ability of resting-state fMRI functional connectivity between the thalamus and the NAcc to predict depressive symptoms after IL-17 antagonism.
- Whether changes in depressive symptoms correlate to peripheral blood immune cell alterations, particularly cells that produce or respond to IL-17.

2.1. PRIMARY ENDPOINT

- Changes in glutamate concentration in the NAcc as measured by 7T MRS.

2.2. SECONDARY ENDPOINT

- Changes in the EEG-informed fMRI coupling between the thalamic and NAcc learning systems.

2.3. EXPLORATORY ENDPOINTS

- Changes in depressive symptoms following IL-17 antagonism and how this relates to a) glutamate concentration in the NAcc b) EEG-informed fMRI thalamic-NAcc systems coupling c) resting-state fMRI functional connectivity between the thalamus and the NAcc.

- Changes in peripheral immune biomarkers in patients before and after IL-17 antagonism.

3.0 STUDY DESIGN

This study will be performed according to the UK Framework for Health and Social Care 2017. All investigators and key trial personnel will complete biennial GCP training.

This is a multi-site, randomised parallel group, placebo waiting list controlled, experimental medicine study. Participants, study investigators, the study statistician and staff performing neuro-imaging and other outcome assessments will be blinded to the treatment allocated from the time of randomisation until database lock.

3.1. STUDY POPULATION

50 participants with active PsD attending clinics in NHS Greater Glasgow and Clyde, NHS Grampian, NHS Lothian, NHS Tayside, NHS Lanarkshire, NHS Forth Valley starting IL-17 antagonism as part of their usual care by either their NHS dermatology clinical care team for psoriasis, or NHS rheumatology clinical care team for PsA, and in line with the licence and SMC/NICE guidance for these agents. The decision to prescribe anti-IL17 treatment for active PsD will be made by the patients' clinical team in advance, and independently, of the study.

Consenting eligible participants will be randomised 1:1 to either immediately receive (fast-tracked) secukinumab/ bimekizumab/ Ixekizumab per normal dose loading regime or a placebo. After study completion participants will return to usual clinical care and continue or start IL17 inhibitor treatment as per clinical care prescription.

3.2. INCLUSION CRITERIA

- Adults ≥18 years < 75years
- Diagnosis of PsO or PsA, made by a dermatologist or rheumatologist
- Selected to start secukinumab/ bimekizumab/ Ixekizumab by their usual dermatology team for PsO or rheumatology clinical team for PsA in line with the license for secukinumab/ bimekizumab/ Ixekizumab and eligible using NICE/SMC criteria.
- No contraindications to MRI - for example metal fragments or implantable devices not compatible with MRI. (no extra x-ray images will be obtained to check placement of metal fragments or clips insitu. Existing images may be used to check for possible contraindications)
- Satisfactory completion of standard pre-biologic safety screening (including, but not limited to, exclusion of latent TB infection according to local protocol, chest X-ray, negative HIV screen, negative Hepatitis screen antibody, negative Hepatitis B surface antigen [Hep B sAg] and negative Hepatitis B anti-core antibody [Hep B cAb])
- Recent (but not within 4 weeks prior baseline) use of intra-muscular or intra-articular steroid injections

- Women of Child-Bearing Potential (WoCBP) must be willing to use of effective contraception for study duration. Further information is provided in appendix 1.
- Willing to participate and give informed consent

3.3. EXCLUSION CRITERIA

- Inability to provide written informed consent
- Severe physical impairment (e.g., blindness, deafness, paraplegia)
- Clinically important, active infections e.g. active TB
- History of inflammatory bowel disease
- Pregnant or breast feeding.
- Severe claustrophobia precluding MRI
- Contraindications to 7T MRI
- Confounding neurological disease including MS, Stroke, Traumatic Brain Injury.
- Previous exposure to IL-17A, IL-17A/F, IL-17R inhibitors or IL-23 (p19/p40) inhibitors in the last 6 months.
- Hypersensitivity to any of the excipients in secukinumab/ bimekizumab/ ixekizumab
- Any clinical, psychological, social or geographical reason which, at the investigator's discretion, would make them unsuitable to take part in the study.

3.4. INDENTIFICATION OF PARTICIPANTS AND CONSENT

Patients with active PsD attending dermatology or rheumatology outpatient clinics in NHS Greater Glasgow & Clyde, NHS Grampian, NHS Lothian, NHS Tayside, NHS Lanarkshire, NHS Forth Valley will be notified of the study by the direct care team.
This verbal agreement to be contacted by researchers will be documented by the direct care team in clinical record. Eligibility will be confirmed by a medically qualified doctor who is part of both the clinical/research team. Contact details of interested patients will be shared by the clinical team with the research team via NHS-to-NHS email. Clinic lists will be screened by members of the direct care team.

If the patient assents to being contacted by the research team, they will be contacted by phone to go through basic screening, address any queries, check for MRI and significant medical condition contraindications and provided with a patient information sheet in electronic or paper form. The research team will give at least 24 hours and recontact and gauge their interest in the study and allow them to ask any questions. At this stage, potential participants will be invited to attend a screening and consent visit that will be conducted at the Imaging Centre of Excellence (ICE) at the Queen Elizabeth University Hospital. At this meeting, participants will be asked again if they have any questions.

Participants will undergo informed consent where two copies of the consent form will be signed (one each for the participant and the site file). A copy of the signed consent form will be inserted into the patient's record or scanned into the electronic patient record (EPR). A letter will be sent to the patient's GP informing them of their participation in the study.

Eligibility will be confirmed by a medically qualified investigator and consent will be taken by a member of the research team. The research team comprises individuals who help to coordinate and perform the study in addition to individuals from the direct clinical care team. In addition to the clinical team, the research team requires access to the patient's medical record to be able to comprehensively collect necessary clinical characterization, e.g. blood results and validate patient reports.
All participants who consent to the study will receive a £10 lovetoshop voucher for taking part.
Those who take part in the 7T fMRI task and the EEG task will receive additional £10 lovetoshop voucher regardless of how well the perform in the cognitive task.

QEUH NHS GG&C will be the main site for all study activities including screening, consent and first administration of IL17/ placebo, this is due to the location of the only 7T MRI scanner in Scotland.

The addition and activation of NHS Lothian and NHS Grampian as sites 02 & 03 is for the participants to have the option to attend injection visits locally between baseline Day 0 and final study visit day 42. Participants from all PIC sites (NHS Lanarkshire, NHS Forth Valley, NHS Tayside) will be required to attend the QEUH NHS Greater Glasgow and Clyde for all study visits.

3.5 WITHDRAWAL OF PARTICPANTS AND PLANNED UNBLINDING

The participant can decide to withdraw from the study at any time for no reason. The Chief Investigator (CI) or co-investigators also have the right to withdraw patients from the study if deemed in the best interests of the patient or in the event of Adverse Events (AEs), protocol violations, administrative or other reasons. Full details of withdrawal should be recorded on the paper/ electronic Case Report Form (eCRF).

Participants may decide to withdraw their initial consent for this study, at this point no further information regarding the participant will be collected. Data relating to the patient that has been collected up to the point of withdrawal will still be used. The notification of withdrawal from the study by the participant can be made via the research team contact details on the PIS or via their usual care team.

Participants who have completed all the study visits and any withdrawn patients will be unblinded using the planned unblinding option within the IVRS.

3.6 RANDOMISATION

Eligible and consenting participants will be randomised 1:1 to receive either immediate (fast tracked) IL-17 treatment (secukinumab/ bimekizumab/ Ixekizumab per normal dose loading regime), or to receive treatment after 8-10 weeks (the routine waiting time). The latter group will receive placebo.

