Exploiting Leading Edge 7T MRI Brain Imaging to Decipher Olumiant's Mode of Analgesic Action in Rheumatoid Arthritis

SOAR

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1	**28.10.2022**	**1.1 Change of Trial Manager**

This study will be performed according to the UK policy framework for health and social care research (version 3.3, 07 November 2017) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

CONFIDENTIAL

CHIEF INVESTIGATOR

Dr Neil Basu

Clinical Senior Lecturer Rheumatology / Honorary Consultant

Institute of Infection, Immunity & Inflammation

Sir Graeme Davies Building

120 University Place

Glasgow

G12 8TA

T: 0141 330 1718

E: neil.basu@glasgow.ac.uk

CO-INVESTIGATORS

Professor Jonathan Cavanagh

Professor of Psychiatry

Institute of Infection, Immunity & Inflammation

Sir Graeme Davies Building

120 University Place

Glasgow

G12 8TA

T: 0141 330 7769

E: Jonathan.Cavanagh@glasgow.ac.uk

Professor Duncan Porter

Honorary Professor of Rheumatology

Gartnavel General Hospital

Dept of Rheumatology

1053 Great Western Road

Glasgow

G12 0YN

T: 0141 211 3492

E: duncan.porter@glasgow.ac.uk

Professor Richard Harris

Director of Pain and Fatigue Neuroimaging

Chronic Pain and Fatigue Research Centre

24 Frank Lloyd Wright Drive

Lobby M, Suite 3100

University of Michigan

48106-5737

T:

E: reharris@med.umich.edu

Professor Daniel Clauw

Professor of Anaesthesiology, Rheumatology and Psychiatry

Chronic Pain and Fatigue Research Centre

24 Frank Lloyd Wright Drive

Lobby M, Suite 3100

University of Michigan

48106-5737

T:

E: dclauw@med.umich.edu

Professor David Porter

Professor in Magnetic Resonance Imaging Physics

University of Glasgow

CCNi

58 Hillhead Street

Glasgow

G12 8QB

T:

E: David.Porter@glasgow.ac.uk

Professor Iain McInnes

Professor of Experimental Medicine

Institute of Infection, Immunity & Inflammation

Sir Graeme Davies Building

120 University Place

Glasgow

G12 8TA

T: 0141 330 8657

E: Iain.McInnes@glasgow.ac.uk

PROJECT MANAGER / STUDY CO-ORDINATOR

Miss Maxine Arnott

Institute of Infection, Immunity & Inflammation

Sir Graeme Davies Building

120 University Place

Glasgow

G12 8TA

T: 07890059695

F: FAX NUMBER

E: Maxine.arnott@glasgow.ac.uk

DATA MANAGEMENT

Institute of Infection, Immunity & Inflammation

Sir Graeme Davies Building

120 University Place

Glasgow

G12 8TA

T:

F: FAX NUMBER

E: EMAIL ADDRESS

SPONSOR

This clinical trial is sponsored by NHS Greater Glasgow and Clyde

Sponsor's representative:

Emma-Jane Gault

Research Governance Officer

Room 327, Wolfson Medical School Building

University of Glasgow

Glasgow

G12 8QQ

T: 0141 330 5519

E: emmajane.gault@glasgow.ac.uk

FUNDING BODY

This clinical trial is funded by Lilly.

Administered by:

Eli Lilly and Company Limited

Lilly House
Priestley Road
Basingstoke
Hampshire
United Kingdom RG24 9NL

T: **+**44 (0) 1256 315000

Exploiting Leading Edge 7T MRI Brain Imaging to Decipher Olumiant's Mode of Analgesic Action in Rheumatoid Arthritis

Chief Investigator: **Dr Neil Basu**
Institute of Infection, Immunity & Inflammation
Sir Graeme Davies Building
120 University Place
Glasgow
G12 8TA

Signature:

Date: 28.10.2022

Sponsor Representative: **Emma-Jane Gault**
Research Governance Officer
Room 327, Wolfson Medical School Building
University of Glasgow
Glasgow
G12 8QQ

Signature:

Date: DATE

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Complete as required, all abbreviations used in the protocol should be defined upon first mention and added to this table

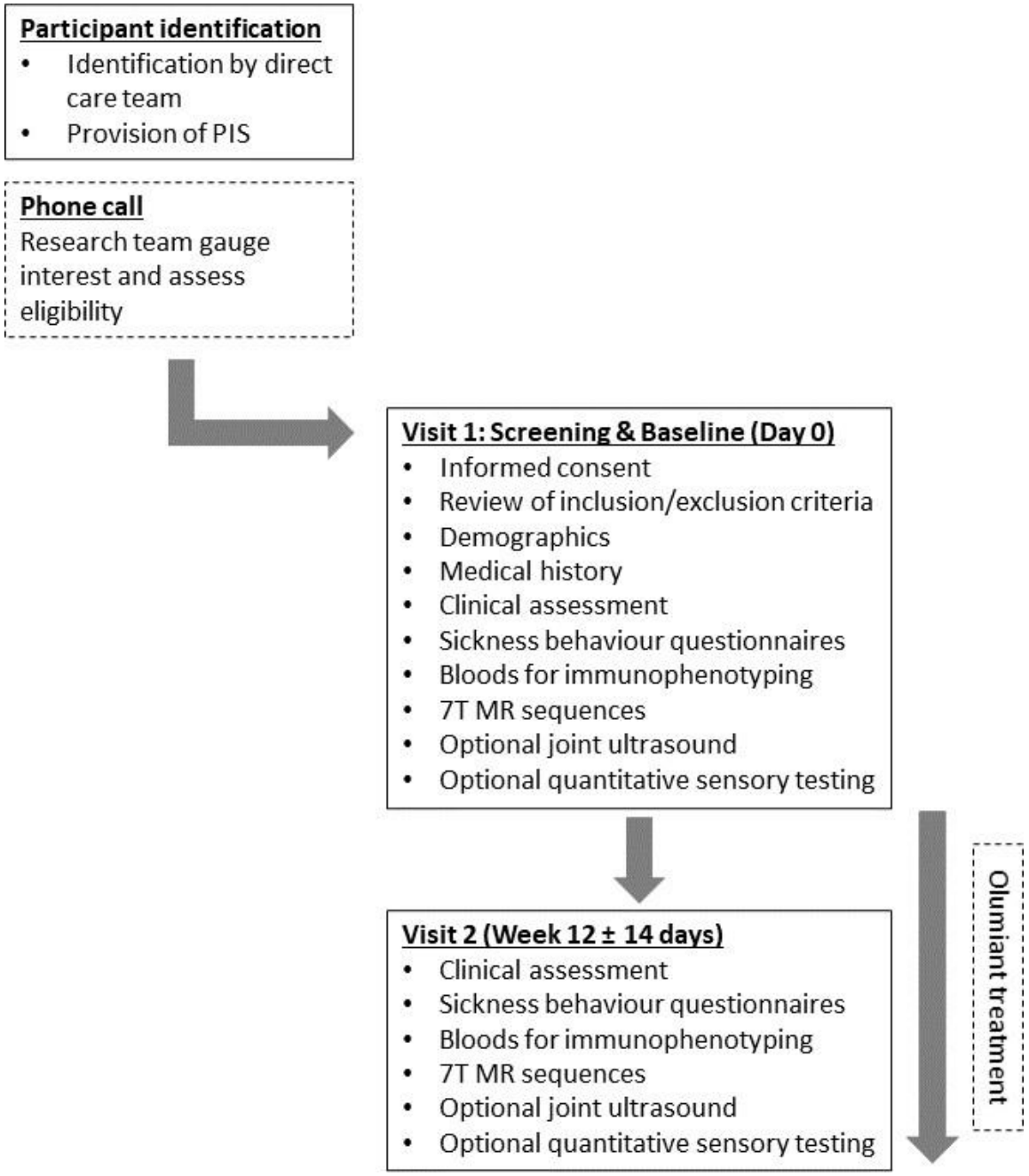
ACR	American College of Rheumatology
AE	Adverse Event
BOLD	Blood oxygenation level dependent
CDAI	Clinical Disease Activity Index
CI	Chief Investigator
CNORIS	Clinical Negligence and Other Risks Indemnity Scheme
CNS	Central Nervous System
DAN	Dorsal Attention Network
DAS	Disease Activity Score
DMARD	Disease-Modifying Anti-Rheumatic Drug
DMN	Default Mode Network
DOI	Digital Object Identifier
eCRF	Electronic case report form
EL	Engagement Leads
EPR	Electronic Patient Record
EPSI	Echo-planar Spectroscopic Imaging
EULAR	European League Against Rheumatism
fMRI	Functional Magnetic resonance imaging
GAIN	Glasgow Arthritis Involvement Network
GluCEST	Glutamate Chemical Exchange Saturation Transfer
ICA	Independent Component Analysis
IMID	Immune-mediated inflammatory diseases
JAK	Janus Kinase
JAKi	Janus Kinase Inhibitor
LIPL	Left Inferior Parietal Lobule
MRS	Magnetic Resonance Spectroscopy
NMDA	N-methyl-d-aspartate
PPI	Patient and Public Involvement
PPT	Pressure Pain Thresholds

