APTITUDE A phase II trial of Tocilizumab in anti-TNF refractory patients with JIA associated uveitis.

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Clinical Trials Research Centre

Arthritis Research UK

Protocol Approval

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General Information

This document describes the APTITUDE trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Clinical Trials Unit; CTU) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the Chief Investigator, Professor Athimalaipet Ramanan via the CTU.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements and waivers to authorise non-compliance are not permitted.
Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTU Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Liverpool Trials Collaborative (LTC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The Clinical Trials Research Centre (CTRC; http://www.ctrc.org.uk/) is a partner of the LTC collaborative. The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Clinical Trials Unit; MC CTU), epilepsy, infection, oral health and obstetrics and gynaecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

Contact Details: Institutions

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1 CONTENTS

Glossary

ABPI	Association of the British Pharmaceutical Industry
AC	Anterior Chamber
ACR	American College of Rheumatology
ADR	Adverse Drug Reaction
AE	Adverse Events
AESI	Adverse Events of Special Interest
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibody
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AqH	Aqueous Humour
AR	Adverse Reaction
CHAQ	Childhood Health Assessment Questionnaire
CHQ	Childhood Health Questionnaire
CI	Chief Investigator
CMO	Cystoid Macular Oedema
CRF	Case Report Form
CRP	C- Reactive Protein
CTA	Clinical Trial Authorisation
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
DMARD	Disease Modifying Anti Rheumatic Drugs
DNA	Deoxyribonucleic acid
dsDNA	Double Stranded DNA
ESR	Erythrocyte Sedimentation Rate
EU	European Union
EUDRACT	European Clinical Trials Database
G/DL	Grams per DeciLiter
GMP	Good manufacturing Practice
GP	General Practitioner
IB	Investigator Brochure
IDSMC	Independent Data and Safety and Monitoring Committee
ICH	International Conference on Harmonisation
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
IL	Interleukin
ILAR	International League Against Rheumatism
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous Therapy
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
KG	Kilogram
LOCS	Lens Opacities Classification System
LogMAR	Logarithm of the Minimum Angle of Resolution
LREC	Local Research Ethics Committee
LTBI	Latent Tuberculosis Infection
MG	Milligram

MG/DL	Milligram / Decilitre
MG/M2	Milligram / Square Meter
MG/KG	Milligram / Kilogram
MC CTU	Medicine for Children Clinical Trials Unit
MHRA	Medicines and Healthcare Products Research Agency
MREC	Main Research Ethics Committee
MTX	Methotrexate
NCR CRF's	No Carbon Required Case Report Forms
NHS	National Health Service
NIHR CRN	National Institute of Health Research Clinical Research Network
NSAIDS	Non Steroid Anti Inflammatory Drugs
OCT	Optical Coherence Tomography
PISC	Patient Information Sheet and Consent Form
PI	Principal Investigator
PPD	Purified Protein Derivative
QA	Quality Assurance
QC	Quality Control
QFT-G	QuantiFERON-TB Gold
QoL	Quality of Life
R&D	Research and Development
RA	Rheumatoid Arthritis
REC	Research Ethics Committee
S/C MTX	Subcutaneous Methotrexate
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SI	Statutory Instrument
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SUN	Standardisation of Uveitis Nomenculture
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TMG	Trial Management Group
TNF	Tumour Necrosis Factor
TOCZ	Tocizilumab
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction
µL	Microlitre
ULN	Upper Limit of Normal
UK	United Kingdom
VEGF	Vascular endothelial growth factor
WBC	White Blood Cell

2 PROTOCOL SUMMARY

Title: A phase II trial of Tocilizumab in anti-TNF refractory patients with JIA associated uveitis.

Phase: Phase II

Population: Children and young people aged ≥ 2 and <18 years fulfilling ILAR diagnostic criteria for JIA with persistently active uveitis that have failed an anti TNF agent and are maintained on a stable dose of methotrexate (MTX).

Study Centres and distribution: The study will take place in 6 centres across the UK that offer a combined paediatric rheumatology and ophthalmology service.

Study Duration: 36 weeks: Patients will be on treatment for 24 weeks and have visits every four weeks during this time, followed by a final follow up visit 12 weeks after stopping treatment.

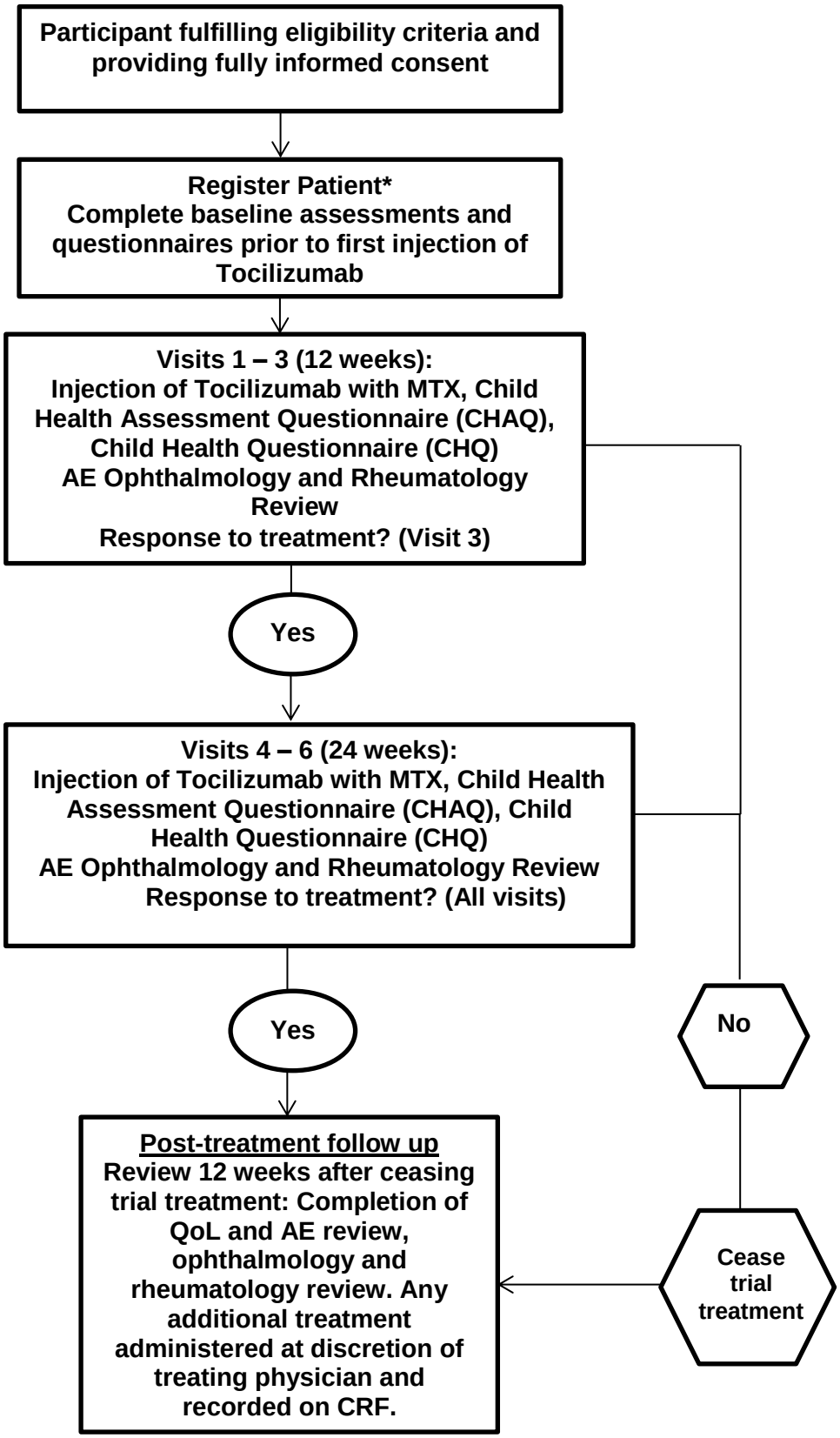
Description of agent/ intervention: This trial is not randomised. All participants will receive injections every 2 weeks or every 3 weeks (dependent upon weight) of Tocilizumab alongside methotrexate (MTX) treatment. The dosage will be calculated based on patient body weight.

Primary objective: The primary objective of this trial is to estimate the clinical response rate of uveitis to Tocilizumab in combination with MTX in children with JIA-associated uveitis who have failed anti-TNF therapy, and to determine whether further research into the use of this intervention for the treatment of anti-TNF refractory JIA-associated uveitis should be conducted.

Secondary objectives:

- To conduct a preliminary evaluation of the short term safety and tolerability of Tocilizumab in combination with MTX with regards to ocular complications of treatment. Adverse events and laboratory assessments.
- To assess the efficacy of treatment with Tocilizumab to permit concomitant medication reduction, in particular topical and parental steroids.
- To determine whether further research into the use of this intervention for the treatment of anti-TNF refractory JIA associated uveitis should be conducted.
- To develop a fully consented, trial-related Bio Bank for subsequent investigation

2.1 Schematic of Study Design:



*Registration should take place no later than 2 weeks after the beginning of screening

3 BACKGROUND INFORMATION

3.1 Introduction

Juvenile idiopathic arthritis (JIA) is the name for a type of arthritis that primarily affects young people and whose cause is unknown. 'Arthritis' means inflammation of the joints, but in JIA the inflammation may also affect the eyes and internal organs. Approximately 1 in 1000 children in the UK develops JIA per annum. Although both genders are affected, JIA is most common in girls. Amongst those children with JIA around 15-25% are at risk of inflammation of the uvea in the eye, known as uveitis[1, 2]. In one third of the children who develop uveitis, the disease is of sufficient severity to cause visual loss, cataracts, increased pressure in the eye and blindness[3-5]. The severity of the disease is partly due to the level of damage in the eye already present when the diagnosis is made. As the disease shows no clear symptoms there is an extensive screening programme to try to minimise the delay in diagnosis.