A central randomisation facility (interactive voice response system, IVRS) will allocate the randomised therapy per participant. The IVRS, based at the Robertson Centre for Biostatistics, will be available by telephone. Randomisation will be stratified by study centre (Glasgow) using randomised permuted blocks of variable size.

The randomisation schedule will be prepared by the study statistician without involvement of the investigators. Once generated, the study statistician will not have access to the live randomisation list.

3.7 EMERGENCY UNBLINDING

A central unblinding facility based at the Robertson Centre for Biostatistics will be available by telephone for emergency unblinding. Notification that emergency unblinding has occurred will be sent to the CI but treatment allocation will not be provided.

Emergency unblinding should be undertaken only where it is essential for participant safety and when knowledge of the treatment will influence the participant's management in a significant fashion. Emergency unblinding will be available via an IVRS which is supported by the Robertson Centre for Biostatistics and will be available at all times.

Participants will be provided with a Study Alert Card that will contain details on emergency unblinding arrangements at Visit 0. Participants will be required to carry the alert card with them at all times and should show the card to any doctors or healthcare professionals who are involved in their care. The Participant Study Alert Card will be collected from patients at the end of their involvement in the study.

In case of emergency unblinding, only those individuals who are required to know treatment allocation should be given this information. All others who are blinded must remain so, including the participant. Unless the participant meets any of the criteria detailed in 10.3, they will be retained in the study at the PI's discretion.

3.8 TRANSITION OF STUDY PARTICIPANTS BACK TO ROUTINE CARE

After study completion participants will return to usual clinical care and continue, or start, IL17 inhibitor treatment as per usual care prescription.

An unblinded member of the research team will be responsible for liaising with the participant's usual care team, which may be at a PIC site, to ensure prescriptions and home delivery arrangements are in place to allow study participants to seamlessly transition to local standard care arrangements for initiation or continuation of IL17 antagonism as necessary. Where a participant withdraws /is withdrawn from the study prior to the last planned study visit, every effort should be made to facilitate the participant's return to standard care arrangements minimising any delays to the commencement (should be within two weeks of withdrawal) or continuation IL17 treatment.

Participants who wish to withdraw from IL17/placebo treatment but continue in the study may do so at the PIs discretion. In this case, patients will be referred back to their direct care team but can continue to attend study visits.

Referring sites will be required to make local arrangements for supply of secukinimab/ bimekizumab/ Ixekizumab, regardless of study randomisation, in the event the participant's Homecare supply has not commenced at the time of study completion to facilitate ongoing treatment continuity.

4.0 STUDY PROCEDURES

4.1. STUDY SCHEDULE for *Secukinumab* participants 150mg/ 300mg

The study will comprise of a 3-week screening phase prior to the baseline 7T MRI & fMRI task and the EEG task before the commencement of weekly subcutaneous loading dose regime injection visits before obtaining a final 6-week 7T MRI scan & fMRI task and EEG task.

Screening and V1 can be combined if all inclusion/ exclusion criteria are met, and screening tests have already been completed by the usual care team and it is deemed safe to proceed by the investigator.

4.1.1. SCREENING VISIT Day -21 to Day -0 Length approx. 1.5 hours

- Informed Consent
- Review of Inclusion/ exclusion
- Medical history
- Demographics
- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Concomitant medications review
- Urine pregnancy test for females of childbearing potential (if applicable)
- Routine blood tests for biological screening (26ml):
    - QuantiFERON TB test
    - Varicella test
    - Hepatitis B
    - Hepatitis C
    - HIV
    - Full blood count
    - ESR
    - CRP
    - Urine and electrolytes
    - LFTs

- Chest X-ray (if not obtained in the past 12 months)
- 7T MRI safety checklist (e.g. implants, tattoos, operation history, hand dominance)
- Stand-alone EEG checklist (e.g. head circumference)

4.1.2. VISIT 1 Day 0 Length approx. 4 hours

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Venous blood sample for peripheral immunophenotyping

- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)
- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Stand-alone EEG checklist (e.g. head circumference,)
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Randomisation
- 1st subcutaneous injection of Secukinumab/placebo
- GP Participation letter

4.1.3. VISIT 2 Day 7 (+/- 2 day) Length approx. 30mins

- 2nd subcutaneous injection of Secukinumab /placebo
- Adverse events/ SAE's/ incidental findings

*Visit optionally available at referring site for participant convenience

4.1.4.VISIT 3 Day 14 (+/- 2 days) Length approx. 30mins

- 3rd subcutaneous injection of Secukinumab / placebo
- Adverse events/ SAE's/Incidental findings

* Visit optionally available at referring site for participant convenience

4.1.5.VISIT 4 Day 21 (+/- 2 days) Length approx. 30mins

- 4th subcutaneous injection of Secukinumab /placebo
- Adverse events/ SAE's/ Incidental findings

* Visit optionally available at referring site for participant convenience

4.1.6. VISIT 5 Day 28 (+/- 2 days) Length approx. 30mins

- 5th subcutaneous injection of Secukinumab /placebo
- Adverse events/ SAE's/ Incidental findings

*Visit optionally available at referring site for participant convenience

4.1.7.VISIT 6 Day 42 (+/- 2 days) Length approx. 4 hours

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Venous blood sample for peripheral immunophenotyping
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)
- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Standalone EEG checklist (e.g. head circumference)
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Adverse events/ SAE's/ Incidental findings
- Unblinding
- Participant Subcutaneous administration training (if required)
- GP Completion letter
- Participant study exit letter- copy to usual care team

4.2. STUDY SCHEDULE for *Bimekizumab* participants 160mg/ 320mg

The study will comprise of a 3-week screening phase prior to the baseline 7T MRI & fMRI task and EEG task before the commencement of 4 weekly subcutaneous injection visit before obtaining a final 6-week 7T MRI scan with fMRI task and EEG task.

*Screening and V1 can be combined if all inclusion/ exclusion criteria are met and screening tests have already been completed by the usual care team and it is deemed safe to proceed by the investigator.

4.2.1. SCREENING VISIT Day -21 to Day -1 Length approx. 1.5 hours

- Informed Consent
- Review of Inclusion/ exclusion
- Medical history
- Demographics
- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Concomitant medications review
- Urine pregnancy test for females of child bearing potential (if applicable)
- Routine blood tests for biological screening (26ml):
    - QuantiFERON TB test
    - Varicella test
    - Hepatitis B
    - Hepatitis C
    - HIV
    - Full blood count
    - ESR
    - CRP
    - Urine and electrolytes
    - LFTs

- Chest X-ray (if not obtained in the past 12 months)
- 7T MRI safety checklist (e.g. implants, tattoos, operation history, hand dominance)
- Stand-alone EEG checklist (e.g. head circumference)

4.2.2. VISIT 1 Day 0 Length approx. 4 hours

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)

- Venous blood sample for peripheral immunophenotyping
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)
- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Stand-alone EEG checklist (e.g. head circumference)
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Randomisation
- 1st subcutaneous injection of Bimekizumab /placebo
- GP Participation letter
- Adverse events/ SAE's/ Incidental findings

4.2.3. VISIT 2 Day 28 (+/- 2 days)	**Length approx. 30mins**

- 2nd subcutaneous injection of Bimekizumab /placebo
- Adverse events/ SAE's/ Incidental findings

*Visit optionally available at referring site for participant convenience

4.2.4. VISIT 3 Day 42 (+/- 2 days)	**Length approx. 4 hours**

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Venous blood sample for peripheral immunophenotyping
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)
- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue

- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Stand-alone EEG checklist (e.g. head circumference)
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Adverse events/ SAE's/ Incidental findings
- Unblinding
- Participant Subcutaneous administration training (if required)
- GP Completion letter
- Participant study exit letter- copy to usual care team

4.3. STUDY SCHEDULE for *Ixekinumab* participants 2 weekly

The study will comprise of a 3 week screening phase prior to the baseline 7T MRI & fMRI task and EEG task before the commencement of 2 weekly subcutaneous injection visit before obtaining a final 6 week 7T MRI & fMRI task and EEG task.