PROMIS	Patient Reported Measurement Information Service
PRP	Patient Research Partner
QST	Quantitative Sensory Testing
RA	Rheumatoid Arthritis
RACE	Research into Inflammatory Arthritis Centre Versus Arthritis
REC	Research Ethics Committee
ROI	Region of Interest
SAE	Serious Adverse Event
SBA	Seed-Based Correlation Analysis
SDAI	Simple Disease Activity Index
STAT	Signal Transducer and Activator of Transcription
7T	7 Tesla
TMG	Trial Management Group
TNF	Tumour Necrosis Factor

STUDY SYNOPSIS

Title of Study	**Exploiting Leading Edge 7T MRI Brain Imaging to Decipher Olumiant's Mode of Analgesic Action in Rheumatoid Arthritis**
Lead Study Centre	University of Glasgow/NHS Greater Glasgow and Clyde
Duration of Study	24 months
Primary Objective	1) To evaluate the effects of Olumiant on Default Mode Network (DMN)-Insula connectivity and insular glutamate levels in rheumatoid arthritis (RA) (neurobiological markers of fibromyalgia). 2) To evaluate the effects of Olumiant on Dorsal Attention Network (DAN)-Left Inferior Parietal Lobule (LIPL) connectivity in RA (neurobiological marker of peripheral inflammation).
Secondary Objective	To explore the relationship between pain, clinical phenotype, peripheral immune markers and their change with MRI markers indicative of CNS pathway function.
Primary Endpoints	The primary neuroimaging metrics of interest are functional connectivity and glutamate concentration
Rationale	The revolution in rheumatoid arthritis therapeutics has been transformative for many patient outcomes. Yet most patients continue to experience life disabling pain. Strikingly, even those who achieve full disease remission with state-of-the-art anti-tumour necrosis factor (TNF) treatments report substantially higher levels of pain when compared to the general population. Such disconnect presents one of the greatest contemporary challenges to the care of patients with RA. Considering the ongoing excess burden of pain in this patient population, RA patients receiving Olumiant, a Janus Kinase (JAK) 1/2 inhibitor, report superior and more rapid pain improvements in comparison to those receiving anti-TNF therapy. However, the majority of this effect could not be explained by markers of peripheral inflammation and remains to be understood.
Methodology	This single-centre, single arm observational cohort study will allow us to investigate Olumiant's mechanism of analgesic action in RA patients.
Sample Size	20 participants
Screening	Patients with active RA attending clinics in NHS Greater Glasgow and Clyde who are scheduled to begin Olumiant as part of their standard NHS clinical care will be asked to contribute to this study by their point of care team.
Inclusion Criteria	• Adults ≥ 18 years < 75 years. • Clinical diagnosis of RA • Selected to start Olumiant by their usual rheumatology clinical team in line with local guidance (previous failure of at least 2 DMARDs and moderate to severe active disease). • Right-handed (to reduce neuroimaging heterogeneity).
Exclusion Criteria	• Inability to provide written informed consent.

	• Severe physical impairment (e.g. blindness, deafness, paraplegia). • Pregnant or breast feeding. • Contraindications to MRI (e.g. severe claustrophobia). • Major confounding neurological disease including Multiple Sclerosis, Stroke, Traumatic Brain Injury, Parkinson's Disease, Alzheimer's Disease • Previous targeted synthetic (e.g. Oluminant, tofacitinib) DMARD exposure. • Co-morbid medical conditions that may significantly impair physical functional status • Medical or psychiatric conditions that in the judgment of study personnel would preclude participation in this study (e.g., malignancy, psychosis, suicidal ideation) • BMI > 40 or unable to lie comfortably in MRI
Product, Dose, Modes of Administration	Olumiant will be administered following standard of care guidelines.
Duration of Study Participation	12 weeks
Statistical Analysis	To assess whether treatment with Olumiant results in a reduction in functional connectivity (DMN-Insula and DAN-IPL) and glutamate quantification, changes in our neuroimaging metrics of interest between time points will be evaluated using paired t-tests. Changes in pain, clinical phenotyping and immunophenotyping measures will be correlated with those significant regions identified from our primary objective. Putative confounders will be explored using general linear models.