3.2 Rationale

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children. Children with JIA also are at risk of inflammation of the uvea in the eye (uveitis). 80% of all paediatric uveitis is secondary to JIA[6, 7]. The major risk factors for development of uveitis in JIA are oligoarticular pattern of arthritis, early onset of arthritis, and antinuclear antibody positivity [8]. In the initial stages of mild to moderate inflammation the uveitis is entirely asymptomatic. This has led to the current practice of screening all children with JIA regularly for uveitis. There is an ongoing HTA/Arthritis-UK funded trial (the SYCAMORE Trial) conducted by our team to assess the efficacy and safety of adamilumab monoclonal anti- TNF agent in the management of MTX-refractory uveitis[9]. This trial commenced in Nov 2011 and continues. The APTITUDE trial is complimentary to SYCAMORE because any potential patients who fail on anti-TNF therapy or who are not eligible for inclusion to SYCAMORE due to previous use (and subsequent disease flare) on anti-TNF therapy are eligible for the APTITUDE trial**.**

Most children with mild to moderate uveitis are managed on topical steroid drops and use of systemic methotrexate (MTX) as an immunosuppressive agent [10, 11]. As a significant proportion of children with moderate-severe uveitis are refractory to MTX [12-14], biologicals in the form of monoclonal anti-TNF agents have been tried. The anti TNF agents are effective only in 30-60 % of the patients based on several retrospective case series[15]. In our own clinical experience the response rate is only 50%[16].

Unfortunately, anti-TNF therapy is not the panacea either for JIA alone, or JIA-associated uveitis. We know that some patients already treated with anti-TNF therapy, may still flare despite anti-TNF therapy. These children have severe recalcitrant disease that is therefore at greater risk of causing significant ocular complications and blindness.

The efficacy of tocilizumab in uveitis and ophthalmology outcomes has not been studied. However, the rationale for anti-IL-6 therapy is strong. Hence the need for a phase II study to give early indications of the clinical effectiveness of Tocilizumab in combination with MTX and to decide whether further research is justified.

Previous studies investigating the effect of Tocilizumab in paediatric arthritis have excluded patients with uveitis. However data available for Tocilizumab in uveitis in adults indicates its potential role for refractory disease[17]. A systematic search of existing data has shown only a couple of case reports[18].

Tocilizumab (trade name RoActemra) is also a biological therapy blocking the action of interleukin (IL)-6. In arthritis, IL-6 causes tiredness, anaemia, and inflammation and damage

to bones, cartilage and tissue. Tocilizumab reduces these effects. Previous studies looking at the effect of Tocilizumab in children have been conducted looking at Rheumatology examinations only. However trial of Tocilizumab in children with the systemic form of JIA have responded dramatically to this treatment in a short time span[19] and became the first drug licenced for use in JIA in fifty years, obtaining NICE approval for this indication. It is also being trialled at present in polyarticular forms of JIA with good effect[20]. However these clinical trials for Tocilizumab state that a diagnosis of Uveitis is part of the exclusion criteria.

In humans, sampling of the anterior chamber fluid (aqueous humour; AqH) in a cohort of patients with uveitis has shown via multiplex immunoassay high levels of IL-6[21]. In vitreous samples from patients undergoing diagnostic or therapeutic vitrectomy for intermediate uveitis, IL-6 was again elevated but did not confer specificity to any specific diagnosis[22]. Most recently were anecdotal reports of success of Tociizumab therapy in refractory uveitis[17, 18.] Most compelling is the work that demonstrated increased gp130 in AqH of active uveitis patients and also a high degree of correlation with IL-6 and IL-6R levels[23]. Consistently, many others have shown the higher levels of IL-6 in ocular fluid during more chronic disease courses[24]. The cause of chronic disease remains unknown but autoinflammation driving a dysregulated innate immunity will encompass an IL-6 mediated inflammatory response, particularly from mononuclear cell populations and is a consistent feature of animal models and human data to date[25]. As such IL-6 is a suitable inflammatory pathway to therapeutically target. In view of the failure of patients with refractory JIA-associated uveitis to either respond, or subsequently flare on anti-TNF therapy, and the strong evidence base for the rationale for targeting IL-6 in the disease pathogenesis, a phase II trial of the potential efficacy, safety and tolerability of anti IL-6 therapy is urgently needed in view of the significant related ocular morbidity.

3.3 Objectives

3.3.1 Primary objectives

The primary objective of this trial is to estimate the response rate to Tocilizumab in combination with MTX in children with JIA-associated uveitis who have already failed anti-TNF therapy, and to determine whether further research into the use of this intervention for the treatment of anti-TNF refractory JIA-associated uveitis should be conducted.

3.3.2 Secondary objectives

To conduct a preliminary evaluation of the short term safety and tolerability of Tocilizumab in combination with MTX in children with JIA-associated uveitis, with regards ocular complications of treatment, adverse events and laboratory assessments.

To assess the efficacy of treatment with Tocilizumab to permit concomitant medication reduction, in particular topical and parenteral steroids

To develop a fully consented, trial-related Bio Bank for subsequent investigation

3.4 Potential Benefits and Risks

3.4.1 Potential Benefits

Tocilizumab, in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more

disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate. Tocilizumab treatment has been shown in a randomized clinical trial of polyarticular-course JIA, as well as systemic-onset JIA, as demonstrating significant improvement, maintained over time, of signs and symptoms and has a safety profile consistent with that for adults with rheumatoid arthritis.
Tocilizumab is now the first choice biologic in children with systemic onset JIA (sJIA) and an important agent in the management of refractory polyarticular JIA. An ongoing Phase 1b, Open-label trial, multicenter study to investigate the pharmacokinetics, and safety of Tocilizumab following subcutaneous administration to patient with polyarticular-course juvenile idiopathic arthritis is currently ongoing across 13 countries worldwide.

3.4.2 Potential Risks

The most commonly reported Adverse Drug Reactions (ADRs) (occurring in ≥ 5% of patients treated with Tocilizumab monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT. The most serious ADRs were serious infections, complications of diverticulitis, and hypersensitivity reactions.

Tocilzumab should not be given to patients that have active infections; careful consideration should also be given for patients that have recurring infections or underlying conditions such as diabetes.

The administration of Tocilzumab should be stopped if a patient develops a serious infection, this should only be started again once the infection is controlled and only if the treating physician has considered the benefit-risk of resuming Tocilizumab.

Diverticular disease is not common in a paediatric population but should be treated immediately if symptoms arise to prevent the risk of gastrointestinal perforations.
There is no known evidence that Tocilizumab treatment shows an effect on demyelinating disorders in a paediatric population although there have been rare reports in adult populations.

There is an increased risk of cardiovascular disorders (hypertension, hyperlipemia etc). Any cardiovascular diseases should be treated as per local practice.

There are risks of local site reactions, including erythema, pain, induration and subcutaneous emphysema among others. Local site reactions should be recorded as an adverse event.

Systemic injection reactions can occur during injection or within 24 hours of inection. This can include hypersensitivity reactions or anaphylactic reactions, signs of hypersensitivity can include fever, chills, pruritus, urticarial, angioedema and skin rash. Cardiopulmonary reactions can include chest pain, hypotension, hypertension and dyspnea. When administering Tocilizumab injections the appropriate medication should be available if there are anaphylaxis or hypersensitivity reactions. Instructions should be given to patients and parents/guardians to recognise the signs or hypersensitivity and anaphylaxis. Patients and parents/guardians should also be instructed to contact the hospital immediately if they

experience any sign of a serious allergic reaction, including shortness of breath, trouble breathing, skin rash, swelling of the lips, tongue, or face, chest pain or feeling dizzy or faint. The patient should be treated according to the standard of care for management of the hypersensitivity reaction. For significant hypersensitivity reactions Tocilizumab must be discontinued immediately.

4 SELECTION OF CENTRES/CLINICIANS

Criteria for the selection of centres will be determined by the Trial Management Group and will be described in the supplementary document 'APTITUDE Site Assessment Criteria'.

Initiation of centres will be undertaken in compliance with CTRC SOPs TM017 and TM018; Centres fulfilling the criteria will be selected to be recruitment centres for the APTITUDE trial and will be opened to recruitment upon successful completion of all global (e.g. MREC and MHRA) and study-specific conditions (e.g. site personnel training requirements) and once all necessary documents have been returned to CTU as detailed in the trial 'greenlight' checklist.

Participating centres will be listed in the 'APTITUDE Participating Centres' log, maintained separately to the protocol.

5 TRIAL DESIGN

5.1 Primary Endpoint

The primary endpoint is response to treatment*.

** Response to treatment is defined as per SUN criteria as a 2 step decrease in the level of inflammation (anterior chamber cells) or decrease to zero between baseline (prior to trial treatment initiation) and after 12 weeks of treatment* [26].

5.2 Secondary Endpoints

1) Safety, tolerability and compliance
   a. Adverse events (AEs), serious adverse events (SAEs) and Adverse Events of Special Interest (AESI)
   b. Laboratory parameters (haematological and biochemical analysis and urinalysis)
   c. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period

2) Use of Corticosteroids over duration of study period and throughout follow up, including:
   a. Total oral corticosteroid dose
   b. Reduction in and rate of systemic corticosteroid dose from entry dose
   c. Topical corticosteroid use (frequency) compared to usage at registration.

3) Optic and Ocular
   a. Visual acuity measured by Age-appropriate LogMAR assessment
   b. Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography (OCT)).
   c. Number of patients who are able to reduce topical or systemic agents for ocular hypertension.
   d. Number of participants with disease control (defined as zero cells, with topical treatment at 12 weeks treatment visit and 24 weeks treatment visit.)
   e. Number of participants entering disease remission (defined as zero cells, without topical treatment at 12 and 24 weeks treatment visit)
   f. Duration of sustaining inactive disease (zero cells, with or without topical treatment.)
   g. Failure to reduce eye drops to 2 drops/day by or at the 12 weeks visit

4) Quality of Life assessment (Childhood Health Questionnaire (CHQ), (Childhood Health Assessment Questionnaire (CHAQ))

5) American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 levels

6) Number participants requiring change in biologic / Disease-modifying anti-rheumatic drugs (DMARDs) therapy due to disease flare of their arthritis or failure to respond to treatment for their arthritis.

7) Number of participants undergoing flare of arthritis, in remissions on and off medication of their JIA and with minimum disease activity[27, 28].

8) Participants score of the Juvenile Arthritis Disease Activity Score (JADAS). The JADAS comprises four components: (1) physician global assessment of disease activity (2) parent/patient global assessment of well-being (3) active joint count, in 27, 71 or 10 joints; and (4) erythrocyte sedimentation rate (ESR).

6 STUDY POPULATION

6.1 Inclusion Criteria

1) Children and young people aged ≥ 2 and <18 years

2) At the time of trial screening the participant must have active anterior uveitis, defined as "2 readings of cellular infiltrate in anterior chamber of SUN criteria grade ≥1+ or more during the preceding 6 weeks, the latest reading must be at the time of screening

3) Participants must have failed MTX (minimum dose of 10mg/m^2, with a maximum dose of 20mg/m^2 and not to exceed 25mg/participant) The participant must have been on MTX for at least 12 weeks and have been on a stable dose of MTX for 4 weeks prior to screening visit.