Screening and V1 can be combined if all inclusion/ exclusion criteria are met and screening tests have already been completed by the Clinical care team and it is deemed safe to proceed by the investigator.

4.3.1. SCREENING VISIT Day -21 to Day -1 Length approx. 1.5 hours

- Informed Consent
- Review of Inclusion/ exclusion
- Medical history
- Demographics
- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Concomitant medications review
- Urine pregnancy test for females of child bearing potential (if applicable)
- Routine blood tests for biological screening (26ml):
    - QuantiFERON TB test
    - Varicella test
    - Hepatitis B
    - Hepatitis C
    - HIV
    - Full blood count
    - ESR
    - CRP
    - Urine and electrolytes
    - LFTs
- Chest X-ray (if not obtained in the past 12 months)
- 7T MRI safety checklist (e.g. implants, tattoos, operation history, hand dominance)
- EEG checklist (e.g. head circumference)

4.3.2. VISIT 1 Day 0 Length approx. 4 hours

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA) & The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI) & Dermatology life Quality Index (DLQI)
- Venous blood sample for peripheral immunophenotyping
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)

- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Stand-alone EEG checklist (e.g. head circumference)
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Randomisation
- 1st subcutaneous injection of Ixekinumab/placebo
- GP Participation letter
- Adverse events/ SAE's/ Incidental findings

4.3.3. VISIT 2 Day 14 (+/- 2 days)	**Length approx. 30mins**

- 2nd subcutaneous injection of Ixekinumab /placebo
- Adverse events/ SAE's/ Incidental findings

*Visit optionally available at referring site for participant convenience

4.3.4. VISIT 3 Day 28 (+/- 2 days)	**Length approx. 30mins**

- 3rd subcutaneous injection of Ixekinumab /placebo
- Adverse events/ SAE's/ Incidental findings

*Visit optionally available at referring site for participant convenience

4.3.5.VISIT 4 Day 42 (+/- 2 days)	**Length approx. 4 hours**

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Venous blood sample for peripheral immunophenotyping
- 3rd/4th subcutaneous injection of Ixekinumab /placebo (only applicable to participants prescribed 2 weekly Ixekizumab by usual care team)
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)
- Hospital and Anxiety depression scale (HADS)

- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history, hand dominance)
- Stand-aloneEEG checklist
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Adverse events/ SAE's/ Incidental findings
- 4th subcutaneous injection of Ixekinumab /placebo
- Unblinding
- Participant Subcutaneous administration training (if required)
- GP Completion letter
- Participant study exit letter- copy to usual care team

4.4. STUDY SCHEDULE for *Ixekinumab* participants 4 weekly

The study will comprise of a 3-week screening phase prior to the baseline 7T MRI & fMRI task and EEG task before the commencement of a 4 weekly subcutaneous injection visit before obtaining a final 6 week 7T MRI & fMRI task and EEG task.

Screening and V1 can be combined if all inclusion/ exclusion criteria are met and screening tests have already been completed by the Clinical care team and it is deemed safe to proceed by the investigator.

4.4.1. SCREENING VISIT Day -21 to Day -1 Length approx. 1.5 hours

- Informed Consent
- Review of Inclusion/ exclusion
- Medical history
- Demographics
- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Concomitant medications review
- Urine pregnancy test for females of child bearing potential (if applicable)
- Routine blood tests for biological screening (26ml):
    - QuantiFERON TB test
    - Varicella test
    - Hepatitis B
    - Hepatitis C
    - HIV
    - Full blood count
    - ESR
    - CRP
    - Urine and electrolytes
    - LFTs
- Chest X-ray (if not obtained in the past 12 months)
- 7T MRI safety checklist (e.g. implants, tattoos, operation history, hand dominance)
- EEG checklist (e.g. head circumference)

4.4.2. VISIT 1 Day 0 Length approx 4 hours

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Venous blood sample for peripheral immunophenotyping
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)

- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire
- Cognitive failures questionnaire
- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Stand-aloneEEG checklist (e.g. head circumference)
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Randomisation
- 1st subcutaneous injection of Ixekinumab/placebo
- GP Participation letter
- Adverse events/ SAE's/ Incidental findings

4.4.3. VISIT 2 Day 28 (+/- 2 days)	**Length approx 30mins**

- 2nd subcutaneous injection of Ixekinumab /placebo
- Adverse events/ SAE's/ Incidental findings

*Visit optionally available at referring site for participant convenience

4.4.4.VISIT 3 Day 42 (+/- 2 days)	**Length approx 4 hours**

- Indices of disease activity for Psoriatic arthritis participants- Disease activity in Psoriatic Arthritis (DAPSA), The Psoriatic Arthritis Impact of Disease (PSADI 12), Psoriasis Area and Severity Index (PASI), Body surface area (BSA), 66/68 joint count
- Indices of disease activity for Psoriasis participants - Psoriasis Area and Severity Index (PASI), Dermatology life Quality Index (DLQI), Body surface area (BSA)
- Venous blood sample for peripheral immunophenotyping
- Montgomery-Asberg Depression Rating scale (MADRS)
- Snaith- Hamilton Pleasure Scale (SHAPS)
- Hospital and Anxiety depression scale (HADS)
- Patient-Reported Outcome Measurement Information System (www.NIHPROMIS.org) :
    - PROMIS- depression
    - PROMIS- anxiety
    - PROMIS- fatigue
    - PROMIS- Sleep related impairment
    - PROMIS- Pain Interference
- FACIT- fatigue
- Sickness Questionnaire
- Fibromyalgia degree – 2011 ACR survey criteria
- Michigan Body Map Regional Pain
- McGill Pain Questionnaire

- 7T MRI Safety checklist (e.g. implants, tattoos, operation history)
- Stand-alone EEG safety checklist
- 7T MRI (MRS, resting-state fMRI, task fMRI)
- EEG
- Adverse events/ SAE's/ Incidental findings
- Unblinding
- Participant Subcutaneous administration training (if required)
- GP Completion letter
- Participant study exit letter- copy to usual care team

5.0 STUDY OUTCOME MEASURES

5.1 PRIMARY OUTCOME MEASURES

The Primary outcome measures will be:

Changes in glutamate concentration in the NAcc as measured by 7T MRS, from Week 0 to Week 6 (before and after IL17 antagonism).

5.2 SECONDARY OUTCOME MEASURES

The secondary outcome measures will be:

Changes in the EEG-informed fMRI coupling between the thalamic and NAcc learning systems before and after IL-17 antagonism, from Week 0 to Week 6 (before and after IL17 antagonism).

5.3 EXPLORATORY OUTCOME MEASURES

Changes in depressive symptoms following IL-17 antagonism and how this relates to a) glutamate concentration in the NAcc b) EEG-informed fMRI thalamic-NAcc systems coupling c) resting-state fMRI functional connectivity between the thalamus and the NAcc.