Participant identification
• Identification by direct care team
• Provision of PIS
Phone call
Research team gauge interest and assess eligibility
Visit 1: Screening & Baseline (Day 0)
• Informed consent
• Review of inclusion/exclusion criteria
• Demographics
• Medical history
• Clinical assessment
• Sickness behaviour questionnaires
• Bloods for immunophenotyping
• 7T MR sequences
• Optional joint ultrasound
• Optional quantitative sensory testing
Visit 2 (Week 12 ± 14 days)
• Clinical assessment
• Sickness behaviour questionnaires
• Bloods for immunophenotyping
• 7T MR sequences
• Optional joint ultrasound
• Optional quantitative sensory testing
Olumiant treatment

Study Procedure	**Visit 1 - Screening & Baseline**	**Visit 2 - 12 week**
Inclusion/exclusion criteria	✓	
Informed consent	✓	
EULAR Disease Activity Score (DAS28)	✓	✓
ACR/EULAR Classification Criteria for RA	✓	
CDAI	✓	✓
SDAI	✓	✓
7-Day Symptom Diary (Numeric Rating Scale)	✓	✓
American College of Rheumatology Fibromyalgia Scale	✓	✓
McGill Pain Questionnaire	✓	✓
Michigan Body Map Regional Pain	✓	✓
PROMIS-Depression	✓	✓
PROMIS-Anxiety	✓	✓
PROMIS-Fatigue	✓	✓
PROMIS-Sleep related impairment	✓	✓
PROMIS-Physical functioning short form	✓	✓
PROMIS-Pain inference	✓	✓
Pain NRS Pain Number Rating Scale	✓	✓
FACIT-Fatigue Scale	✓	✓
Global Impression Of Change (participant)		✓
Cognitive Failures Questionnaire	✓	✓
Sickness Questionnaire	✓	✓

Demographics	✓	
BMI	✓	
Drug Assessment	✓	✓
Past Medical History	✓	
Blood sample for immunophenotyping*	✓	✓
7T magnetic resonance protocol	✓	✓
Ultrasound of joints**	✓	✓
Quantitative sensory testing (QST)**	✓	✓
Recording of Adverse Events		✓

* Blood sample schedule outlined in 4.4 LABORATORY TESTS
** Consent to these procedures is optional

1 INTRODUCTION

1.1 RATIONALE

The revolution in rheumatoid arthritis (RA) therapeutics has been transformative for many patient outcomes. Yet most patients continue to experience life disabling pain[1]. Strikingly, even those who achieve full disease remission with state-of-the-art anti-TNF treatments report substantially higher levels of pain when compared to the general population[2]. Such disconnect presents one of the greatest contemporary challenges to the care of patients with RA.

Considering the ongoing excess burden of pain in this patient population, the RA-BEAM trial presented welcome data. RA patients randomised to Olumiant, a JAK1/2 inhibitor, reported superior and more rapid pain improvements in comparison to those receiving anti-TNF therapy[3]. However, the majority of this effect could not be explained by markers of peripheral inflammation and remains to be understood[4].

1.2 BACKGROUND

We believe that RA is a mixed pain state i.e. pain pathways exist in addition to established peripheral inflammatory nociceptive mechanisms. In particular, the central nervous system (CNS) may have an important role in determining RA pain. Recently our group were the first to delineate distinct neurobiological pain signatures in the brains of RA patients by employing 3T functional connectivity magnetic resonance imaging (fcMRI) – a recent adaptation of functional MRI data that examines the synchrony of neural activity which modulates the efficiency and extent of neuronal transmission between brain regions. Specifically, we identified and replicated two distinct pain signatures: a) enhanced functional connectivity between the Default Mode Network (DMN) and insula which was unrelated to levels of peripheral inflammation but, intriguingly, is an established neurobiological marker of fibromyalgia (an archetypal CNS determined chronic pain disorder)[5] and b) enhanced functional connectivity between the Dorsal Attention Network (DAN) and the left inferior parietal lobule (LIPL)[6] which was related to levels of peripheral inflammation.

Pre-clinical experiments have not only implicated the JAK- signal transducer and activator of transcription (STAT) pathway with peripheral immune system functioning but also the brain[7, 8]. In the CNS, this pathway promotes gene expression associated with inflammation which in turn generates pro-nociceptive cytokines such as TNFα[8]. However, there is now also emerging evidence to support the pathway's direct role in synaptic transmission and neurotransmitter receptor modulation. Specifically, the JAK-STAT pathway appears important in N-methyl-d-aspartate (NMDA) related synaptic plasticity – a ubiquitous glutamate receptor of the human brain. Their induction is selectively blocked by JAK inhibitors and JAK2 knockdown abolishes NMDA functioning[7]. Increases in glutamate and subsequent binding to NMDA receptors cause chaotic and incoherent neuronal functional activity[9]. In human studies of fibromyalgia, we have consistently evidenced both elevated glutamate levels within the insula and dysfunctional neural connectivity[10, 11]. Moreover, we have shown that fibromyalgia pharmacotherapy (pregablin), considered to reduce neural glutamate, rectifies both insular glutamate and pro-nociceptive brain functional connectivity (DMN-insula)[12]. JAK inhibition (JAKi) may facilitate the reduction of glutamate-NMDA binding and ultimately pain alleviation by normalising the functional activity of these same neural connections.

There are clear practical constraints of sampling fresh human brain tissue in order to interrogate these possible mechanisms. Instead, neurobiological surrogate imaging measures may be employed. In Glasgow we benefit from the only clinical based ultra-high resolution 7T MRI scanner in the UK. Unlike lesser resolutions, 7T can distinguish the resonance of glutamate from other metabolites and so more precisely quantify our chemical of interest. Further, the superior spatial resolution of 7T enhances capacity to indirectly measure neuronal functional connectivity.

1.3 STUDY HYPOTHESIS

We hypothesise that Olumiant's mechanism of analgesic action is determined by at least two factors. The first is related to those pathways seen in fibromyalgia, mediated via DMN-insula connectivity and insular glutamate. The second is related to peripheral inflammation, mediated via DAN-LIPL.

2 STUDY OBJECTIVES

1) To evaluate the effects of Olumiant on DMN-Insula connectivity and insular glutamate levels in RA (neurobiological markers of fibromyalgia).

2) To evaluate the effects of Olumiant on DAN-LIPL connectivity in RA (neurobiological marker of peripheral inflammation).

3) To explore the relationship between pain, clinical phenotype, peripheral immune markers and their change with MRI markers indicative of CNS pathway function.