4) Participants must have failed an anti TNF agent and have been on at least one anti-TNF agent regardless of dose for at least 12 weeks at any time previously.
If a participant has received previous treatment with any of the following biologic agents, these must have been discontinued according to the following timelines prior to registration:

   Infliximab 8 weeks prior to registration.
   Etanercept 2 weeks prior to registration.
   Adalimumab 4 weeks prior to registration.
   Abatacept 8 weeks prior to registration.
   Canakinumab 20 weeks prior to registration.
   Rilonacept 6 weeks prior to registration.
   Anakinra 1 week prior to registration

   If a patient has been on another biologic agent not listed above then please contact the trial team for appropriate washout period

5) Written informed consent of participant or parent/legal guardian, and assent where appropriate.

6) Participant and parent/legal guardian willing and able to comply with protocol requirements.

7) For participants of reproductive potential (males and females), use of a reliable means of contraception throughout their trial participation (abstinence is an acceptable method of contraception as long as this is the usual and preferred lifestyle of the patient.)

8) Post pubertal females must have a negative serum pregnancy test within 14 days prior to registration.

9) Able to commence trial treatment within 2 weeks of the screening visit.

6.2 Exclusion Criteria

1) Uveitis without a diagnosis of JIA fulfilling ILAR diagnostic criteria for JIA (all subgroups that have uveitis).

2) Currently on Tocilizumab or has previously received Tocilizumab.

3) Previous registration into the APTITUDE trial

4) Participation in another clinical trial of investigational medicinal product within the last 4 weeks or 5 serum half-lives (whichever is longer) prior to registration

5) More than 6 topical steroid eye drops per day per eye at time of registration (dose must be stable for 1 week prior to registration)

6) For patients on Prednisone or Prednisone equivalent, change of dose within 4 weeks prior to registration

7) Patients on Prednisone or Prednisone equivalent with a dose >0.2mg/kg per day

8) No intraocular injection of disease modification agents including steroids and anti-VEGF within 4 weeks prior to registration.

9) No intraocular surgery for previous 12 weeks prior to registration or expected/panned for duration of study.

10) Lack of recovery from recent surgery or surgery within 6 weeks at the time of registration

11) Intra-ocular pressure ≥ 25mm Hg at time of registration.

12) Patients requiring systemic therapy with oral anti-glaucoma medication.

13) No disease modifying immunosuppressive drugs, other than MTX in the 4 weeks prior to registration

14) History of active tuberculosis of less than 24 weeks treatment

15) Latent TB not successfully treated for at least 4 weeks prior to registration (a test for latent tuberculosis infection (LTBI) must be performed within 12 weeks prior to registration)

16) Auto-immune, rheumatic disease or overlap syndrome other than JIA.

17) Females who are pregnant, lactating, or intending to become pregnant during trial

18) Known human immunodeficiency virus infection or other condition characterized by a compromised immune system

19) Any history of alcohol or drug abuse within 24 weeks prior to registration

20) Any active acute, sub-acute, chronic, or recurrent bacterial, viral, systemic fungal, infection or any major episode of infection requiring hospitalisation or treatment with IV antibiotics within 4 weeks of registration or treatment with oral antibiotics within 2 weeks of registration

21) History of reactivation or new onset of a systemic infection such as herpes zoster or Epstein−Barr virus within 8 weeks prior to registration

22) Hepatitis B surface antigen or hepatitis C antibody positivity or chronic viral or autoimmune hepatitis

23) History of concurrent serious gastrointestinal disorders

24) Evidence of current serious uncontrolled concomitant cardiovascular (including hyperlipidemia), nervous system, pulmonary (including obstructive pulmonary disease), renal and hepatic disease

25) History of or current cancer or lymphoma

26) Persistently poorly controlled severe hypertension (>95th percentile for height / age)

27) Uncontrolled diabetes mellitus

28) History of severe allergic or anaphylactic reactions to human, humanized or murine monoclonal antibodies

29) No live attenuated vaccines (including seasonal nasal flu vaccine, varicella vaccine for shingles or chickenpox, MMR or MMRV, oral polio vaccine and vaccines for yellow fever, measles, mumps or rubella) 4 weeks prior to registration, throughout the duration of the trial and for 8 weeks following the last dose of study drug

30) Previous treatment with any cell-depleting therapies, including investigational agents or approved therapies (e.g.CAMPATH, anti-CD4, anti-CD5, anti- CD3, anti-CD19 and anti-CD20)

31) Treatment with intravenous gamma globulin or plasmapheresis within 24 weeks of registration

32) Any previous treatment with alkylating agents such as chlorambucil, or with total lymphoid irradiation

33) Any significant medical or surgical condition that would risk the patient's safety or their ability to complete the trial

34) Any joint injections within 4 weeks prior to registration

35) Any psychological condition that in the opinion of the principal investigator would interfere with safe completion of the trial

36) Demonstrations of clinically significant deviations from the following laboratory parameters:

Serum creatinine > 1.5 × the upper limit of normal (ULN) for age and sex
AST or ALT > 1.5 × the ULN for age and sex
Total bilirubin > 1.3 mg/dL (>23 µmol/L)
Platelet count < 150 × 10^3/µL (< 150,000/mm3) (< 150 x 10^9/L)
Hemoglobin < 7.0 g/dL (< 4.3 mmol/L)
White blood cell (WBC) count < 4,000/mm3 (< 4.0 × 10^9/L)
Neutrophil count < 2000/mm3 (< 2.0 × 10^9/L)

6.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient (or parent/legal representative) should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation if appropriate, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the patient's condition becomes stable, unless the participant explicitly also withdraws consent for follow-up.

6.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient or for follow-up via GP. A copy of the patient CRFs should be provided to the new site. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The CTU should be notified in writing of patient transfers.

6.3.2 Discontinuing Trial Intervention

Discontinuation of trial treatment does not mean that a patient is removed from the trial as generally, follow-up will continue unless the patient explicitly removes consent for this
If a patient wishes to stop trial treatment, centres should nevertheless explain the importance of remaining on trial follow-up, or failing this, of allowing routine follow-up data to be used for trial purposes.

Patients may stop trial treatment for any of the following reasons:

a. Parent/ legal representative (or, where applicable, the patient) removes consent.
b. Unacceptable toxicity.
c. Intercurrent illness preventing further treatment.
d. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

6.3.3 Removal from Trial Completely

Patients are free to remove consent at any time without providing a reason. Patients who wish to remove consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study and the CTRC should be informed in writing and the withdrawal section of the CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish. If the participant explicitly states that they wish to withdraw from the trial completely and that they do not want their data to be included in the final analyses, please contact the APTITUDE trial coordinator to request a Participant Data Withdrawal CRF.

7 REGISTRATION

7.1 Screening

Several assessments are required to be undertaken as part of the research activity in order to establish eligibility, requiring that written informed consent (or proxy consent in the case of minors) is obtained prior to formal trial screening. For this reason, centres are encouraged to adopt a pre-screening procedure in order to identify potentially eligible patients prior to their attending clinic review.

Formal screening involves the collection of baseline data. All patients considered for the trial will be recorded on the screening log and have a unique screening number that will be used on trial documents. Assessments for consideration of trial entry which are not undertaken as part of routine care should only be undertaken following provision of written consent. All screening assessments should be completed, and results collated to verify eligibility in a timely manner to ensure that treatment can be commenced within 2 weeks of obtaining written consent. Assessment activities are summarised here and detailed descriptions of assessments are provided in section 9. Once all eligibility criteria have been assessed, full eligibility must be confirmed. Full eligibility may only be confirmed by a doctor who has been authorised to do so on the site Delegation Log; a record of this confirmation must be made in the patient's medical notes

During screening you should:

1) Obtain or verify that written informed consent has been obtained from non-minors (aged 16-18 years inclusive) or proxy consent for minors (aged <16 years), with assent of minors, where appropriate.

2) Carry out assessments to confirm eligibility and determine baseline parameters:
    a. Demographics / medical/ ophthalmic/ surgical history and past medical history.
    b. Detailed rheumatology assessments
    c. Detailed ophthalmology assessments
    d. Review concurrent medication and medication history in relation to eligibility
    e. Detailed Systems Physical examination
    f. Haematological laboratory assessments
    g. Biochemical laboratory assessments
    h. Tanner score
    i. Height, weight and vital signs (heart & respiratory rate, temperature and blood pressure)
    j. Standard ACR Pedi Core Set outcome variables
    k. Urinalysis (microscopy)
    l. Serum Pregnancy Test
    m. PPD Tuberculin skin test or local equivalent
    n. Completion of CHQ/CHAQ.
    o. Collection of Biobank samples

3) Eligible patients can now be registered on study (see 7.2)

4) Consent/assent forms and the Baseline CRF of eligible patients should be submitted to the CTU within 7 days of the visit occurring

5) The outcome for patients found to be ineligible after completing assessments will be recorded on screening logs (CRFs do not require to be forwarded to the CTU)

6) Patients who fail screening may be re-screened after a minimum period of one week after their last screening, the original screening number should be used for all re-screens.

7.2 Registration

Registration will be undertaken by delegated individuals at trial sites. A patient may only be registered once full eligibility has been confirmed by a doctor and written informed consent has been obtained.

Participants will be registered using a secure (24-hour) web based registration programme. Participant registration number will be displayed on a secure webpage following confirmation of eligibility. In the event of an internet connection failure between the centre and the registration system, the centre should contact the CTRC immediately to try and resolve the problem.

Registration: web access https://ctrc.liv.ac.uk/Randomisation/Aptitude
If there are any problems with the web registration please contact the CTRC helpdesk on: 0845 68 00 951

Designated staff will be trained to use the web registration system during the initiation process. After staff are trained they will be issued with a personal login and password details.

Following successful registration, a prescription request form should be sent to the pharmacy department.

8 TRIAL TREATMENT

Tocilizumab (Investigational Medicinal Product; IMP), in combination with methotrexate (MTX) (Non Investigational Medicinal Product; NIMP), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X-ray and to improve physical function when given in combination with methotrexate.

Tocilizumab has also been to shown to be effective for the treatment of polyarticular JIA in controlled trials. It is also effective in the treatment of systemic onset JIA.

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of RA. All patients treated with Tocilizumab should be given the Patient Alert Card. Suitability of the patient for subcutaneous home use should be assessed and instruct patients to inform a healthcare professional if they experience symptoms of an allergic reaction before administering the next dose. Patients should seek immediate medical attention if developing symptoms of serious allergic reactions, see section 3.4.3

8.1 Investigational Medicinal Product - Tocilizumab

8.1.1 Supply and Accountability of Tocilizumab

8.1.1.1 Supply

When a site has been given the greenlight to begin recruitment and has been confirmed by the trial co-ordinator then initial shipment can be requested from Roche by sending the drug delivery request form to welwyn.cpg_general@roche.com and aptitude@liv.ac.uk. It is the responsibility of sites to manage drug inventory as there are no automated processes in place. Subsequent requests can be sent to Roche following the same process highlighted above. Supply will normally be sent to sites within 3-5 days unless unexpected delays occur. Sites will need to factor in the delivery time when requesting new supply.