1. Changes in components of low mood, which are:
    a. Fatigue (FACIT-F, PROMIS fatigue)
    b. Hyperalgesia (American College of Rheumatology Fibromyalgia scale- ACR FM)
    c. Pain (Pain-PROMIS pain interference, McGill Pain Questionnaire, Michigan Body Map Regional Pain Intensity)
    d. Sleep disturbance (PROMIS- Sleep related impairment)
    e. Mood (Hospital Anxiety Depression Scale- HADS, PROMIS-Depression, PROMIS-Anxiety, Sickness Questionnaire)
    f. Cognition (Cognitive failures questionnaire)

2. Changes in measures of disease activity as measure by indices of PsO or PsA which are:

    Psoriatic arthritis participants
    a. Disease activity in Psoriatic Arthritis (DAPSA)
    b. The Psoriatic Arthritis Impact of Disease (PSADI 12)
    c. Psoriasis Area and Severity Index (PASI)
    d. Body surface area (BSA)
    e. 66/68 joint count

    Psoriasis participants:
    a. Psoriasis Area and Severity Index (PASI)
    b. Dermatology life Quality Index (DLQI)
    c. Body surface area (BSA)

3. Changes in peripheral immune biomarkers in patients before and after IL-17.

6. LABORATORY TESTS

Cytokines (including IL-17A, IL-17F, TNF and IL-6), chemokines and other relevant biomarkers of inflammation will be measured using Meso-Scale Discovery (MSD) electro-chemiluminescence assays using an MSD Sector Imager 6000 (Biomax 800325) before and after IL-17 antagonism, and in relation to clinical and neuroimaging outcomes. Plasma will be stored in a biobank for future metabolomic evaluation outwith the present proposal. We will monitor differences in peripheral cellular sources of IL-17A/F in patients before and after IL-17A antagonism, using established flow cytometry or CyTOF pipelines to phenotype CD4+ or CD8+ T cells, MAIT cells, iNKT cells and gamma delta T cells in combination with expression of type 17 markers (IL-17A, IL-17F, CCR6, CXCR6, CD161). This will give an indication of the potential cellular sources of IL-17A/F and how these link to changes in our neurobiological metrics of interest and depressive symptoms.

Number of Bottles	Sample bottle	Week 0	Week 6
1	SST tube (8.5ml)	✓	✓
1	PAXgene RNA tube (2.5ml)	✓	✓
2	EDTA tube (10ml)	✓	✓
1	EDTA tube (4ml)	✓	✓
5	Heparin (10ml)	✓	✓

Immunophenotyping blood sample total at Day 0 and Day 42 85mls. Blood samples will be processed and analysed as described in the ELATE lab protocol at the University of Glasgow Laboratory.

7.0 7T MRI

Participants will be asked to lie supine in the ultra-high resolution 7T multimodal MRI scanner at The Imaging Centre of Excellence, based in a comprehensive clinical setting in Glasgow. Using a MAGNETOM Terra 7T scanner (Siemens Healthcare, Erlangen, Germany) and a single channel transmit, 32 channel receive radiofrequency head coil (Nova Medical, Wilmington, MA), we will obtain neurobiological surrogate measures of glutamate, functional connectivity, and fMRI task activity:

Glutamate Imaging – a magnetic resonance spectroscopy scan will be undertaken in order to detect the glutamate concentration. A single voxel sequence will be employed with semi-LASER preparation. A 14×10×13 mm3 voxel will be placed in the left nucleus accumbens and shimming of the static magnetic field will be performed using advanced methods best suited to MRS acquisition at 7T, such as FASTMAP. Spectra will be analysed and quantified in JMRUI or LCModel.

Functional connectivity - a resting state BOLD-fMRI scan will be undertaken. Functional connectivity MRI (fcMRI) investigations are conducted with subjects resting in the scanner. Ten minutes of whole-brain resting state fMRI data will be collected using a simultaneous-multi-slice (SMS) echoplanar-imaging (EPI) sequence of factor=3. A whole-brain T1-weighted structural image will also be collected using a twice magnetization-prepared rapid gradient echo (MP2RAGE) sequence. During the resting state, subjects will be instructed not to undertake any particular task and to stay awake with their eyes open on a fixation cross. Whole brain coverage will be performed. Data will be pre-processed and analysed using software such as statistical parametric mapping (SPM) version 12 (SPM12, Wellcome Department of Cognitive Neurology, London,

United Kingdom) and the Conn (Cognitive and affective neuroscience laboratory, MIT, Cambridge, USA) functional connectivity toolbox, all running on MATLAB 2023a.

Upon collection of resting state fcMRI data, pre-processing steps will include the removal of physiological artefacts, motion correction, realignment, registration, normalization and smoothing. Connectivity indices will be generated from matrices informed by our a priori determined regions of interest (Thalamus - Nucleus Accumbens).

fMRI task- after resting state has been obtained the fMRI will be completed using a cognitive reinforcement-learning task. Before the scan starts the study team will prepare the participant by practicing this task outside the scanner room to make sure that this can be completed and any questions answered before being positioned in the 7T scanner space. The practice will be part of both baseline and follow up sessions and take approximately 40-45mins before the scan starts. Regardless of how well they perform in the cognitive task all participants will be awarded the full £10 lovetoshopvoucher.

8.0 fMRI EEG FUSION

The acquisition of simultaneous 7TfMRI with EEG required the use of a closed head coil. The higher-than-average BMI of our study population, poor core strength and limited head space of the coil has proven challenging. Therefore, the 7T MRI/MRS imaging and EEG acquisition will occur sequentially rather than simultaneously within the same research session.

Our fMRI EEG fusion hypothesis is based on earlier findings using a reinforcement learning task in healthy controls and combined 3TfMRI-EEG (Fouragnan et al., Nature Comms, 2015). Specifically, using the EEG signals we had identified a fast ('early') system, initiating an automatic alertness response following negative outcomes, while in parallel down-regulating activity of a slower ('late') reward-updating system, to promote avoidance learning. EEG-informed analysis of the fMRI identified the source of the systems in the Thalamus and Nucleus Accumbens (NAcc) and demonstrated that the connectivity strength between these nodes in the fMRI modulated reward-seeking behaviour across individuals.

We will use these findings as a benchmark to understand the role of IL-17 in mediating depressive symptoms while leveraging the increased signal-to-noise ratio (SNR) at 7T. We hypothesise that strength of coupling between the Thalamus and NAcc will be attenuated in the context of IL-17-driven inflammation and will be correlated with less frequent switching behaviour following negative outcomes and ultimately depressive symptoms. This coupling will be re-established following IL-17 antagonism.

Our original plan was to use the same EEG-informed fMRI approach to identify the relevant clusters in the Thalamus and NAcc. However, since we know these target nodes *a priori*, we will use stand-alone 7T fMRI with a more suitable headcoil (NOVA coil that also captures the primary end point of this study), introduce anatomically defined masks for these areas and proceed with the proposed Thal-NAcc connectivity analysis as normal.

A stand-alone EEG will be obtained on the same participants (in an adjacent room, following fMRI scanning) and attempt a post-hoc fusion of the EEG-fMRI datasets to further validate our hypothesis. For analysis the study team will jointly model the separate fMRI and EEG datasets to formally establish a link – e.g. compute the strength of the Thal-NAcc coupling in the fMRI (based on the region-of-interest analysis outlined above), which we will then correlate with the temporal lag of the early-late systems as captured in the EEG. Based on our earlier findings (Fouragnan et al., Nature Comms 2015), this temporal lag forms a proxy of the relative influence of the early (Thalamus) system onto the late (NAcc) system. This offers another opportunity to formally test the role of IL-17 on the spatiotemporal link between Thal-NAcc in reward-seeking behaviour.

Participants are required to have measurements taken of their head, to ensure an appropriate cap is used.