2.1 PRIMARY ENDPOINT

The primary endpoints are changes in:

- brain functional connectivity (DMN-Insula and DAN-LIPL) as measured by 7T MRI
- insular glutamate signal as measured by 7T MRS

Between baseline and visit 2 (week 12)

2.2 SECONDARY ENDPOINT(S)

- Changes in clinical phenotype, pain, depression and anxiety as measured by:
    - EULAR Disease Activity Score (DAS28)
    - CDAI
    - SDAI
    - 7-Day Symptom Diary (Numeric Rating Scale)
    - American College of Rheumatology Fibromyalgia Scale
    - McGill Pain Questionnaire
    - PROMIS-Depression
    - PROMIS-Anxiety
    - PROMIS-Fatigue
    - PROMIS-Sleep related impairment
    - PROMIS-Physical functioning short form
    - PROMIS-Pain inference
    - Pain Number Rating Scale
    - FACIT-Fatigue Scale
    - Global Impression of Change (participant)
    - Cognitive Failures Questionnaire
    - Sickness Questionnaire
    - Synovitis score (from joint ultrasound)
    - Pain sensitivity variables (from QST measures)

- Changes in inflammatory cytokines/chemokines Between baseline and visit 2 (week 12)

3 STUDY DESIGN

This study will be performed according to the UK policy framework for health and social care research (version 3.3, 07 November 2017).

The trial design is detailed below and is summarised in STUDY FLOW CHART and SCHEDULE OF ASSESSMENTS. The trial is a single-centre observational cohort study to test the hypothesis that Olumiant's mechanism of analgesic action is determined by at least two factors, the first relating to pathways seen in fibromyalgia, and the second relating to peripheral inflammation.

3.1 STUDY POPULATION

The study will involve participants aged over 18 years with RA who are scheduled to start outpatient Olumiant as part of standard clinical practice, who meet the inclusion criteria below and who have none of the specified exclusion criteria. All will give full informed consent.

3.2 INCLUSION CRITERIA

- Adults ≥ 18 years < 75 years.
- Clinical diagnosis of RA
- Selected to start Olumiant by their usual rheumatology clinical team in line with local guidance (previous failure of at least 2 DMARDs and moderate to severe disease active disease)
- Right-handed (to reduce neuroimaging heterogeneity)

3.3 EXCLUSION CRITERIA

- Inability to provide written informed consent.
- Severe physical impairment (e.g. blindness, deafness, paraplegia).
- Pregnant or breast feeding.
- Contraindications to MRI (e.g. severe claustrophobia).
- Major confounding neurological disease including Multiple Sclerosis, Stroke, Traumatic Brain Injury, Parkinson's Disease, Alzheimer's Disease
- Previous targeted synthetic (e.g. Oluminant, tofacitinib) DMARD exposure.
- Co-morbid medical conditions that may significantly impair physical functional status
- Medical or psychiatric conditions that in the judgment of study personnel would preclude participation in this study (e.g., malignancy, psychosis, suicidal ideation)
- BMI > 40 or unable to lie comfortably in MRI

3.4 IDENTIFICATION OF PARTICIPANTS AND CONSENT

Patients with active RA attending clinics in NHS Greater Glasgow and Clyde who are scheduled to begin Olumiant as part of their standard NHS clinical care will be asked to contribute to this study by their point of care team. The direct care team will notify patients of the study, provide a participant information sheet and seek their consent for the research team to contact them by telephone. at least 24 hours later to gauge their interest in the study and allow them to ask any questions. Eligibility will be confirmed by a medically qualified investigator. A record will be kept on the CRF detailing if the telephone call was made, if contact was indeed established and the outcome of the telephone call.

If the patient is interested and eligible, they will be invited to attend Visit 1 where they will first undertake informed consent. At this meeting, subjects will be asked again if they have any questions and those who wish to participate will be asked to sign the consent form. Two copies will be signed (one each for the participant and the site file) and 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 to inform them of their participation in the study.

Consent will be taken by a member of the research team.

Reasonable travel expenses will be reimbursed.

3.5 WITHDRAWAL OF SUBJECTS

Participants can decide to withdraw from the study at any time without providing a reason. The participant needs to request this formally and a withdrawal document will be completed and signed by the research staff. They have the option to either withdraw from the study completely or from parts of it.

Participants will have the option to remain in the study irrespective of stopping treatment. 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, loss of capacity for continuous consent, administrative or other reasons. Full details of withdrawal will be recorded on the 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 unless the participant specifies they do not wish this to happen. Any stored blood samples that can still be identified as the participants will be destroyed if the participants wish this.

4 TRIAL PROCEDURES

4.1 STUDY SCHEDULE

The study will comprise of a total of 2 research visits.

4.1.1 Screening & Baseline (Day 0)

- Informed consent
- Review of inclusion / exclusion criteria
- ACR/EULAR Classification Criteria for RA
- EULAR Disease Activity Score (DAS28)
- CDAI
- SDAI
- 7-Day Symptom Diary (Number Rating Scale)
- American College of Rheumatology Fibromyalgia Scale[13]
- McGill Pain Questionnaire[14]
- Michigan Body Map Regional Pain
- PROMIS-Depression
- PROMIS-Anxiety
- PROMIS-Fatigue
- PROMIS-Sleep related impairment
- PROMIS-Physical functioning short form
- PROMIS-Pain inference
- Pain Number Rating Scale
- FACIT Fatigue Scale
- Cognitive Failures Questionnaire[15]
- Sickness Questionnaire[16]
- 7T MRI protocol
- Ultrasound of joints of interest
- Quantitative sensory testing (QST)
- Blood draw for immunophenotyping
- Demographics
- BMI
- Drug Assessment
- Past Medical History

Estimated visit time 4 hours

4.1.2 VISIT 2 : Week 12 ± 14 days

- ACR/EULAR Classification Criteria for RA
- EULAR Disease Activity Score (DAS28)
- CDAI
- SDAI
- 7-Day Symptom Diary (Number Rating Scale)
- American College of Rheumatology Fibromyalgia scale

- McGill Pain Questionnaire
- Michigan Body Map Regional Pain
- PROMIS-Depression
- PROMIS-Anxiety
- PROMIS-Fatigue
- PROMIS-Sleep related impairment
- PROMIS-Physical functioning short form
- PROMIS-Pain inference
- Pain Number Rating Scale
- FACIT Fatigue Scale Global Impression of Change (participant)
- Cognitive failures questionnaire
- Sickness Questionnaire
- 7T MRI protocol
- Ultrasound of joints of interest
- Quantitative sensory testing (QST)
- Blood draw for immunophenotyping
- Drug assessment

Estimated visit time 3.5 hours

4.2 BRAIN IMAGING PROTOCOLS

4.2.1 MRI and MRS Protocols

Subjects 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 functional connectivity and glutamate:

1) 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 2017a.

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 (DMN-Insula and DAN-IPL).

2) 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 20x20 mm3 voxel will be placed in the R posterior insula 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.