8.1.1.2 Accountability

Trial specific accountability logs will be provided to pharmacy teams to record details of drug receipt, dispensing, returns and disposal.

8.1.2 Packaging, Labelling, Storage and Stability

Packaging	
Labelling	Sites will be provided with trial labels to be attached to the medication. IMP's should be labelled in accordance with regulation 46 SI2004/1031 and the detailed guidance provided in annex 13 of the EU good manufacturing practice (GMP) guide
Storage	Tocilizumab should be stored at (2°C–8°C) and should not be kept in a freezer

	The pre-filled syringes should be in the outer carton in order to protect from light and moisture. Once removed from the refrigerator, Tocilizumab must be administered within 8 hours and should not be kept above 30°C.
Stability	The shelf life of Tocilizumab is 30 months

8.1.3 Formulation of Tocilizumab

Pharmacotherapeutic group: Immunosupressants, Interleukin inhibitors ATC code: L04AC07

The IB will be supplied for use as reference safety information and is provided as a document supplementary to the protocol.

Active ingredient	
Excipients	L-Histidine, L-Histidine monohydrochloride monohydrate, L-Arginine, L-Arginine hydrochloride, L-Methionine, Polysorbate 80, Water for injections
Pack Size(s)	4 pre filled syringes
Route of Administration	Subcutaneous use
Storage temperature / time	2°C–8°C
Supplier's name	Roche

Tocilizumab 162 mg solution for injection in pre-filled syringe and can vary colour from colourless to slightly yellow in appearance. Each pre-filled syringe contains 162 mg of Tocilizumab in 0.9 ml. Tocilizumab is a recombinant humanized, anti-human monoclonal antibody of the immunoglobulin G1 (IgG1) sub-class directed against soluble and membrane-bound interleukin 6 receptors.

8.1.4 Preparation, Dosage and Administration of Tocilizumab

Patients will receive Tocilizumab dosed according to body weight (BW):

Patients weighing **≥ 30 kg** dosed with 162 mg of Tocilizumab every **two** weeks

Patients weighing **< 30 kg** dosed with 162 mg of Tocilizumab every **three** weeks

Tocilizumab is supplied in a single use pre-filled syringe fitted into a needle safety device. After removing the pre-filled syringe from the refrigerator the pre-filled syringe should be allowed to reach room temperature (18°C to 28C°) by waiting for 25 to 30 minutes, before injecting Tocilizumab. The syringe should not be shaken. After removing the cap the injection must be started within five minutes, to prevent the medicine from drying out and blocking the needle. If the pre-filled syringe is not used within five minutes of removing the cap, it must be disposed of in a puncture resistant container and then a new pre-filled syringe should be used.

8.1.5 Precautions Required for Tocilizumab

Live and attenuated vaccines should not be given concurrently with Tocilizumab (including seasonal nasal flu vaccine, varicella vaccine for shingles or chickenpox, MMR or MMRV, oral polio vaccine and vaccines for yellow fever, measles, mumps or rubella) 4 weeks prior to registration, throughout the duration of the trial and for 8 weeks following the subject's last dose of study drug.

Tocilizumab should not be used with other biological agents. There is no experience with the use of Tocilizumab with TNF antagonists or other biological treatments for RA, sJIA or pJIA patients. Tocilizumab is not recommended for use with other biological agents. Women of childbearing potential must use effective contraception during and up to 12 weeks after treatment. Tocilizumab should not be used during pregnancy unless clearly necessary. Tocilizumab has a minor influence on the ability to drive and use machines. For significant hypersensitivity reactions Tocilizumab must be discontinued immediately.

8.1.6 Dose Modifications

Patients will receive Tocilizumab dosed according to body weight (BW), with patients weighing ≥ 30 kg dosed with 162 mg of Tocilizumab every two weeks and patients weighing < 30 kg dosed with 162 mg of Tocilizumab every 3 weeks. A window of -3/+3 days will be allowed for injections.

Patients who miss two consecutive doses or three doses in total of Tocilizumab injection should cease trial treatment and will be recorded as a withdrawal from treatment.

If a patient weighing < 30 kg at baseline has an increase in body weight to > 30 kg at three successive clinic visits, the patient will then be dosed according to the ≥ 30-kg body weight regimen which will be 162 mg of Tocilizumab every two weeks. Similarly, if a patient weighing ≥ 30 kg at baseline has a decrease in his or her body weight to < 30 kg at three successive clinic visits, the patient will then be dosed according to the < 30-kg body weight regimen which will be 162 mg of Tocilizumab every 3 weeks.

8.1.7 Dose Interruptions

If total bilirubin is > 3 mg/dL (>51.3 µmol/L), Tocilizumab must not be administered and repeat liver function tests should take place in 1 week. If bilirubin persists and is > 3 mg/dL, permanently stop study drug. If bilirubin returns to below the ULN, Tocilizumab administration should resume.

If ALT or AST is > 3 × the ULN, refer to the guidance provided in appendix A. Patients withdrawn from the study because of elevated liver function tests must have repeat tests performed, as clinically appropriate, until levels return to those collected at baseline. If the patient's liver function tests have not returned to baseline within 24 weeks (or sooner if deemed necessary by the investigator), an ultrasound and/or liver biopsy should be considered.

If absolute neutrophil count is < 1000/mm^3 (<1.0 x 10^9/L) or platelet count is < 100,000/mm^3,(<100 x 10^9/L) Tocilizumab should not be administered. A repeat blood sample should be collected prior to the next dose of study drug to verify that hematologic values are above these minimum values required for dosing. If absolute neutrophil count is < 500/mm^3 or platelet count is < 50,000/mm^3, Tocilizumab must be permanently discontinued.

8.1.8 Dose Discontinuation

If any of the following occur then Tocilizumab must be permanently discontinued:

- Anaphylactic or other serious hypersensitivity reaction
- Malignancy
- Pregnancy or positive pregnancy test
- Congestive heart failure
- Gastrointestinal perforation
- A diagnosis active TB, or non-compliance with or early discontinuation of therapy for latent TB
- A reaction suggestive of serum sickness and not representative of signs and symptoms of any other recognized clinical syndromes
- Withholding of more than three consecutive doses because of abnormal liver function tests
- Two consecutive bilirubin values (collected at least 1 week apart) > 3 mg/dL
- Two step increase in the SUN cell score from baseline in the trial eye and non-trial eye (if applicable) over 2 consecutive readings

8.1.9 Concomitant Medications/Treatments

Any medication (including over the counter medicines such as paracetamol, antacids, mineral supplements, NSAIDs, anti-inflammatory eye drops and herbal preparations) that the participant is receiving at the time of registration, or receives during the study, must be recorded on the appropriate case report form (CRF) along with the reason for use, dates of administration, dosage form, dose and dose frequency.

8.1.10 Medications Permitted

- Low dose of steroids (≤0.2mg/kg/day of prednisone or prednisolone equivalent medication orally) are permitted during the active phase of the trial. Prednisone or prednisone equivalent dose must be unchanged for at least 4 weeks prior to registration. Weaning of systemic steroids whilst registered in the trial is at the discretion of the treating clinician.
- Topical steroid eye drops with maximum of 6 drops/ day at registration (this dose must have been stable for at least 1 week prior to registration). The use of topical steroid eye drops and intraocular steroid is allowed in the non-trial eye if applicable
- Failure to reduce eye drops to 2 drops/ day by or at the 12 week visit will be considered a treatment failure and the participant should cease trial treatment.
- After 12 weeks topical treatment must be kept at twice per day. At 24 weeks topical treatment can be reduced as the clinician determines, but not increased for the length of the trial.
- Intraocular pressure medication apart from systemic treatment with acetazolamide
- Maxidex, Predforte or equivalent – preparation to be stipulated at screening and to remain unchanged for individual throughout treatment-phase of trial
- Intra-articular joint injections; the participant:
  - Must not receive more than two intra-articular joint injections in a single session
  - Must have no more than a total of four injections during 24 weeks treatment
  - Must have no joint injections within 4 weeks of registration

8.1.11 Medications Not Permitted

The use of non-permitted medications during the trial is not allowed. Patients who are given non-permitted medications should cease trial treatment.

- Intra-ocular or peri-ocular corticosteroid injection within 4 weeks prior to screening and for the duration of trial treatment. Peri-ocular steroids are not allowed in the non-trial eye.
- The introduction of oral steroids, or increase in oral steroids, is not permitted at any time during the trial which includes the non-trial eye.
- Intravenous methylprednisolone at any time
- Other biologic therapies, including: etanercept, infliximab, golimumab; rituximab, abatacept, anakinra.
- Cyclosporine, Mycophenolate Mofetil, Azathioprine, Lefunamide, Sulfasalazine, hydroxychloroquine, any other disease modifying, anti-rheumatic drug
- Systemic treatment with acetazolamide

8.2 Non-Investigational medicinal Product – Methotrexate

All participants will be prescribed methotrexate in conjunction with their allocated trial treatment. Supply of Methotrexate must continue as per local practice.

Patients will be allowed to change the route of Methotrexate during the trial. This should be recorded on the concomitant medication form. For any queries regarding reduction of MTX please contact the APTITUDE trial co-ordinator.

Participants will record Methotrexate administrations in the patient treatment diary.

8.3 Co-registration Guidelines

To avoid potentially confounding issues, patients should not be recruited into other trials. Individuals who have participated in a trial testing a medicinal product within four weeks preceding screening will be ineligible for the APTITUDE trial. Patients who have previously taken part in SYCAMORE may be approached to take part in this trial.

9 ASSESSMENTS AND PROCEDURES

After obtaining written consent (and assent where appropriate) from the participant, parent or legal guardian, a medical/ophthalmic history will be taken and recorded on the appropriate CRF with particular emphasis on other disorders of relevance and allergies.

Separate sections on the CRF will be provided to record the JIA and uveitis specific medical/ophthalmic history and the participant's other medical/surgical history. Medication (prescription, over-the-counter, and herbal supplements) use over the four weeks prior to the screening visit will also be recorded. Physical examination, measures of disease activity and complications, medication history, surgical history and laboratory tests (haematological and biochemical analysis and urinalysis) will be performed at the screening visit and will be repeated at each subsequent trial visit.