9.0 STUDY MEDICATION

Participants who are eligible for the study will be randomised via IVRS to receive either planned IL17 treatment (Dose determined by usual clinical care team) or placebo:

- **IL17 (SECUKINUMAB 150mg or 300mg every week for 5 doses)**
  (BIMEKIZUMAB 160mg or 320mg every 4 weeks)
  (IXEKIZUMAB 160mgs for one dose then 80mgs 2 weekly or 4 weekly)

or

- **PLACEBO (Normal Saline 0.9%)**

Further details of treatment schedules are given below.

9.1. ADMINISTRATION SCHEDULE AND MAINTENANCE OF BLINDING

It is not possible within the available resources to fully blind the treatment allocation (IL17 or placebo). Therefore, a pragmatic approach has been adopted for the study. The administration procedure and care provided immediately after for secukinimab/ bimekizumab/ Ixekizumab and placebo administration must be standardised to minimise the potential for participants to determine treatment allocation. All injections must be administered by an appropriately trained health care professional. Investigators and staff performing neuro-imaging and other outcome assessments will remain blinded to the treatment allocated from the time of randomisation until database lock.

In order to maintain the participant blind, doses of secukinimab/ bimekizumab/ Ixekizumab and placebo will be prepared in a separate area out of view of the participant. A screen will be placed so that the participant is unable to view skin cleansing, study medicine administration or disposal of the used syringe into the sharps container post-administration. The following administration sites may be used abdomen (at least 5cm from the navel) or front of thighs depending on patient preference. A different injection site must be used for each injection – each new injection site should be at least 3cm from the previous injection site. Injections must not be made to areas that are red, hard, bruised or tender. Similarly, injections must not be made in scars, stretch marks, other lesions or areas of skin that show psoriasis. The injection site must be documented at each treatment visit. The syringe must not be shaken prior ro administration.Doses must be administered within +/- two days of the planned date of administration once the participant has started receiving the secukinimab/ bimekizumab/ Ixekizumab or placebo.

The table below outlines the time the study medicine should be taken out of the fridge prior to administration and guidance for visual inspection.

Drug	Strength	Required time out of fridge prior to administration	Inspection prior to administration
Secukinumab	150mg	20 minutes	The liquid should be clear. The colour may vary from colourless to slightly yellow. You may see small air bubbles. This is normal. Do not use if there are visible particles or the liquid is cloudy or distinctly brown.
Secukinumab	300mg	30-45 minutes	

Bimekizumab	160mg 320mg	30-45 minutes	The liquid should be clear to slightly opalescent. Its colour may vary from colourless to pale brownish-yellow. You may see air bubbles in the liquid. This is normal. Do not use if the medicine is cloudy, discoloured, or has particles.
Ixekizumab	80mg	30 minutes	The liquid should be clear. The colour may vary from colourless to slightly yellow. There may be small air bubbles, This is normal. Do not use if there are visible particles or if the solution is cloudy and/or discoloured.

There is a risk of hypersensitivity reactions after administration of secukinumab/bimekinumab/ixekinumab. These reactions include anaphylaxis, angioedema, urticaria and, rarely, latent hypersensitivity reactions. If an anaphylactic or other serious allergic reaction occurs, treatment should be discontinued, and appropriate therapy initiated immediately.

For patients receiving secukinumab: The needle cap contains a derivative of natural rubber latex. No natural rubber latex has been detected in the cap. However, the product has not been tested in patients with latex sensitivity and therefore the potential risk of hypersensitivity reactions cannot be ruled out.

Participants will be blinded to the treatment allocation until week 6. Researchers who are not involved in assessing outcome measures will be unblinded to treatment allocation and on completion of the planned unblinding via IVRS, will inform the participant at the end of the week 6 visit. Investigators and staff performing neuro-imaging and other outcome assessments, as well as the study statistician, will remain blinded to the treatment allocated from the time of randomisation until database lock. Details of planned and emergency unblinding procedures can be found in 3.7.

Healthcare professionals responsible for treatment decisions relating to secukinimab/ bimekizumab/ Ixekizumab or placebo must have appropriate specialist training and experience. Should participants in either the active treatment or placebo arm meet standard care requirements for a temporary stop to treatment, the decision to stop and restart will be taken by an investigator experienced in the management of PsO or PsA. Consideration must be given locally on maintenance of the blind.

9.2 TREATMENT SCHEDULE

Doses of secukinumab/ placebo must be administered within +/- 2 days of the weekly planned date of administration once the participant has started receiving the secukinimab or placebo.

Doses of bimekizumab/ placebo will be administered within +/- 2 days of the 4 weekly planned date of administration once the participant has started receiving the bimekizumab or placebo.

Doses of Ixekizumab/ placebo will be administered within +/- 2 days of the 2 or 4 weekly planned date of administration once the participant has started receiving the Ixekizumab or placebo.

9.3 IL17 DOSE

Secukinumab, bimekizumab and Ixekizumab are both widely used in clinical practice globally and across the UK as a first/second-line biologic disease modifying antirheumatic drug (DMARD), in line with national/international NICE (TA350,TA445, TA723, TA916, TA442, TA537)) treatment recommendations.

Initial dosing of Secukinimab at week 0, 1, 2, 3, 4 and maintenance doses will be determined by the standard care team. This will be 150mg or 300mg. This will be administered by the study team once confirmed and randomisation has occurred for secukinimab/ placebo allocation.

Initial dosing of bimkizumab at week 0 & 4 and maintenance doses will be determined by the standard care team. This will be 160mg or 320mg. This will be administered by the study team once confirmed and randomisation has occurred for bimekizumab/ placebo allocation.

Initial dosing of Ixekizumab at week 0 & 4 or week 0, 2 & 4, maintenance doses will be determined by the standard care team. The initial dose will be 160mgs then 80mg dose will either be given 2 or 4 weekly. This will be administered by the study team once confirmed and randomisation has occurred for Ixekizumab/ placebo allocation.

9.5 PLACEBO

Sodium chloride 0.9% for injection will be used as a placebo. A 1ml volume will be drawn up into a suitable sized syringe and labelled in accordance with standard practice at site. The dose will be administered as a subcutaneous injection in line with the Secukinumab/ Bimekizumab/ Ixekizumab dosing regimen. No dose adjustments are permitted.

Prior to administration, the prepared placebo syringe should be visually inspected for discolouration and particulate matter prior to administration.

10.0 CONCOMITANT MEDICINES

10.1. PERMITTED CONCOMITANT MEDICINES

Concomitant medicines are permitted at the PIs discretion provided doses are expected to remain consistent throughout the study. The use of conventional disease-modifying anti-rheumatic drugs (cDMARDs) and topical steroids is permitted. (≤10mg of prednisone or the equivalent per day) will be permitted. Intra-articular and intramuscular triamcinolone can be used, but not within 4 weeks of the baseline.

10.2. PROHIBITED CONCOMITANT MEDICINES

Biologic disease-modifying drug therapy including but not limited to: adalimumab, etanercept, golimumab, infliximab, certolizumab, abatacept, tocilizumab, sarilumab, rituximab, tofacitinib, apremilastor Upadacitinib **are prohibited.**

Live vaccines should not be given concurrently with study medicine. Non-live and inactivated vaccinations should only be administered after discussion with usual care team.

Previous exposure to IL-17A, IL-17A/F, IL-17R inhibitors or IL-23 inhibitors in the last 6 months.

10.3. INTERACTIONS

Secukinumab, bimekizumab and ixekizumab may reverse the suppression of cytochrome P450 (CYP450) isoenzymes caused by cytokines which the monoclonal antibodies antagonise. Therefore, with higher levels of CYP450, levels of medicines metabolised via this route may be reduced. The manufacturers advise patients taking CYP450 substrates with narrow therapeutic ranges e.g. ciclosporin, theophylline and warfarin, should be monitored closely for reduced efficacy/concentration of treatment when starting secukinumab, ixekizumab or bimekizumab.