In addition, multi-voxel techniques will be employed to provide quantitative maps of glutamate concentration across the brain. These will include chemical exchange saturation transfer (CEST) in the glutamate-weighted form, or GluCEST, which indirectly measures the glutamate present in tissue by measuring the chemical exchange between the glutamate amine spins and the protons present in the bulk water. GluCEST will be applied in one axial slice and one sagittal slice, chosen from the T1 acquisition. The sequence parameters will be slice thickness of 5 mm, field-of-view of 200 x 200 mm2, matrix size 192 x 192, TR = 16 s, a saturation pulse train of 10 x 100 ms pulses followed by a FLASH readout with flip angle = 10°, TR/TE = 5.5/2.6 ms.

Should any incidental clinically relevant abnormal MRI scan findings be observed that in the opinion of the Investigator may put the participant at risk, a referral will be made to the appropriate speciality**.** Any incidental finding review will be managed according to Glasgow Centre for Research Imaging (CRIF) processes and Glasgow Clinical Trials Unit (CTU) SOPs.

4.2.2 Ultrasound Protocol

Rheumatoid arthritis is characterised by synovitis with symmetrical involvement. An optional ultrasound scan of pre-determined joints and up to 2 symptomatic joints with active disease will be performed at baseline and at the 12-week visit. This will provide a robust surrogate measure of peripheral inflammation.

The wrists, MCPs, PIPs joints of hands, knees, MTPs of both feet, and the 2 most symptomatic joints (if applicable) will be scanned and graded using the EULAR-OMERACT combined score[17]. The ultrasonographic evaluation will further characterise the synovium involvement in the participants and will help to evaluate the response to treatment.

4.2.3 Quantitative Sensory Testing Protocol

Quantitative Sensory Testing (QST) is a standardised methodology to study pain sensitivity in humans. A QST protocol includes a series of noxious and non-noxious stimuli delivered to a patient, followed by a semi-objective method for the patient to rate their perception of each stimulus. In this study, participants will have the option to complete a fully validated QST battery to characterise pain sensitivity as a sickness behaviour variable. All participants who consent to this procedure will undergo familiarisation training prior to data collection to reduce QST-related anxiety.

Pressure pain sensitivity (15-20 minutes) will be assessed using a digital algometer with a 1 cm^2 rubber probe to quantify pressure pain thresholds (PPT) at multiple body sites. Pressure will be manually increased at a rate of 50 kPA/s (1000 kPa max). Participants will press a response button to indicate their first sensation of pain. Pressure intensity at the time of button press is recorded as the PPT. Measurements will be conducted 3 times per site (with 20s intervals) with means used for analysis.

The multimodal automated sensory testing (MAST) system[18] will be performed. The MAST testing will be not be performed in ineligible patients with recent or habitual use of artificial nails. The MAST system will apply pressure at the thumbnail in a controlled systematic manner to derive a measure of pressure intensity that evokes a moderate level of pain (i.e., Pain = 50/100), as well as PPT and tolerance metrics (note inflamed joints will be avoided). The system delivers an ascending series of discrete pressures (5s duration; 4 kg/cm^2/s ramp rate) at 20s intervals, beginning at 0.25 kg/cm^2 and increasing in 0.25-0.50 kg/cm_2 steps. Pain intensity will be rated verbally after each stimulus on a 0-100 numerical rating scale (NRS). The test will be terminated at a maximum pressure of 10 kg/cm^2 or when subjects reach their tolerance. This ascending test will be followed by a random staircase paradigm. MAST pain ratings will be used to interpolate *Thumb Pain = 50*, defined as the pressure intensity that evokes a moderate level of pain (i.e., 50/100). Other variables that will also be derived include: 1) thumb-PPT, defined as the first

thumb pressure in a series of at least two consecutive thumb pressures that elicited a pain rating > 0, and 2) *Pressure Pain Tolerance (thumb-TOL)*, defined as the highest pressure tolerated.

Cuff algometry (10 minutes) will be used to measure deep muscle tonic pain. This consists of a computer-controlled air compressor which delivers varying degrees of pressure to a Velcro-adjusted cuff applied to one gastrocnemius muscle. We will conduct a brief calibration procedure to a find a pressure intensity that evokes moderate pain and then apply that intensity for 6 minutes. Pain and sensory unpleasantness ratings will be obtained every 60s.

Temporal Summation (4 minutes) is an effect where there is an increase in the perceived intensity of pain in response to sequential stimuli of equal physical strength. A 256 or 512 mN pinprick stimulus will be applied once to the dominant forearm, followed by a train of 10 identical stimuli (1 Hz). Following the single stimulus and the train of 10 stimuli, patients will report the pain intensity of the pinprick sensation verbally using a 0-100 NRS. This procedure will be repeated thrice. The mean pain rating of the three stimulus trains will be divided by the mean pain rating of the single stimuli to calculate a wind-up ratio (WUR); a WUR >1 indicates temporal summation[19].

Aversion to visual stressors (10 minutes) will be used to probe mechanisms of Global Sensory Sensitivity that bypass somatic peripheral receptors and the spinal cord. Specifically, participants will be presented with a flashing blue/yellow checkerboard pattern (see APPENDIX). Participants will be acclimatised to a dark room with their eyes perpendicularly aligned 15-inch away from a 15-inch high-resolution, calibrated LED monitor displaying the visual stimulus. Illuminance will be verified using a calibrated light meter. Each visual stimulus intensity level and the entire task will be rated on both sensory intensity and unpleasantness scales with overall task ratings.

The MAST system is being used as a Research Tool and not for clinical purposes.

4.3 STUDY OUTCOME MEASURES

4.3.1 Primary Outcome Measure(s)

The primary outcome measures will be:

1. brain functional connectivity (DMN-Insula and DAN-LIPL) as measured by 7T MRI
2. insular glutamate signal as measured by 7T MRS

Between baseline and visit 2 (week 12) following Olumiant treatment in RA.

4.3.2 Secondary Outcome Measure(s)

The secondary outcome measures will be:

- Changes in clinical phenotype, pain, depression and anxiety as measured by
  - EULAR Disease Activity Score (DAS28)
  - CDAI
  - SDAI
  - 7-Day Symptom Diary (Number Rating Scale)
  - American College of Rheumatology Fibromyalgia Scale
  - McGill Pain Questionnaire
  - Michigan Body Map Regional Pain
  - PROMIS-Depression
  - PROMIS-Anxiety

- PROMIS-Fatigue
- PROMIS-Sleep related impairment
- PROMIS-Physical functioning short form
- PROMIS-Pain inference
- Pain Number Rating Scale
- FACIT Fatigue Scale
- Global Impression of Change (Participant)Cognitive Failures Questionnaire
- Sickness Questionnaire
- Synovitis score (from joint ultrasound)
- Pain sensitivity variables (from QST measures)

- Changes in inflammatory cytokines/chemokines

from baseline (day 0) to Visit 2 (week 12), following Olumiant treatment in RA.