Visits will be conducted as highlighted in the study visits and assessments table. The visits are calculated from the date of the first dose of IMP. With regards to treatment timelines, one month's treatment is defined as four weeks; after commencing treatment the dates of each subsequent visit should be made at four weekly intervals from the date of the first dose of IMP. A window of -7 days/+7 days is allowed for these monthly visits, however for determining treatment response there should be an interval of at least three weeks between assessments. This means that if a patient attends a visit late (within the +7 days window) then their next visit must not be early. The next visit must either be on the date as scheduled applying the 4 weekly interval from first dose of IMP, or may be in the +7 day period. Should any visits be performed outside of the scheduled intervals these should be recorded on the 'unscheduled visit' CRF.

Trial intervention should be given up to and including week 24. Patients weighing <30kg will be given a maximum of 9 injections and patients weighing ≥30kg will be given a maximum of 13 injections.

Table 1: Visits and Assessment Table

Assessment (Procedure/ Activity)	**Screening**	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**
Weeks		0 (-7/+7 days)	4 (-7/+7 days)	8 (-7/+7 days	12 (-7/+7 days)	16 -7/+7 days)	20 (-7/+7 days)	24 (-7/+7 days)	36 (-7/+7 days)
	Screening	Baseline/ Registration	Study Visit	Study Visit	Assessment of endpoints	Study Visit	Study Visit	End of treatment	End of trial
Written and informed consent	X								
Confirm consent	X	X	X	X	X	X	X	X	X
Assessment of eligibility criteria	X	X							
Review of Medical/ Ophthalmic/ Surgical History	X								
Review of concomitant medications	X	X	X	X	X	X	X	X	X
Pregnancy test	X		X	X	X	X	X	X	X
Purified protein derivative (PPD) Tuberculin Skin Test/ Test latent TB as locally performed	X								
Urinalysis	X	X	X	X	X	X	X	X	X
Study intervention (Injection)		X	X	X	X	X	X	X	
Compliance with study intervention		X	X	X	X	X	X	X	
Physical Examination		X	X	X	X	X	X	X	X
Vital signs (heart and respiratory rate and blood pressure)	X		X	X	X	X	X	X	X
Height/ Weight	X	X	X	X	X	X	X	X	X
Dispense treatment diary		X	X	X	X	X	X	X	
CHQ		X	X	X	X	X	X	X	X
CHAQ		X	X	X	X	X	X	X	X
Haematological analysis	X	X*	X	X	X	X	X	X	X
Biochemical analysis	X	X*	X	X	X	X	X	X	X
ANA dsDNA ENA		X						X**	
Samples for Biobank		X			X				X
Vision Assessments#	X	X	X	X	X	X	X	X	X
Optical coherence tomography	X		X	X	X	X	X	X	X
AC cells and flare assessment#	X	X	X	X	X	X	X	X	X
BIO Score	X		X	X	X	X	X	X	X
Cataract scoring	X		X	X	X	X	X	X	X
Goldman tonometry or tonopen	X		X	X	X	X	X	X	X
Standard ACR Pedi Score Set Outcome Variables		X	X	X	X	X	X	X	X
Tanner Score		X			X			X	X
Assessments of Adverse and Serious Adverse Events		X	X	X	X	X	X	X	X

* Biochemical and Haematological taken at screening can be used at baseline only if taken with 2 weeks of baseline visit# Tests do not need to be repeated if screening and baseline visit occurs on the same day

** Test should be conducted if patients withdraw or stop treatment prior to week 24

Procedures for assessing Efficacy

9.1.1 Ophthalmic Assessments

Ophthalmic assessment of disease activity and ocular complications will take place by slit lamp bio-microscopy for uveitis activity (at maximum illumination), including cells and flare in anterior and posterior chambers, using SUN criteria[29].

9.1.1.1 Sun Criteria

SUN Criteria is a quantitative assessment of cell number in the anterior chamber which is graded 0-4 (see table below). With no fully validated measures in paediatric uveitis, SUN criteria are the most robust currently available; the investigators are currently engaged in international collaborative efforts to reach consensus on their use and complete their validation in paediatric uveitis.

Table 2: The SUN Working Group Grading Scheme for Anterior Chamber Cells

The SUN Working Group Grading Scheme For Anterior Chamber Cells	
Grade	Cells in field*
0	<1
0.5+	1-5
1.0+	6-15
2.0+	16-25
3.0+	26-50
4.0+	>50
SUN = Standardisation of Uveitis Nomenclature *Field size – 1mm by 1mm slit beam	

Table 3: SUN Working Group Grading Scheme for Criteria for Grading Presence of AC flare

SUN Working Group Grading Scheme for Criteria for Grading Presence of AC flare	
Grade	Description
0	None
1+	Faint
2+	Moderate (Iris and lens details clear)
3+	Marked (Iris and lens details hazy)
4+	Intense (Fibrin or plastic aqueous)

9.1.1.2 Vision

Using age-appropriate LogMAR visual acuity (Kays pictures and standard LogMAR.)

9.1.1.3 Fundoscopy

Fundoscopy to assess: Disc swelling, or macular oedema and other structural changes in macular (epiretinal membrane) and optic nerve (neovascularisation, glaucomatous neuropathy) and retina (neovascularisation, retinal detachment) Fundoscopy is to be

assessed at trial entry and then at trial exit. Additional dilated fundoscopy can be done in between if clinically indicated, if the participant is in anterior remission, then it is not mandatory to undertake this assessment for the purposes of the trial.

9.1.1.4 Optical coherence tomography (OCT)

Optical coherence tomography (OCT; at least stratus II) for macular oedema and macular foveal thickness; where units available to do so (non-invasive). Within units - same OCT to be used throughout study.

9.1.1.5 Vitritis

Assessment of vitritis and vitreous haze. Grading can be assessed through the binocular indirect ophthalmoscope (BIO SCORE) [30]

Table 4: Binocular indirect ophthalmoscope (BIO SCORE)

Bio Score	Fundus details
0	Clear view
1	Haze, but vessel details visible
2	Vessels visible but no detail
3	Disc, but not vessels, is visible
4	No view (disc or vessels)

9.1.1.6 Cataract Score

Cataract score (LOCS III grading) [31].

9.1.1.7 Intraocular pressure

Intraocular pressure by Goldmann tonometry, tonopen, Icare or instrument as used in local practice, as clinically deemed appropriate at the clinical trial setting.

9.1.1.8 Other structural Changes

Presence or absence of other structural changes including extent of band keratopathy, synechiae, iris bombe, membrane formation and neovascularisation.

9.1.1.9 Physical Examination

A full musculoskeletal and systems physical examination will be performed at each trial visit including detailed joint count. Vital Signs will also be measured including resting blood pressure and heart rate, with the participant in the sitting position, respiratory rate and oral body temperature. Body weight and height: will be measured at screening and at each trial visit.

9.1.2 Rheumatology Assessments

Standard ACR Paediatric Core Set outcome variables [32] will be assessed at baseline and throughout the trial. The table below (adapted from Giannini *et al [32])* summarises the 6 core set variables.

Table 5: Paediatric Core Set Criteria

Paediatric Core Set Criteria
Physician global assessment of disease activity (10cm visual analogue scale)
Parent/ Patient assessment of overall wellbeing (10cm visual analogue scale)
Functionality ability (Childhood Health Assessment Questionnaire
Number of joints with active arthritis
Number of joints with limited movement
Erythrocyte sedimention rate, normalised to a 0-1 scale

From these core outcome variables, the following rheumatology outcome variables will be determined during data analysis, according to published methodology, namely:

- The ACR Paediatric 30, 50, 70, 90 and 100 levels. These are defined as 30%, 50%, 70%, 90% and 100% improvement respectively in a minimum of three variables in the core set with worsening of one variable by no more than 30% as defined in the ACR criteria[32].
- Episode(s) of disease flare, defined as a minimum of 40% worsening in at least 2 out of 6 components, with no more than one component improving by >30% [33]
- Ability to achieve clinical remission as defined by standardised definitions of inactive disease, remission on medication and remission off medication and with minimum disease activity [27, 28] (see references)
- The Juvenile Arthritis Disease Activity Score, or JADAS [34]. The JADAS comprises four components: (1) physician global assessment of disease activity (2) parent/patient global assessment of well-being (3) active joint count, in 27, 71 or 10 joints; and (4) erythrocyte sedimentation rate (ESR). The JADAS is calculated as a sum of scores from its four components, giving global scores of 0-57, 0-101 and 0-40 for the JADAS-27, JADAS-71 and JADAS-10 respectively.

9.2 Procedures for Assessing Safety

9.2.1 Adverse Events

An assessment of adverse events will be undertaken at each study visit from baseline to study completion. These reviews will be carried out by the PI or other delegated staff member conducting the visit. Requirements for adverse event reporting are detailed fully in pharmacovigilance section.

9.2.2 Screening for Tuberculosis

If participant has not previously been tested a test for latent tuberculosis infection (LTBI) must be performed within twelve weeks prior to the baseline visit according to local practice guidelines including those with a prior history of BCG administration. Multiple puncture tests such as the Tine and Heaf tests are not acceptable. The purified protein derivative (PPD) tuberculin skin test and the QuantiFERON®-TB Gold (QFT-G) (or local equivalent) are acceptable screening assays for latent TB in this study. The TB test results should be interpreted according to local guidelines for immunocompromised patients, even though the patients entering this study may or may not be immunocompromised at baseline. The purpose of using this definition is to maximize the likelihood of detecting latent TB.

- Participants who are PPD / QFT-G (or local equivalent) positive according to local guidelines at registration will require a chest x-ray.
- Participants with recent (within 24 weeks of screening visit) positive PPD (≥ 5 mm) who are being treated with prophylaxis may be eligible for trial entry. In these circumstances, documentation of:
- The positive PPD
- A chest x-ray report from the date of the positive PPD

- Documentation of treatment detail and duration
- Treatment of participants who have a positive PPD skin test / QFT-G (or local equivalent) and/or abnormal chest x-ray should be managed in accordance with regional/national guidelines, and initiated at least 4 weeks prior to registration. Treatment for latent tuberculosis must be started with anti-tuberculosis therapy in accordance with local/national recommendations. Those with positive PPD at registration must have been treated with anti-tuberculosis therapy for at least 4 weeks prior to registration and chest radiograph is negative for active tuberculosis.

9.2.3 Urinalysis

Urinalysis will also be carried out at each study visit; a fresh aliquot of urine will be tested for protein, glucose, blood, leukocyte esterase, specific gravity, and pH by dipstick. A microscopic urinalysis will be obtained at screening only if relevant abnormalities greater than trace and the results recorded on the CRF. Subsequently, microscopic urinalysis will be obtained only if relevant abnormalities greater than trace are noted on the dipstick analysis.