10.4. DISCONTINUATION OF STUDY MEDICINES

The study medication should be permanently and immediately discontinued in case of the following situations:

1. Serious infection requiring hospitalisation, including sepsis, tuberculosis, and opportunistic infections such as invasive fungal infections, which rule out the continuation of the study drug as determined by the Investigator.
2. Clinically significant abnormal laboratory result(s) or AE(s), which rule out continuation of the study drug, as determined by the Investigator.
3. The patient develops symptoms of inflammatory bowel disease.
4. The Investigator believes it is in the best interest of the subject.
5. The participant requests withdrawal from the study.
6. Commencement of prohibited medicines.
7. Any other potentially serious condition as judged by the investigator which may place the participant at additional risk should they continue within the study.

Participants may also be withdrawn from the study in the event they are significantly non-compliant with study procedures to the extent that the participant would be at risk for continued participation in the study as determined by the investigator.

At the end of their study involvement, ALL participants will be returned to NHS standard care. Arrangements will be made such that all participants transition to NHS standard care with Secukinimab/ bimekizumab/ Ixekizumab without interruption to prevent inappropriate treatment delay. During the study, participants will be trained to use secukinimab/ bimekizumab/ Ixekizumab pen self-injectors in preparation for their use in routine care.

11.0 STUDY SUPPLIES

11.1. SUPPLY OF STUDY TREATMENT

The study site will be responsible for procurement of all secukinumab/ bimekizumab/ Ixekizumab and placebo (vials containing 0.9% sodium chloride for injection) via usual NHS supply mechanisms for medicines.

11.2. STORAGE OF STUDY TREATMENT

All study drugs must be stored in a secure location and will be dispensed by pharmacy who will be delegated this task by the Investigator. Supplies of IL17 and placebo must be stored in accordance with the relevant Summary of Product Characteristics. Pre-filled syringes of IL17 must be stored in the outer carton in order to protect from light and stored in a refrigerator a 2°C - 8°C. Do not freeze.

Pharmacy will label secukinumab/ bimekizumab/ Ixekizumab or the placebo vial in accordance with requirements for a dispensed medicine. They should also add additional label to include participant and visit number. Further information is provided in the study medicines management and accountability manual.

11.3. DRUG ACCOUNTABILITY

Secukinumab/ bimekizumab/ Ixekizumab and placebo (0.9% sodium chloride for injection) will be dispensed by pharmacy at each treatment visit in response to a signed prescription from an Investigator delegated this responsibility on the site study delegation log.

Accurate records of the quantity of study medicines dispensed for each participant for traceability purposes will be maintained including the brand/manufacturer, batch number and expiry date.

12.0 PHARMACOVIGILANCE

12.1. DEFINITIONS OF ADVERSE EVENTS

Adverse Event (AE) – Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR) – Any untoward and unintended response in a subject to whom an investigational medicinal product has been administered which is related to any dose administered to that subject.

12.2. SERIOUS ADVERSE EVENT (SAE) OR SERIOUS ADVERSE REACTION (SAR)

Any adverse event or adverse reaction that:

a) Results in death
b) Is life threatening

c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability or incapacity
e) Consists of a congenital anomaly or birth defect
f) Is otherwise considered medically significant by the investigator
g) Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above

12.3. RECORDING AND REPORTING OF ADVERSE EVENTS

AEs occurring during this timeframe must be recorded in patient notes, assessed, reported, analysed, and managed in accordance with the UK Policy Framework for Health and Social Care Research and the study protocol. All AEs must be assessed for seriousness.

Where an AE or SAE requires recording; full details including the nature of the event, start and stop dates, severity, relationship to secukinumab/ bimekizumab/ Ixekizumab or any of the study specific scanning procedures (MRI and EEG). The outcome of the event will be recorded in the patient's medical notes and CRFs and events will be monitored and followed up until satisfactory resolution and stabilization.

Any adverse event or adverse reaction that:
a) Results in death
b) Is life threatening
c) Requires hospitalisation or prolongation of existing hospitalisation
d) Results in persistent or significant disability or incapacity
e) Consists of a congenital anomaly or birth defect
f) Is otherwise considered medically significant by the investigator
g) Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above.

Secukinumab
SAEs should be assessed to determine if the event is causally related to secukinumab and expectedness of related events will be assessed against the SmPC Cosentyx 150 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk).

Bimekizumab
SAEs should be assessed to determine if the event is causally related to bimekizumab and expectedness of related events will be assessed against the SmPC Bimzelx 160 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

Ixekizumab
SAEs should be assessed to determine if the event is causally related to Ixekizumab and expectedness of related events will be assessed against the SmPC Taltz 80 mg solution for injection in pre-filled syringe - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)

MRI scans
MRI/MRs scanning is a safe scanning procedure with no exposure to ionising radiation. MRI imaging is contraindicated in individuals with certain metallic implants such as pacemakers, certain artificial heart valves and cochlear implants or a history of eye injury resulting from metallic shards.

All participants will be screened for contraindications both before study enrolment and immediately before MRI scanning. No subject will be enrolled for the MRI component of the study if a

contraindication is found. The possible distress involved in MR scanning. Some people find MR scanning claustrophobic, however we will exclude people who suffer from claustrophobia and/or panic disorders.

EEG
Electroencephalogram is considered a safe procedure. All participants will be screened for contraindications both before study enrolment and immediately before the EEG procedure.

Where an event meets the criteria of an SAE and is both:

Related: that is, it resulted from administration of study medicines or any of the research procedures,

And

Unexpected: that is against the procedure events listed above as an expected occurrence.

The SAE is considered a Related and Unexpected Serious Adverse Event (RUSAE) and must be reported to the Sponsor.

The assessment of causality and expectedness must be carried out by an authorised clinician.

It is the responsibility of the local investigators to report all suspected serious adverse reaction to secukinumab/ bimekizumab via the MHRA Yellow Card reporting system. This should be carried out according to local policies and in accordance with the guidance provided on the Yellow Card website https://yellowcard.mhra.gov.uk/

13.0 REPORTING TO THE SPONSOR

All RUSAEs must be reported to the Pharmacovigilance Office immediately (within 24 hours) using the generic non-CTIMP SAE form which is available from http://www.glasgowctu.org/data/SAE_non-CTIMP.pdf. The SAE form should be completed and signed by appropriately delegated staff. The form should be faxed or e-mailed to the PV Office (pharmacovig@glasgowctu.org) and a copy placed in the Study Site File. If necessary a verbal report can be given by contacting the PV Office on 0141 330 4744. This must be followed up as soon as possible with a signed written (or electronic) report.

If all of the required information is not available at the time of initial reporting, the investigator must ensure that any missing information is forwarded to the PV Office as soon as this becomes available. The report should indicate that this information is follow-up information for a previously reported event.

The Sponsor in liaison with the CI will carry out an assessment of expectedness prior to submission of the event to the REC.

13.1. REPORTING OF RUSAES TO THE ETHICS COMMITTEE

The PV office will report all RUSAEs to the ethics committee within 15 days of the PV office becoming aware of the event, via the 'report of serious adverse event form' for non-CTIMPs published on the Health Research Authority web site. http://www.hra.nhs.uk/documents/2015/02/safety-report-form-non-ctimp.docx. The form will be completed by the Sponsor and will be signed by the Chief Investigator prior to submission.