4.4 LABORATORY TESTS

Sample Type	Visit 1: Baseline	Visit 2 (12 weeks)
SST tube (8.5ml)	✓	✓
PAXgene RNA tube (2.5ml)	✓	✓
EDTA tube (2 x 10ml)	✓	✓
EDTA tubes (4ml)	✓	✓

Blood samples will be processed and analysed as described in the SOAR Lab Protocol.

5 Study Medication

5.1 OLUMIANT TREATMENT SCHEDULE & ADMINISTRATION

Olumiant (4mg) will be administered in line with standard of care guidance. This is the standard dose in line with license for use in active moderate to severe RA. A dose adjustment from 4mg to 2mg is permitted during the study depending on side-effects.

5.1.1 Olumiant Treatment After the Study

At the end of their study involvement, all participants will be returned to NHS standard care. Arrangements will be made such that all participants continue NHS standard care with Olumiant without interruption.

5.2 ONCOMITANT MEDICINES

5.2.1 Permitted Concomitant Medicines

Concomitant medicines are permitted at the PIs discretion. Maintenance of stable doses of conventional synthetic DMARDs, nonsteroidal anti-inflammatory drugs, analgesics, or glucocorticoids (≤10 mg of prednisone or the equivalent per day) will be permitted. Intra-articular and intramuscular triamcinolone can be used, but not within 8 weeks of the baseline and 12-week assessments.

5.2.2 Prohibited Concomitant Medicines

Biologic disease modifying antirheumatic drug therapy with adalimumab, etanercept, golimumab, infliximab, certolizumab, abatacept, tocilizumab, sarilumab, rituximab, tofacitinib, apremilast or upadacitinib.

5.3 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 if determined so 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 Investigator believes it is in the best interest of the subject.
4. The participant requests withdrawal from the study.
5. Commencement of prohibited medicines.
6. 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 trial 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 continue with NHS standard care treatment with Olumiant without interruption.

5.3.1 Supply of Study Treatment

The study site will be responsible for procurement of all Olumiant via usual NHS supply mechanisms for medicines.

6 PHARMACOVIGILANCE

6.1 DEFINITIONS OF ADVERSE EVENTS (AEs)

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.

6.2 SERIOUS ADVERSE EVENT (SAE)

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

6.3 RECORDING AND REPORTING OF ADVERSE EVENTS

Reports of Serious Adverse Events (SAE), drug exposure during pregnancy, non-serious Adverse Events (AE) and misuse and abuse of the study drug, other medication errors and uses outside of what is foreseen in the protocol (irrespective if a clinical event has occurred) should be submitted to the Research Ethics Committee (REC) using the Non-CTIMP safety report to REC form.

Only reports of SAEs and non-serious AEs that are 1. related to the study (i.e. they resulted from administration of any of the research procedures) and 2. unexpected (i.e. not listed in the protocol as an expected occurrence) should be submitted.

These should be sent within 15 days of the CI becoming aware of the event. There is no requirement for annual safety reports in addition to the information provided through the annual progress report.

Related Unexpected Serious Adverse Event (RUSAE)
Any SAE thought to be related to a trial specific procedure performed on that subject that is thought to be unexpected; that is the event is not listed within the protocol or would not be expected to occur when carrying out the trial specific procedure in normal clinical practise.
Recording and reporting of adverse events

The study is considered to be of low risk and is primarily an observational study. The MRI scanning procedure is the principal trial specific procedure and safety reporting will be focussed around this procedure

Adverse events and serious adverse events will be collected only during the period of time the participant attends clinic for their MRI scan i.e. from the time the participant begins preparation for the scan until 24 hours post scan.

In addition to Sponsor requirements the investigators have a contractual agreement with the MAH to report any SARs suspected to be related to olumiant within 15 days of investigator awareness. These events should be recorded and reported in line with the manufacturers requirements.

Recording of adverse events

AEs occurring during this timeframe must be recorded, 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.

Recording and reporting of serious adverse events

Where an SAE requires recording; full details including the nature of the event, start and stop dates, severity, relationship to research product and/or trial procedures, and the outcome of the event will be recorded in the patient's medical notes and CRFs.). These events will be monitored and followed up until satisfactory resolution and stabilization.

SAEs should be assessed to determine if the event is related to the MRI scanning procedures and assessed for expectedness against the list of expected events detailed below.

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 below 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.

Expected events related to the MRI scanning procedure

The MRI procedure is painless and not uncomfortable. The primary risks known to occur from MRI are due to the magnet's ability to pull metal objects towards it. This pull can cause metal objects in the body (e.g. surgical clips or staples) to move and cause bleeding or disruption of surrounding tissue. Metal objects carried or worn by a person (e.g. jewellery, hair clips, tools) can be pulled towards the magnet and, if free to fly through the air, could strike an individual. The MRI can cause pacemakers or stimulators implanted in the body to malfunction. There may be some slight discomfort from noise produced by the MRI machine.
Prior to inclusion in the study, the presence of potential MR risks, such as pacemakers, surgical clips or metallic surgical devices will be excluded by medical and surgical history using a standard review form. Participants will be asked to complete and sign a safety screening form and will be instructed to bring or wear clothing without metal fasteners, and remove jewelry and any other metal objects from their body. Participants will wear foam earplugs or headphones to reduce the loud noises made by the scanner. During the performance of MRI, the volunteers will be monitored at all times by research personnel associated with the project. They will be able to communicate with the examiner and, if needed, can terminate or take a break from the procedure at any time

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.

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.

Reporting of SAEs related to olumiant to the MAH

The investigators must report all serious adverse events that are suspected to be related to olumiant within 15 days of becoming aware of the event. SAEs can be submitted using the Sponsors generic SAE reporting form that can be downloaded from the following location https://glasgowctu.org/Home/00-safety-reporting/.

7 STATISTICS AND DATA ANALYSIS

7.1 STATISTICAL ANALYSIS PLAN

The study will have a comprehensive Statistical Analysis Plan, which will govern all statistical aspects of the study, and will be agreed by the Trial Management Group (TMG).. To assess whether treatment with Olumiant results in a reduction in functional connectivity (DMN-Insula and DAN-IPL) and glutamate quantification, changes in our neuroimaging metrics of interest between time points will be evaluated using paired t-tests. Changes in pain, clinical phenotyping and immunophenotyping measures will be correlated with those significant regions identified from our primary objective. Putative confounders will be explored using general linear models.

7.2 PRIMARY EFFICACY ANALYSIS

The primary outcomes are changes in brain functional connectivity (DMN-Insula and DAN-LIPL) and changes in insular glutamate signal from baseline (day 0) to Visit 2 (week 12), following Olumiant treatment in RA.

Resting state fMRI data will be pre-processed to control transient head movements and parcellated into cortical areas and subcortical nuclei before estimation of a functional connectivity matrix for each subject under each treatment condition. Topological analysis of weighted graphs derived from these matrices will estimate brain network properties such as weighted nodal degree and modular community structure,

which are known to be sensitive to the effects of peripheral CRP and are hypothetically expected to be indicative also of the effects of Olumiant treatment on functional brain networks.