9.2.4 Serum pregnancy test

Designated trial personnel will perform a serum pregnancy test for all post-pubertal female participants at the screening visit. There must be evidence of a negative serum pregnancy test for all post pubertal females within 14 days before their first dose of trial drug. Subsequently, serum pregnancy tests will be undertaken every 4 weeks for the duration of treatment and a final test 12 weeks after their final dose of trial drug.

9.2.5 Tanner Score

Secondary sexual development will be measured at baseline and at weeks 12 and 24 during receipt of treatment. This will be done either by self- assessment or by clinical examination. The Tanner score[35] will also be assessed at early withdrawal from trial treatment and 12 weeks at post treatment follow up visit. This will be done on participants of ALL ages, if the participant has reached full sexual maturity then this assessment will only take place at screening.

9.2.6 Haematological Laboratory Assessments

Routine haematological assessments of full blood count will be required for the study (to include haematocrit, haemoglobin, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, platelet count and ESR), which will be analysed in local laboratories. If ESR is unable to be tested then plasma viscosity may be accepted. Results from Haematological assessments taken during the screening period can be used for the results at the baseline/registration visit as long as screening is within two weeks as defined within the protocol. For safety purposes, an auto- antibody screen (ANA, dsDNA and ENA) should also be carried out at the baseline and 24 week visits, this should also be conducted if patients withdraw or stop treatment prior to week 24.

9.2.7 Biochemical laboratory Assessments

Routine biochemical assessments of renal and liver function tests) are required for the study (to include C- Reactive protein (CRP), urea, creatinine, sodium, potassium, calcium, inorganic phosphate, glucose, chloride, bicarbonate, total bilirubin, Lipids, alanine aminotransferase [ALT], aspartate aminotransferase [AST]), which will be assessed in local laboratories. Results from Biochemical assessments taken during the screening period can be used for the results at the baseline/registration visit as long as screening is within two weeks as defined within the protocol.

9.3 Other Assessments

9.3.1 Compliance with Study Treatment

9.3.1.1 Participant Diaries

The participant or the parent/guardian of a participant will maintain a diary for all trial and other medications that are administered outside of the trial visit (i.e. at home).

For *trial treatment* the diary will collect information on:

(i) Vial number
(ii) Time/ date of administration
(iii) Volume/dose
(iv) Any problems with administration/ protocol adherence

For other *prescribed* medications the diary will record:

(i) Medicine name
(ii) Dose prescribed
(iii) Number of times per day medicine was taken
(iv) Number of days/ weeks supplied

For *over the counter* medicines, the diary will record:

(i) Name of medicine
(ii) Cost

9.3.1.2 Pharmacy/Clinical Accountability

Any discernible departure from the protocol regarding trial drug administration will be recorded onto the CRF (see IMP accountability section)

9.3.2 Quality of Life

Patients will be administered Childhood Health Assessment Questionnaires (CHAQ)[36] and Child Health Questionnaires (CHQ)[37] at baseline and each visit throughout the trial.

9.3.2.1 Child Health Assessment Questionnaire

Childhood Health Assessment Questionnaire (CHAQ)[36] is the most widely used functional measure of disability in JIA both in routine clinical practice throughout the UK and clinical trials. Translated into many languages and validated in respective cultures and countries, it is easily completed and scored. It consists of eight domains, enquiring about the child / young person's ability to manage a range of activities of daily living on a 5 point scale. Completion of the questionnaire will be checked by staff

9.3.2.2 Child Health Questionnaire

The Child Health Questionnaire (CHQ)[37] is a generic measure of quality of life used in JIA. It explores a number of important domains including self-esteem, emotional and behavioural difficulties, and family impact. Completion of the questionnaire will be checked by staff.

9.3.3 Collection of Bio bank Samples

A sample collection will be developed, integral to the trial in accordance with Arthritis Research UK's guidelines on detailed clinical and related material banks (http://www.arthritisresearchuk.org/). Written information will be provided to families for this part of the study and written informed consent (with assent where appropriate) obtained. Patients who do not give consent to provide samples to the Bio Bank will still be eligible to take part in the main part in the trial.

RNA, DNA and serum samples should be collected pre-treatment and at two time points post treatment (at baseline, 12 weeks and 36 weeks). The baseline sample must be taken before trial treatment is started. The next sample should be collected at 12 weeks after starting treatment. If for a very specific reason a sample cannot be taken at 12 weeks, then it should be taken at the very next visit / opportunity. The 3rd (and final) sample should be taken at 36 weeks.

9.4 Loss to Follow-up

If any of the trial participants are lost to follow up, contact will initially be attempted through the PI or designated research staff at each centre. If the lead investigator at the trial centre is not the participant's usual clinician responsible for their specialist care then follow up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participants GP will be asked to contact the participants or their family to provide follow up information to the recruiting centre. This information will be included on the Patient Information Sheet. Wherever possible, information on the reason for loss to follow up will be recorded.

9.5 Trial Closure

The end of the trial is the date of database lock as defined in the trial related Data Management Plan. At the time of database lock, data entry privileges are withdrawn from the trial database. The trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Data and Safety Monitoring Committee (IDSMC.) Should the trial be closed prematurely, all active participants (receiving treatment or in follow-up) will be called in for a final follow-up visit and assessments will be undertaken as per schedule. Ongoing care will be at the discretion of the treating clinician.

10 STATISTICAL CONSIDERATIONS

10.1 Outcome Measures

10.1.1 Primary

The primary endpoint is response to treatment*.

** Response to treatment is defined as per SUN criteria as a 2 step decrease in the level of inflammation (anterior chamber cells) or decrease to zero between baseline (prior to trial treatment initiation) and after 12 weeks of treatment [26].*

10.1.2 Secondary

1) Safety, tolerability and compliance
a. Adverse events (AEs), serious adverse events (SAEs) and Adverse Events of Special Interest (AESI)
b. Laboratory parameters (haematological and biochemical analysis and urinalysis)

c. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period

2) Use of Corticosteroids over duration of study period and throughout follow up, including:
a. Total oral corticosteroid dose

b. Reduction in and rate of systemic corticosteroid dose from entry dose

c. Topical corticosteroid use (frequency) compared to usage at registration.

3) Optic and Ocular
a. Visual acuity measured by Age-appropriate LogMAR assessment

b. Number of participants with resolution of associated optic nerve or macular oedema (as assessed by slit lamp biomicroscopy or optical coherence tomography (OCT)).

c. Number of patients who are able to reduce topical or systemic agents for ocular hypertension.

d. Number of participants with disease control (defined as zero cells, with topical treatment at 12 weeks treatment visit and 24 weeks treatment visit.)

e. Number of participants entering disease remission (defined as zero cells, without topical treatment at 12 and 24 weeks treatment visit)

f. Duration of sustaining inactive disease (zero cells, with or without topical treatment.)

g. Failure to reduce eye drops to 2 drops/day by or at the 12 weeks visit

4) Quality of Life assessment (Childhood Health Questionnaire (CHQ), Childhood Health Assessment Questionnaire (CHAQ))

5) American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 levels

6) Number participants requiring change in biologic / Disease-modifying anti-rheumatic drugs (DMARDs) therapy due to disease flare of their arthritis or failure to respond to treatment for their arthritis.

7) Number of participants undergoing flare of arthritis, in remissions on and off medication of their JIA and with minimum disease activity [27, 28]

8) Participants score of the Juvenile Arthritis Disease Activity Score (JADAS). The JADAS comprises four components: (1) physician global assessment of disease activity (2) parent/patient global assessment of well-being (3) active joint count, in 27, 71 or 10 joints; and (4) erythrocyte sedimentation rate (ESR).

10.2 Sample Size

As this is a two-stage trial the proposed sample size is a maximum of 22 patients with persistently active uveitis who have failed an anti TNF agent and are maintained on a stable dose of methotrexate (MTX).

10.3 Interim Monitoring and Analyses

The trial is designed as a two-stage procedure, with stopping being considered at a single interim analysis at the end of stage one after 10 patients have been recruited[38].

Formal interim analyses of the accumulating data will be performed at regular intervals (as described above) for review by an Independent Data Monitoring and Safety Committee (IDSMC). These analyses will be performed at the Clinical Trials Unit. The IDSMC will make recommendations to the Trial Steering Committee as to the continuation of the trial.

10.4 Analysis Plan

Before any formal analysis is carried out, a full statistical analysis plan will be written.

In the final analysis, point estimates and confidence intervals will be computed using a two-stage design in which early stopping may be allowed for either futility or efficacy[38]

11 PHARMACOVIGILANCE

11.1 Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

Adverse Event (AE)

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

Adverse Reaction (AR)

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Unexpected Adverse Reaction (UAR)

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:
In the case of a product with a marketing authorization, in the summary of product characteristics for that product
In the case of any other investigational medicinal product, in the investigator's brochure relating to the product in question.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- Other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Adverse Event of Special Interest (AESI)
The following adverse events are of special interest and their occurrence monitored:.

- Serious and/or medically significant infections
- Myocardial infarction/acute coronary syndrome (MI/ACS)
- Gastrointestinal perforations
- Malignancies
- Anaphylaxis/Hypersensitivity reactions
- Demyelinating disorders
- Stroke
- Serious and/or medically significant bleeding events
- Serious and/or medically significant hepatic events

11.2 Notes on Adverse Event Inclusions and Exclusions

11.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents
- Overdose of medication without signs or symptoms

11.2.2 Do Not Include

- Medical or surgical procedures - the condition which leads to the procedure is the adverse event
- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Prolongation of hospital stay due to social factors, for example, geographical location of the participant’s home
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient’s condition

All adverse events should be recorded in the patient's medical notes, and on the appropriate sections of the CRF.

11.2.3 Reporting of Pregnancy

Designated trial personnel will perform a serum pregnancy test at the screening visit for all post-pubertal female participants. This will be four weekly for the duration of treatment administration and a further test twelve weeks after administration of the last dose of study drug. It is recommended that contraceptive precautions should be taken up to 24 weeks after study treatment has ceased. Any pregnancy which does occur during the course of the study should be reported to the CTRC immediately as an SAE. The investigator should discuss the risks of continuing with the pregnancy with the participant and the possible effects on the foetus if they continue on trial treatment. It is at the investigator's discretion to decide whether the individual should be instructed to stop taking study drugs. All pregnancies that occur during trial treatment, or within twelve weeks of finishing treatment, need to be followed up until delivery and neonatal outcome (defined as 4 weeks from delivery) and reported separately.