13.2. RECORDING AND REPORTING OF SCAN IMAGES

All scans will be reviewed and reported by a qualified neuroradiologist. Should brain imaging reveal any unexpected abnormalities the Principal Investigator (PI) will then be informed and will discuss the finding with the neuroradiologist. The PI, or a clinician associated with the study, will agree onward referral following local policies, in conjunction with the study neuroradiologist.

13.3. PREGNANCY

Pregnancy is not considered an AE unless a negative or consequential outcome is recorded for the mother or child/foetus. If the outcome meets the serious criteria, this would be considered an SAE and must be reported as per SAE reporting procedure above.

Any pregnancy occurring in a female study participant or female partner of a male study participant who becomes pregnant while participating in the study will be reported by the PI (or designee) to the Chief Investigator and the sponsor using the sponsor Pregnancy Reporting Form (available at http://www.glasgowctu.org/complete-paper-sae.aspx) within two weeks of the PI first becoming aware of the pregnancy.

14.0 ASSESSMENT OF SAFETY

Biologic screening will be performed as part of the assessment of safety to proceed from the screening/ consent visit to the baseline/ 1st administration visit. This will be completed along side the inclusion/ exclusion criteria.

Those who fail the screening safety requirements after the informed consent process will be recorded as a screen failure. An example of this would be clinically significant blood sampling results, active TB, positive pregnancy test or incidental findings that require a referral as a result of the tests performed as part of the screening visit.

At each study visit AE's & SAE's will be recorded. If at any time during the infusion a reaction is noted and the study medic informed.

All questionnaires completed at the study visits will be reviewed by study staff and answers will be monitored for results that may require review by the study medic and a further referral deemed appropriate by the CI after discussion with the participant. Questionnaires can be issued in paper or electronic form. If issued in paper the results will be transcribed into the Castor to facilitate statistical analysis. Completed paper forms will be filed in the site file for source data verification.

All MRI's will be reviewed by a qualified radiologist. If there are any incidental findings found at the time of the MRI scan and deemed clinically significant the CI, participant and standard care team will be notified. A diagnosis may not be possible and a further referral for investigation will be actioned by the research study medic.

All MRI images will have patient identifiable information removed and study code added before being upload to XNAT data storage system for analysis purposes. Radiology reports will be available in the participant electronic record.

15. STATISTICS AND DATA ANALYSIS

15.1. STATISTICAL ANALYSIS PLAN

A detailed statistical analysis plan will be agreed prior to database lock and unblinding of the study statistician.
Clinical and immunological data will be descriptively summarised for each randomised treatment group using means, standard deviations, medians, upper and lower quartiles for continuous data and counts and percentages for categorical data. Transformations of continuous data may be considered as required, depending on the distribution of the data. Outcomes will be analysed using appropriate generalised linear regression models for the distribution of the data and the difference between the randomised treatment groups for each outcome will be estimated with corresponding 95% confidence intervals. For each randomised group, correlations between continuous outcome measures of interest (e.g., glutamate and depressive symptoms) will be explored. Models may be extended to include other variables of interest.

The Robertson Centre of Biostatistics will lead analyse for all data generated and collected in the data capture form in relation to Indices of disease and questionnaires. Data capture forms can be completed in paper or electronic form, transcribed into Castor and filed in the site file for source data verification.

The analysis if MRI data collected as part of the study will be led by Professor Neil Basu. The analysis if the EEG and fMRI data will be led by Dr Marios Philiastides.

Resting-state MRI: Functional Connectivity will be performed by CONN (http://www.nitrc.org/projects/conn), a Matlab-based cross-platform software for the computation, display, and analysis of functional connectivity in fMRI. Connectivity indices will be generated for our specified regions of interest. We will also include data-driven seed-to-voxel and miltivariate approaches to investigate whole brain connections. These analyses will be adjusted for multiple testing.

Glutamate MRI spectroscopy: Recent work has shown that 1H magnetic resonance spectroscopy (MRS) measurements at 7 Tesla have an increased ability to quantify and distinguish glutamine and glutamate in vivo compared to studies at 3 Tesla.

To assess whether treatment with IL17 antagonism results in a reduction in functional connectivity (Thalamus - Nucleus Accumbens) and glutamate quantification, changes in our neuroimaging metrics of interest between time points will be evaluated using paired t-tests and then contrasted. Putative confounders will be explored using general linear models. Changes in behavioural assessments, clinical phenotyping (including synovitis score) and peripheral blood phenotyping measures will be similarly analysed and descriptively compared with the MRI metrics.

15.2. POWER CALCULATION

Assuming glutamate is a continuous normally distributed outcome, we will have 80% power to detect a difference between the randomised groups of 0.8 standard deviations on a two-sided t-test with a 5% significance level and recruiting 25 patients per group. Glutamate will be captured pre-randomisation and post-treatment, so the planned analysis will include a linear regression adjusting for the baseline glutamate value. Assuming a correlation of at least 0.4 units between baseline and follow-up with regards this outcome and allowing for up to 10% loss to follow-up, we plan to recruit a total of 50 patients to ensure 80% power. Sample size calculation provided using NQuery v9.2.1.0 This sample size is also consistent with what we have previously used for task-based simultaneous EEG-fMRI studies (23, 27).

15.3. SAFETY ANALYSIS

The safety data (serious adverse events) – both numbers of subjects and events – will be summarised by randomised group and overall using descriptive statistics. No formal statistical tests comparing the groups will be pre-specified.

15.4. SOFTWARE FOR STATISTICAL ANALYSIS

The statistical software to be used will be specified in the Statistical Analysis Plan. It is likely to be either SAS 9.4 for Windows, Cary, NC, USA or R version 3.2.4 (R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.), or higher versions of those programs.

15.5. SAMPLE SIZE

We will recruit 50 PsD patients with active disease for whom anti-IL-17 treatment is indicated as part of standard clinical care, in line with NICE/ SMC treatment guidance. The decision to prescribe anti-IL-17 treatment for active PsD will be made by the patients' usual clinical team in advance, and independently, of the study.

Consenting eligible participants will be randomised 1:1 to either immediately receive (fast-tracked) secukinumab 150mg or 300mg sc per normal dose loading regime for five weeks/ bimekizumab 160mg/ 320mg per normal dose loading regime for 4 weeks/ Ixekizumab 160mg once then 80mg every 2 or 4 weeks or a placebo.

After the treatment period, placebo recipients will receive IL17 as per standard care if not already delivered.

15.6. MANAGEMENT AND DELIVERY

Data from electronic case report forms will be captured on CASTOR EDC (eCRF) platform and held on the University of Glasgow server. In the event the eCRF is not available, study staff will use the paper CRF's and transcribe to the eCRF when available. All paper CRFs will be stored securely as part of the site file for source data verification. The data will not hold any identifiable information and only study subject number will used in place of name, DOB or NHS number. Access will be limited to those who require to input data captured at study visits. Once all data entered has been verified it will be exported in a format that is acceptable to Robertson Centre for Biostatistics. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan.

The Sponsor of this study, NHS Greater Glasgow and Clyde, will act as the data controller.

16. STUDY CLOSURE / DEFINITION OF END OF STUDY

The end of the study should be outlined clearly.

Please see example text below.

The study will end when one or more of the following situations applies:

i. The planned sample size has been achieved;
ii. Last participant, last study visit;
iii. The Independent Data Monitoring Committee (IDMC) has advised discontinuation, e.g. because of safety concerns about the study, or a statistically significant difference in clinical outcomes is evident between the two treatments;
iv. There is insufficient funding to support further recruitment, and no reasonable prospect of additional support being obtained;
v. New information makes it inappropriate to continue to randomise participants to one or other arm of the study;
vi. Recruitment is so poor that completion of the study cannot reasonably be anticipated.