Objective 1 and 2: To assess whether treatment with Olumiant results in a reduction in functional connectivity (DMN-Insula and DAN-IPL) and glutamate levels, changes in our neuroimaging metrics of interest between time points will be evaluated using paired t-tests.

7.3 SECONDARY EFFICACY ANALYSIS

The secondary outcomes are changes in pain, clinical phenotype, peripheral immune markers and their change with MRI markers indicative of CNS pathway function from baseline (day 0) to Visit 2 (week 12), following Olumiant treatment in RA.

Changes in pain, clinical phenotyping and immunophenotyping measures will be correlated with those significant regions identified from our primary objectives. Putative confounders will be explored using general linear models.

7.4 SAFETY ANALYSIS

The safety data (serious adverse events) – both numbers of subjects and events – will be summarised overall using descriptive statistics.

7.5 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.

7.6 SAMPLE SIZE

Based on the only previous study to examine and evidence fMRI changes pre- and post- RA treatment (n=10)[20] and our previous MRS study in fibromyalgia (n=17)[12] we estimate that a group sample size of n=20 will be sufficient to detect significant neuroimaging changes (n=3 dropout). Moreover, the enhanced sensitivity of 7T and our capacity to apply hypothesis-based region of interest analysis, based on our recent work, will afford greater reserves of power which in turn will enable testing of putative confounders. A sample size of n=17 should be sufficent to measure changes in our optimal outcomes (fMRI and MRS)

7.7 MANAGEMENT AND DELIVERY

All files will receive a Digital Object Identifier (DOI), with associated metadata being listed in the University of Glasgow Research Data Registry and the DataCite metadata store. The DOI of each dataset will be included in any publication reporting it, allowing each dataset to be identified and accessed by researchers reading the publication. DOIs will also be linked with appropriate records in the University's publication repository to enhance visibility of datasets. All statistical analyses will be conducted according to a pre-specified Statistical Analysis Plan.

8 TRIAL CLOSURE / DEFINITION OF END OF TRIAL

The end of the study is defined as database lock after the last data collection. The end of the study will be reported to the Sponsor and REC within 90 days, or 15 days if the study is terminated prematurely.

9 DATA HANDLING

9.1 CASE REPORT FORMS / ELECTRONIC DATA RECORD

Case Report Forms (CRF), including medical outcomes, and questionnaires are completed during the assessment visits at the local study site either on paper or online in the secure database. All participants will have the option to complete the questionnaires online in the database or on paper depending on personal preference. Completed paper pain diaries will be returned either by pre-paid envelope, phone or online.

Personal data, including postal address, phone numbers (landline and mobile), email addresses, and anonymised data files for study outcomes will be stored in locked filing cabinets (hard copy) and in a NHS GGC approved database as well as secured shared drives with access via password controlled computers (university and NHS networks) by study staff only (electronic data).

A study-specific, NHS GGC approved, eCRF will be established. The eCRF will be developed by the study team using Castor and access to the eCRF will be restricted, with only authorised, site-specific personnel able to make entries or amendments to participants' data. It is the investigator's responsibility to ensure completion and to review and approve data captured in the eCRF.

Data will be validated at the point of entry into the eCRF and at regular intervals during the study. Data discrepancies will be flagged and any data changes will be recorded in order to maintain a complete audit trail (e.g. reason for change, date change made, who made change).

9.2 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, whichever is longer. In line with the University of Glasgow's Code of Good Research Practice study data will be retained for a minimum of 10 years.
Archive coded information will be retained for a maximum of 10 years after the end of this trial and for its transmission outside the European Economic Area.

10 TRIAL MANAGEMENT

10.1 ROUTINE MANAGEMENT OF TRIAL: TRIAL MANAGEMENT GROUP

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

11 STUDY AUDIT

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

12 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 TMG and any required amendment forms will be submitted to the REC and sponsor.

The CI 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, and Research and Development (R&D) office(s). Amendments to the protocol or other study documents will not be implemented without these approvals.

13 ETHICAL CONSIDERATIONS

13.1 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 a REC before participants are recruited into this clinical 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.

13.2 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.
Participants will be asked to provide permission to allow their de-identified data to be transferred out of the European Economic Area or United Kingdom.
Anonymised data will be transferred between the University of Glasgow and the University of Michigan.

14 INSURANCE AND INDEMNITY

The SOAR study is sponsored by NHS Greater Glasgow and Clyde. The sponsor will be liable for negligent harm caused by the design of the trial. NHS indemnity is provided under the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

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

15 FUNDING

The study is supported by an Investigator Initiated grant from Lilly "*Exploiting Leading Edge 7T MRI Brain Imaging to Decipher Olumiant's Mode of Analgesic Action in Rheumatoid Arthritis* ".

16 ANNUAL REPORTS

Annual progress reports will be submitted to REC on the anniversary of the ethics favourable opinion. A copy of this report will also be sent to the Sponsor.

In addition to the traditional academic routes of communication and dissemination via peer reviewed publication and national and international conferences, we will also use Research into Inflammatory Arthritis Centre Versus Arthritis (RACE) and Glasgow Arthritis Involvement Network (GAIN) Patient Research Partner (PRP) networks to develop local patient and public involvement (PPI) groups. Supported by Engagement Leads (EL) already in place at each institution, RACE PRPs will form a key part of our communications programme. A PRP member from each institution already attends quarterly centre meetings, accompanied by institutional ELs.

1. Walsh DA, McWilliams DF. Mechanisms, impact and management of pain in rheumatoid arthritis. *Nat Rev Rheumatol* 2014; **10**(10)**:** 581-592.

2. McWilliams DF, Walsh DA. Factors predicting pain and early discontinuation of tumour necrosis factor-α-inhibitors in people with rheumatoid arthritis: results from the British society for rheumatology biologics register. *BMC Musculoskelet Disord* 2016; **17:** 337.

3. Taylor PC, Keystone EC, van der Heijde D, Weinblatt ME, del Carmen Morales L, Reyes Gonzaga J *et al.* Baricitinib versus Placebo or Adalimumab in Rheumatoid Arthritis. *New England Journal of Medicine* 2017; **376**(7)**:** 652-662.

4. Taylor PC, Lee YC, Fleischmann R, Takeuchi T, Perkins EL, Fautrel B *et al.* Achieving Pain Control in Rheumatoid Arthritis with Baricitinib or Adalimumab Plus Methotrexate: Results from the RA-BEAM Trial. *J Clin Med* 2019; **8**(6)**:** 831.

5. Basu N, Kaplan CM, Ichesco E, Larkin T, Harris RE, Murray A *et al.* Neurobiologic Features of Fibromyalgia Are Also Present Among Rheumatoid Arthritis Patients. *Arthritis & Rheumatology* 2018; **70**(7)**:** 1000-1007.