11.3 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below. Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 11.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

11.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 6.
If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigators. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 6: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. N.B. An alternative cause for the AE should be given
Unlikely	There is little evidence to suggest there is a causal relationship

	(e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

11.5 Expectedness

It is not a regulatory requirement for a reporting physician to provide their opinion of expectedness. Therefore, the reporting physician at the research site will not be asked to make the assessment of expectedness. The assessment of expectedness will be made by the CI (or designated other) using the reference IB for APTITUDE following receipt of the SAE form at CTRC.

All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP and graded as serious, and also graded as **unexpected** by the CI (see reference IB for list of Expected Adverse Events) will be reported as a SUSAR.

11.6 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable. When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative); not resolved/ongoing; ongoing at final follow-up; fatal or unknown.

11.7 Reporting Procedures

All adverse events should be reported. All AE's should be reported for 30 calendar days after cessation of the investigational medicinal product. Depending on the nature of the event (AE/SAE/SAR/SUSAR) the appropriate reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the CTRC in the first instance. A flowchart is given below to aid in determining reporting requirements.

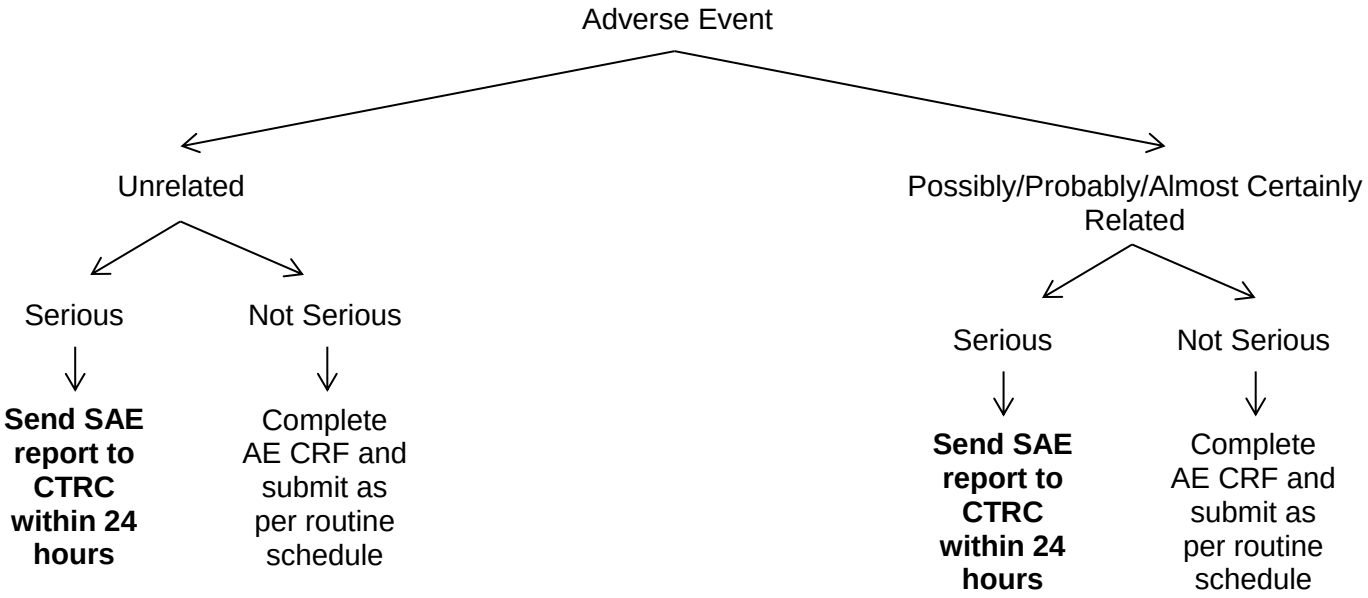
11.7.1 Non serious ARs/AEs

All such events, should be recorded on an Adverse Event Form, which should be transmitted to the CTRC following trial visit.

11.7.2 Serious ARs/AEs/SUSARs

All serious events whether related or unrelated should be reported within 24 hours of the local site becoming aware of the event. The SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The CTRC will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required locally.



11.8 Responsibilities – Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.

All SAEs must be reported immediately by the investigator to the CTRC on an SAE form unless the SAE is specified in the protocol as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Table 7: Minimum information required for reporting

Minimum information required for reporting:

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

i. The SAE form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SAEs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the CTRC. As soon as possible thereafter the responsible investigator should check the SAE form, make amendments as appropriate, sign and re-send to the CTRC. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting an SAE to the CTRC research sites should also telephone the appropriate trial co-ordinator/data manager on telephone number **0151 795 8780** to advise that an SAE report has been submitted.

iii. Send the SAE form by fax (within 24 hours) to the CTRC:

Fax Number: 0151 795 8770

If fax resources are not available at site then the SAE form should be submitted via email using SAE form provided without patient identifiable data.

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).

v. In the case of an SAE the subject must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

vi. Follow-up information is noted on another SAE form by ticking the box marked 'follow-up' and faxing to the CTRC as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
vii. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

11.9 Responsibilities – CTRC

The CTRC is undertaking duties delegated by the trial sponsor, University Hospitals Bristol NHS Foundation Trust, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and, if required, the research ethics committee as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the CTRC is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the CTRC first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

Staff at the CTRC will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SAEs received for seriousness, expectedness and causality. Investigator reports of suspected SARs will be reviewed immediately and those that are SUSARs identified and reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

The CTRC will send all copies of all SAE and AESI reports to Roche up to resolution of the event within the timeframes agreed in the safety data and exchange agreement.

11.10 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of SAE and ADR reporting rates across sites. The CTRC in conjunction with the CI and sponsor will produce and submit the Development Safety Update Reports (DSUR) containing a list of all SARs to regulatory authority and MREC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the CTRC to carry out site visits if there is suspicion of unreported AEs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

If a significant safety issue is identified, either upon receipt of an individual case report or upon review of aggregate data, e.g. by the IDSMC, this will be communicated to participating investigators as soon as possible.

11.11 Contact Details and Out-of-hours Medical Cover

Contact cards will be given to patients detailing contacts for out of hour's medical cover. No out of hours medical cover will be provided by the APTITUDE team, although local emergency clinical care out of hours will continue to be provided as per local practice. The contact card will carry information about the patient's treatment as part of the APTITUDE trial. This will enable their treating clinician in the event of an emergency, to make appropriate and informed decisions about their care.

12 ETHICAL CONSIDERATIONS

12.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

We consider the specific ethical issues relating to participation in this trial to be:

Informed consent in a paediatric population: The parent or legal representative of the child will have an interview with the investigator, or a delegated member of the investigating team, during which opportunity will be given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They will be provided with written information and contact details of a member of the research team at the centre, from whom further information about the trial may be obtained, and will be made aware of their right to withdraw the child from the trial at any time without the child or family being subject to any detriment in the child's treatment. Children will receive information, according to their capacity of understanding, about the trial and its risks and benefits and their assent will be obtained, where appropriate.

12.2 Ethical Approval

The trial protocol has received the favourable opinion of NRES committee London-South East but must undergo independent review at the R&D offices at participating sites. The local R&D office should be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to CTU before the site is initiated and patients recruited.

Proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Age and stage-of development specific Patient Information and Consent Forms (PISC) should also be implemented and patient assent obtained where appropriate. The right of the parent/ legal representative to refuse consent for the minor to participate in the trial without giving reasons must be respected. After the patient has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the patient. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis. Similarly, the parent/legal representative of the patient remains free to withdraw the patient at any time from the protocol treatment and trial follow-up without giving reasons and without prejudicing the further treatment of the minor.

12.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Written informed consent is required

for all trial participants. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. This trial will be recruiting minors and young people over the age of 16 years and informed consent processes will reflect the legal and ethical requirements to obtain valid informed consent for trial participants.

All of the recruiting investigators are experienced rheumatologists and ophthalmologists familiar with imparting information to families and young people. When potentially eligible minors and young people are identified, they/ their parent/ the person with parental responsibility will be approached by the investigator, or a designated member of the investigating team, during which an opportunity will be given to understand the objectives of the trial.

Information will be provided to potential participants and their families verbally and in writing. All will have the opportunity to discuss the project with the responsible investigator at site and/or a designated member of the research team. Discussions will be supported with detailed written and ethically approved Patient Information Sheets and Consent forms (PISC) provided directly to young people able to consent for themselves (defined in statutory instrument 2004 No.1031 as aged ≥16 years) and parents / legal guardian of minors (aged <16 years). Age and stage of development appropriate information leaflets will be provided to minors and their assent obtained, where appropriate. Careful presentation will be made of the known risks of the disease and trial medications, and possible benefits, as well as a detailed explanation of the trial procedures and protocol.

Upon completion of the above, proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the trial. Both the person obtaining consent and the parent/legal representative must personally sign and date the form. A copy of the informed consent document will be given to the parent/legal representative for their records. The original copy will be filed in the participant's medical notes and a further copy of the signed consent form will be filed in the Investigators Site File. One final copy of the consent form should be sent to the CTU.

* A mother automatically has parental responsibility for her child from birth. However, this is not the case for fathers. Conditions for fathers gaining parental responsibility varies throughout the UK and is summarised below. Practitioners should verify that the consenting parent has parental responsibility to do so.

For births registered in England and Wales
In England and Wales, if the parents of a child are married to each other at the time of the birth, or if they have jointly adopted a child, then they both have parental responsibility. Parents do not lose parental responsibility if they divorce, and this applies to both the resident and the non-resident parent. This is not automatically the case for unmarried parents. According to current law, a mother always has parental responsibility for her child. A father, however, has this responsibility only if he is married to the mother when the child is born or has acquired legal responsibility for
his child through one of these three routes:

- (from 1 December 2003) by jointly registering the birth of the child with the mother
- by a parental responsibility agreement with the mother
- by a parental responsibility order, made by a court

For births registered in Scotland
A father has parental responsibility if he is married to the mother when the child is conceived, or any time after that date. An unmarried father has parental responsibility if he is

named on the child's birth certificate (from 4 May 2006). Alternatively, unmarried fathers can also be named following a re-registration of the birth.

For births registered in Northern Ireland
A father has parental responsibility if he is married to the mother at the time of the child's birth. However he does not have parental responsibility if he marries the mother after the birth. An unmarried father has parental responsibility if he is named on the child's birth certificate (from 15 April 2002). Alternatively, unmarried fathers can also be named following a re-registration of the birth.

For births registered outside the UK
If a child is born overseas and then comes to live in the UK, the parental responsibility rules apply for the UK country in which they live.