17. DATA HANDLING

17.1. RANDOMISATION

A central randomisation facility (interactive voice response system, IVRS) will allocate the randomised therapy per participant. The IVRS, based at the Data Centre, will be available by telephone. A central unblinding facility based at the Data Centre will also be available by telephone. Notification of any unblinding will be sent to the CI.

17.2. CASE REPORT FORMS / ELECTRONIC DATA RECORD

An electronic case report form (eCRF) will be used to collect study data. In the event the eCRF is not available, study staff will use the paper CRF's and transcribe to the eCRF when available. The CASTOR EDC eCRF will be developed by the study co-ordinator and Co grant holders at the study University of Glasgow and access to the eCRF will be restricted, with only authorised, site-specific personnel able to make entries or amendments to their participants' data. All paper CRFs will be stored securely as part of the site file for source data verification. It is the investigator's responsibility to ensure completion and to review and approve data captured in the eCRF.

All data handling procedures will be detailed in a Study Specific Data Management Plan. Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

17.3. RECORD RETENTION

To enable evaluations and/or audit from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link record), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with ICH GCP, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. Data will be retained at the Data Centre for a minimum of 5 years.

18. STUDY MANAGEMENT

18.1. ROUTINE MANAGEMENT OF STUDY: STUDY MANAGEMENT GROUP

The study will be co-ordinated by the Trial Management Group. The Trial Management Group normally includes those individuals responsible for the day-to-day management of the study, such as the CI, statistician, study manager, research nurse, and data manager. The role of the group is to monitor all aspects of the conduct and progress of the study, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the study itself.

Trial

19. STUDY AUDIT

This study may be selected randomly for audit by NHS Greater Glasgow and Clyde governance team following the annual audit plan.

20. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the Trial coordinator and any required amendment forms will be submitted to the regulatory authority, REC and sponsor.

The CI and TSC will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.

Before the amended protocol can be implemented, favourable opinion/approval must be sought from the original reviewing REC, MHRA and Research and Development (R&D) office(s).

21. ETHICAL CONSIDERATIONS

21.1. ETHICAL CONDUCT OF THE STUDY

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008] and Fortaleza [2013]).

Favourable ethical opinion will be sought from an NHS research ethics committee before participants are entered into this study. Participants will only be allowed to enter the study once they have provided written informed consent.

The CI will be responsible for updating the REC of any new information related to the study.

21.2. INFORMED CONSENT

Written informed consent will be obtained from each study participant.

The research nurse or investigator will explain the exact nature of the study in writing, provision of participant information sheet, and verbally. This will include the known side-effects that may be experienced, and the risks of participating in this study. Participants will be informed that they are free to withdraw their consent from the study or study treatment at any time.

22. INSURANCE AND INDEMNITY

The ELATE study is sponsored by NHS Greater Glasgow and Clyde. The University of Glasgow will be liable for negligent harm caused by the design of the study. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).
It will be confirmed prior to the study starting that insurance cover will be provided automatically under the current policy. The insurance cover will be subject to NHS indemnity being in place and REC approval being obtained.

The NHS has a duty of care to patients treated, whether or not the patient is taking part in a study, and the NHS remains liable for clinical negligence and other negligent harm to patients under its duty of care.

As this is a clinical-led study, there are no arrangements for no-fault compensation.

23. FUNDING

The study is supported by a grant from the Medical Research Council

319603 Evaluating the role of IL-17as an orchestrator of peripheral central cross talk in depressive symptoms (ELATE Study).

24. DISSEMINATION OF FINDINGS

Our publications evidence a strong and consistent track record in open access research outputs from our previous grant awards. We will target the highest impact general biomedical and speciality (e.g., Annals of Rheumatic Disease and Lancet Psychiatry) journals. We will remain consistent with DORA recommendations. This coverage will be supplemented by presentations at conferences and will be summarised on our institution's website and social media platforms. Together, our team bring thought leadership in numerous disciplines and are regular organisers and plenary speakers of international conferences and workshops.

PPI:

We have consulted with our established Glasgow Arthritis Involvement Network (GAIN) PPI group linked to our Versus Arthritis centre of excellence (http://www.race-gbn.org/patientinvolvementinresearch/), via remotely held forums. These people with a mixture of IMIDs, including PsD, consistently report great frustration about how their underlying long-term condition affects their mental health and how health care providers commonly overlook such 'invisible' co-morbidities. There was unanimous support for our innovative focus on the brain and direct advice to mitigate issues such as procedural tolerability, placebo exposure and the magnitude of burden on the patient per the study protocol.

Although this is a highly technical project, PPI has a crucial role, and we have budgeted time for a patient partner with lived experience of PsD (TM, Lanarkshire) as part of the study team. He has already reviewed the proposal and provided feedback and will co-design public engagement and dissemination activities with us.

Public communication:

Nationally, we work closely with patient organizations, such as Versus Arthritis (IMcI is a trustee), to promote awareness of our research through virtual and face to face meetings. Locally, the University of Glasgow is a signatory of the UKRI Concordat for Engaging the Public with Research. For example, we have an established, and European award winning, musculoskeletal health engagement team - Rheumatosphere - which delivers regular activities at public events, such as the Europe-wide scientific engagement events with Explorathon and the Glasgow Science Centre (GSC). Most recently, we have focused our efforts on serving under-represented communities by engaging with rural Scottish communities to raise awareness of a wide range of musculoskeletal problems.

We will continue these activities, but also build on this previous experience to deliver depression specific annual public engagement events of the course of the grant. In year 2 we will address Goal 4 of UKRI's Public Engagement (PE) vision (listen to public concerns and aspirations). It is clear from our previous engagement that PsD patients are frustrated and often feel hopeless about the future given the limited availability of treatments. It is vital to listen to these concerns in a wider forum, convey the importance of basic research in providing future solutions and offer assurance that the scientific community is rapidly mobilising to address their concerns. To realise these objectives, we will seek to participate and utilise the Glasgow Science Centre's Curious About: Our Body Festival as a forum to listen and provide an overview of current depression research. This festival brings a broad audience of schools and families. Crucially, we will invite feedback which will enable us to develop a lay video summary of our findings in Year 3 (co-designed with our patient partner), which will be distributed across patient organisations.

Industry:

We have established and active links with biotech and pharmaceutical industrial partners, whether through existing translational inflammation research projects (e.g., Glasgow-Lilly Discovery Centre), leadership of, and participation in, national/international consortia (E.g., IMID-Bio), or participation in early phase clinical trials (e.g., NESOS, neural modulation device manufacturers). Such relationships will continue to be fostered where they catalyse translation of our research findings.

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Appendix 1: Women of child-bearing potential and contraception requirements

Women of Child-Bearing Potential (WoCBP) must be willing to use effective contraception for study duration. Contraception must be established prior to the commencement of study procedures.

Note: WOCBP are advised to use adequate contraception during treatment and to continue it's use (post-treatment) for

- Secukinumab – 20 weeks
- Bimekizumab – 17 weeks
- Ixekizumab – 10 weeks

For the purpose of this study, a woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Effective contraception: It is anticipated that for many participants, usual contraception requirements for WoCBP commencing secukinumab, ixekizumab or bimekizumab as part of standard care may be sufficient for study entry but for the avoidance of doubt, contraception will be reviewed prior to entry with effective contraception defined as

- combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- use of a barrier method e.g., condoms
- true sexual abstinence[4]

Footnotes

1. An interaction between secukinumab, bimekizumab, ixekizumab with contraception is not anticipated.
2. Contraception methods that in the context of this guidance are considered to have low user dependency.
3. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.
4. In the context of this guidance true sexual abstinence refers to: When this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not

acceptable methods of contraception. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.