6. Schrepf A, Kaplan CM, Ichesco E, Larkin T, Harte SE, Harris RE *et al.* A multi-modal MRI study of the central response to inflammation in rheumatoid arthritis. *Nature Communications* 2018; **9**(1)**:** 2243.

7. Nicolas CS, Amici M, Bortolotto ZA, Doherty A, Csaba Z, Fafouri A *et al.* The role of JAK-STAT signaling within the CNS. *Jakstat* 2013; **2**(1)**:** e22925.

8. Salaffi F, Giacobazzi G, Di Carlo M. Chronic Pain in Inflammatory Arthritis: Mechanisms, Metrology, and Emerging Targets-A Focus on the JAK-STAT Pathway. *Pain Res Manag* 2018; **2018:** 8564215.

9. Haroon E, Chen X, Li Z, Patel T, Woolwine BJ, Hu XP *et al.* Increased inflammation and brain glutamate define a subtype of depression with decreased regional homogeneity, impaired network integrity, and anhedonia. *Translational Psychiatry* 2018; **8**(1)**:** 189.

10. Harris RE, Sundgren PC, Craig AD, Kirshenbaum E, Sen A, Napadow V *et al.* Elevated insular glutamate in fibromyalgia is associated with experimental pain. *Arthritis Rheum* 2009; **60**(10)**:** 3146-3152.

11. Napadow V, LaCount L, Park K, As-Sanie S, Clauw DJ, Harris RE. Intrinsic brain connectivity in fibromyalgia is associated with chronic pain intensity. *Arthritis Rheum* 2010; **62**(8)**:** 2545-2555.

12. Harris RE, Napadow V, Huggins JP, Pauer L, Kim J, Hampson J *et al.* Pregabalin rectifies aberrant brain chemistry, connectivity, and functional response in chronic pain patients. *Anesthesiology* 2013; **119**(6)**:** 1453-1464.

13. Wolfe F, Clauw DJ, Fitzcharles M-A, Goldenberg DL, Katz RS, Mease P *et al.* The American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia and Measurement of Symptom Severity. *Arthritis Care & Research* 2010; **62**(5)**:** 600-610.

14. Melzack R. The McGill Pain Questionnaire: major properties and scoring methods. *Pain* 1975; **1**(3)**:** 277-299.

15. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The Cognitive Failures Questionnaire (CFQ) and its correlates. *British Journal of Clinical Psychology* 1982; **21**(1)**:** 1-16.

16. Andreasson A, Wicksell RK, Lodin K, Karshikoff B, Axelsson J, Lekander M. A global measure of sickness behaviour: Development of the Sickness Questionnaire. *Journal of Health Psychology* 2016; **23**(11)**:** 1452-1463.

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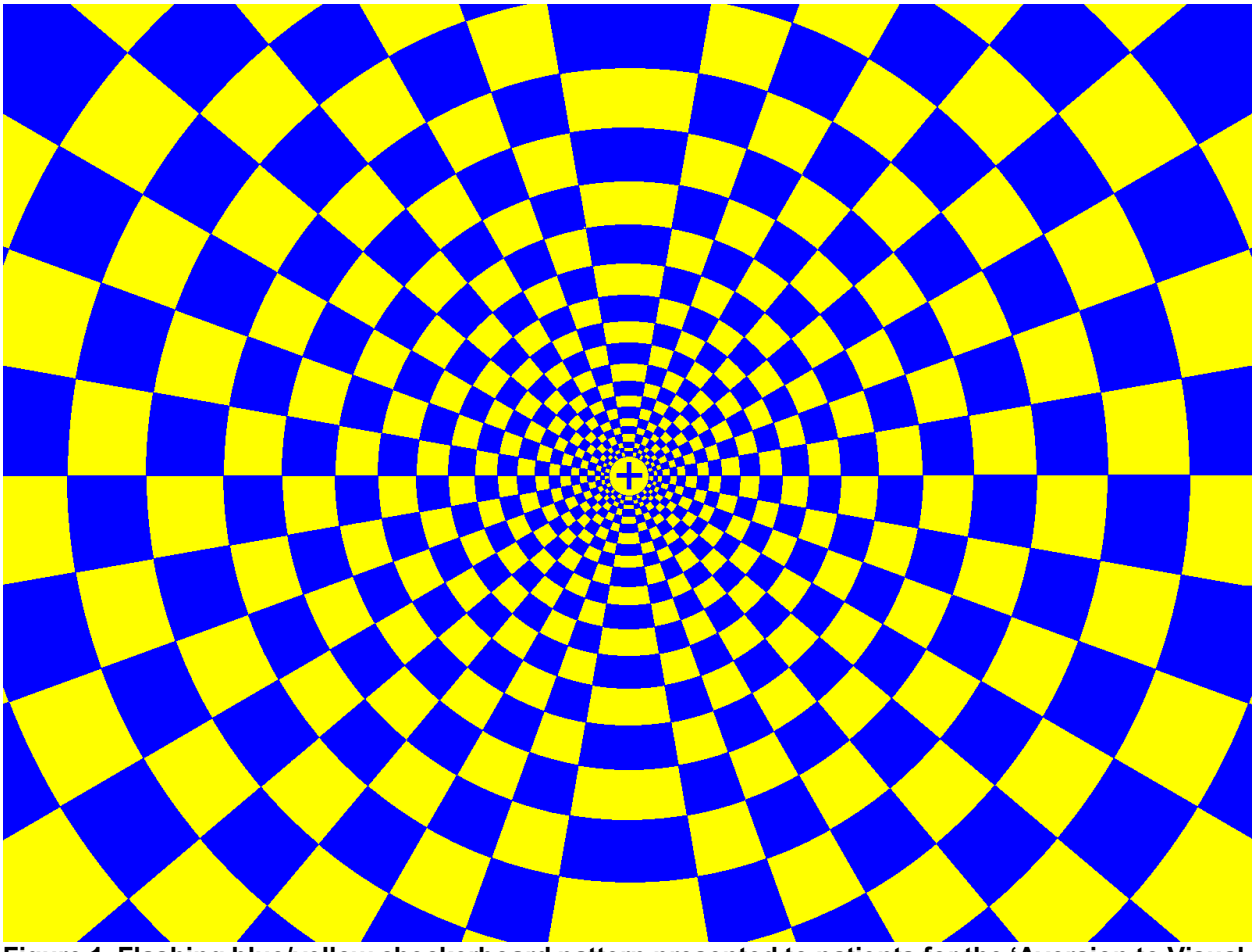

Figure 1. Flashing blue/yellow checkerboard pattern presented to patients for the 'Aversion to Visual Stimulus' component of the QST protocol.