12.3.1 Assent in minors

If capable, and under appropriate circumstances, minors should approached to provide assent by a member of the research team with experience with minors. Age-and-state-of-development IEC-approved Patient information Sheet and Assent forms, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks should be used. The minor should personally write their name and date the assent form, which is then signed by the parent/legal representative and the researcher.

Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Assent should be take where appropriate and documented in the patient notes, however the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative.

12.3.2 Minors reaching 16 years during trial participation

A participant involved in the study that reaches the age of 16 (and is therefore deemed competent to provide consent) should be re-consented at their next scheduled visit after their 16th Birthday. The same process will be followed as for competent adults aged 16-18 at the time of consent

12.4 Study Discontinuation

In the event that the study is prematurely terminated, participants will be treated according to standard clinical care. The process for participants who withdraw early from trial treatment or from the trial completely is described in section 6.3.3.

13 REGULATORY APPROVAL

This trial falls within the remit of the EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial has been registered with the MHRA and has been granted a Clinical Trial Authorisation (CTA). The CTA reference is 2015-001323-23.

14 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A detailed risk assessment is performed for each trial coordinated by the CTU to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial and are described in the Trial Monitoring Plan. Monitoring can take the form of on-site visits or central monitoring

Details of the monitoring to be carried out for the APTITUDE study are included in the APTITUDE Trial Monitoring Plan.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 17

14.1 Risk Assessment

In accordance with the CTRC SOP TM005 the trial risk assessment is completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Trial Statistician and supervising Statistician
- Information Systems team
- CTRC Director

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs propose a three level categorisation for the potential risk associated with the IMP, assigned according to the following categories:

Type A *'no higher than that of standard medical care';*
Type B *'somewhat higher than that of standard medical care';*
Type C *'markedly higher than that of standard medical care'.*

The APTITUDE trial has been categorised as a type B trial as Tocilizumab is being used for a new indication (different patient population/disease group).

This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

14.2 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the*

pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).

In order to resolve possible discrepancies between information appearing in the CRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the CRF. APTITUDE Source document lists will be produced for each site.

The CRF will be considered the source document for data where no prior record exists and which is recorded directly in the CRF.

Date(s) of conducting informed consent process and assent, where appropriate, including date of provision of patient information, registration number and the fact that the patient is participating in a clinical trial (including treatment) should be added to the patient's medical record chronologically. Where assent is appropriate but not obtained a reason should be noted in the medical record.

14.3 Data Capture Methods

The study case report form (CRF) is the primary data collection instrument for the study. All data requested on the CRF must be recorded. CTU will supply Case Report Forms (CRFs) and guidance on how the CRF should be completed.

14.4 Central Monitoring

Data stored at CTU will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data queries. Data query forms will be produced at the CTU from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond the queries providing an explanation/resolution to the discrepancies and return the data query forms to CTU. The forms will then be filed along with the appropriate CRFs and the appropriate corrections made on the database. There are a number of monitoring features in place at the CTU to ensure reliability and validity of the trial data, to be detailed in the APTITUDE monitoring plan.

14.5 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Information Sheet and Informed Consent Form provided to trial participants. Clinical site monitoring will be detailed in the APTITUDE trial monitoring plan.

14.6 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Case report forms will be labelled with the patient's initials and unique trial screening and/or registration number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The CTU will be undertaking activities requiring the transfer of identifiable data:
Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the CTU by recruiting centres, which requires that name data will be transferred to the CTU. This transfer of identifiable data is disclosed in the PISC. The CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

Relevant sections of trial participant's medical records and data collected during the study may be looked at by responsible individuals from the research team, regulatory authorities, sponsor or from their local NHS Trust, where it is relevant to the participant taking part in the study. This is detailed in the PISC and permission for this access is provided in writing at the time of registration.

14.7 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, site visits will be conducted and source verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The minimum key staff required to be recorded on the delegation log in order for the site to be eligible to be initiated will be determined by TMG;
- The PI and other key staff from each centre will attend site initiation training, coordinated by the CTU, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol;
- The Trial Coordinator at the CTU will verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;
- The Trial Management Group is to monitor screening, registration and consent rates between centres;
- Data quality checks will be undertaken in line with the APTITUDE Data Management Plan;
- Independent oversight of the trial will be provided by the Independent Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

14.8 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH

E6, Guideline for Good Clinical Practice)) including the Investigator Site File and Pharmacy Site File, until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The CTU undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The CTU will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

15 INDEMNITY

The APTITUDE trial is sponsored by University Hospitals Bristol NHS Foundation Trust and co-ordinated by the MC CTU in the University of Liverpool.

The University Hospitals Bristol NHS Foundation Trust cover for negligent harm is in place through the Clinical Negligence Scheme for Trusts. For NHS sponsored research HSG(96)48 reference no.2 refers 'If there is any negligent harm during the study when the NHS body owes a duty of care to their person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim'.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

16 FINANCIAL ARRANGEMENTS

This study is funded by Arthritis Research UK. Contractual agreements will be in place between the sponsor and collaborating sites that will describe financial arrangements. Tocilizumab is to be provided by Roche to sites for the duration of the trial.

17 TRIAL COMMITTEES

17.1 Trial Management Group (TMG)

The TMG will be responsible for the day-to-day running and management of the trial and will meet frequently during set-up and, reducing frequency as the trial progresses (at least 3 times per year). **Refer to the TMG terms of reference and trial oversight committee membership document for further details**.

17.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. **Refer to the TSC terms of reference and trial oversight committee membership document for further details**

17.3 Independent Data and Safety Monitoring Committee (IDSMC)

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety, trial conduct and external data. They will first convene to approve the protocol, agree their charter and define frequency of subsequent meetings (at least annually).
The IDSMC will provide a recommendation to the Trial Steering Committee concerning the continuation of the trial. **Refer to the IDSMC charter and trial oversight committee membership document for further details.**

18 PUBLICATION

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Trial Management Group will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial. Roche will conduct a factual accuracy check on publications and support of acknowledgment will be included in all publications

The members of the TSC and IDSMC should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

19 PROTOCOL AMENDMENTS

19.1 Version 1 09/04/2015

Original Approved version.

19.2 Version 2 28/08/2015

Page Number	Section	Change Made
10	2	Number of centres updated to 6
11	2.1	Schematic of study design corrected to show that patients who respond to treatment at 3 months complete the treatment period and do not cease trial treatment at 12 weeks
18	6.1	ILAR diagnostic criteria from inclusion criteria 1 merged with exclusion criteria 1
18	6.1	Clarification of definition of active anterior uveitis added to inclusion criteria 2
18	6.1	Inclusion criteria's 4 and 5 merged into one criteria
19	6.2	Previous registration added as an exclusion
19	6.2	Exclusion criteria updated to state that patients on oral anti-glaucoma therapy are excluded
19	6.2	Clarification added to exclusion criteria stating that patients need to be on stable eye drops for 1 week prior to screening
19	6.2	Untreated latent TB criteria from exclusion 14 added to exclusion 15
20	6.2	Exclusion criteria 29 removed as is covered in exclusion criteria 28 (immunization with live/attenuated vaccine)
20	6.2	Exclusion criteria added excluded patient who have had joint injections with 4 weeks prior to registration.
23	7.2	Method of registering patients amended to instruct sites to register patients via an online registration system
25	8.1.3	References to SmPC replace with IB
26	8.1.6	Text added stating that patients who have an increase in weight over 30kg or decrease in weight to less than 30kg should switch dosing regimen.
26	8.1.7	Text added giving guidance for interrupting trial treatment
26	8.1.8	Text added giving guidance on discontinuing trial treatment
27	9	Text added to confirm that patients should receive trial injections up to and including week 24.
27	8.1.10	Medications permitted updated to confirm that Systemic treatment with acetazolamide is not allowed
27	8.1.10	Medications permitted updated to confirm that patients need to be on stable dose of eye drops 1 week prior to screening
28	8.1.11	Medications not permitted updated to include Systemic treatment with acetazolamide is not allowed
30	9	Table of assessment updated to clarify which assessments are done at screening and which are done at registration
38	10.3	Information added confirming that interim analysis is carried out after 10 patients have been recruited
40	11.1	Adverse event of special interest list updated in line with

		AESI guidance from Roche
62	22	Appendix added giving guidance for liver function tests

19.3 Version 3 05/11/2015

Page Number	Section	Change Made
4	N/A	Trial management and monitoring details updated
10	2	Secondary outcome to develop a fully consented, trial-related Bio Bank for subsequent investigation added
13	3.3.2	Secondary outcome to develop a fully consented, trial-related Bio Bank for subsequent investigation added
30	9	Clarification to visit windows. Amendment made to minimum time needed between visits for assessing response to trial treatment.

19.4 Version 3.1 11/01/2016

Page Number	Section	Change Made
33	9.1.1.4	OCT section updated to state that macular foveal thicknes results will be collected

19.5 Version 3.2 14/07/2016

Page Number	Section	Change Made
18	5.2	JADAS added as a secondary endpoint
29	8.2	Text added instructing sites to contact trial co-ordinator for any queries relating to reduction of MTX.
31	9	Text added to state that ANA, dsDNA and ENA test should be conducted if patients stop treatment or withdraw before week 24
35	9.2.6	Text added to state that ANA, dsDNA and ENA test should be conducted if patients stop treatment or withdraw before week 24
39	10.1.2	JADAS added as a secondary endpoint
42	11.7.1	Text amended to reflect that local investigators do not assess expectedness
43	11.7.2	Flow chart amended to show that site investigators assess relationship and seriousness of adverse events only.
45	11.8	Contact details for reporting serious adverse events updated

19.6 Version 4.0 31/05/2017

Page Number	Section	Change Made
4	Contact	Trial telephone and fax details updated

	Details: Institutions	
21	6.2	White blood cell (WBC) count criteria amended to 4,000/mm3 (<4.0 x 109/L)
21	6.2	Platelet count added in 10^9/L to correspond with CRFs
21	6.2	Neutrophil count amended to < 2,000/mm3 (< 2.0 × 109/L)
23	7.1	Text added to state that full eligibility must be confirmed by a doctor on the delegation log
24	7.2	Text added to state that a patient may only be registered once full eligibility has been confirmed.
27	8.1.7	Total Bilirubinin µmol added to correspond with CRF
27	8.1.7	Neutrophil count in x10^9/L added to correspond with CRF
27	8.1.7	Platelet count in x10^9/L added to correspond with CRF
28	8.1.8	Guidance adding for discontinuing treatment for the trial and non-trial eye.
28	8.1.10	Guidance added for medication allowed in the non-trial eye
28	8.1.11	Guidance added for medication not allowed in the non-trial eye
45	11.8	Fax number for reporting SAEs updated and clarification to time point for reporting SAEs

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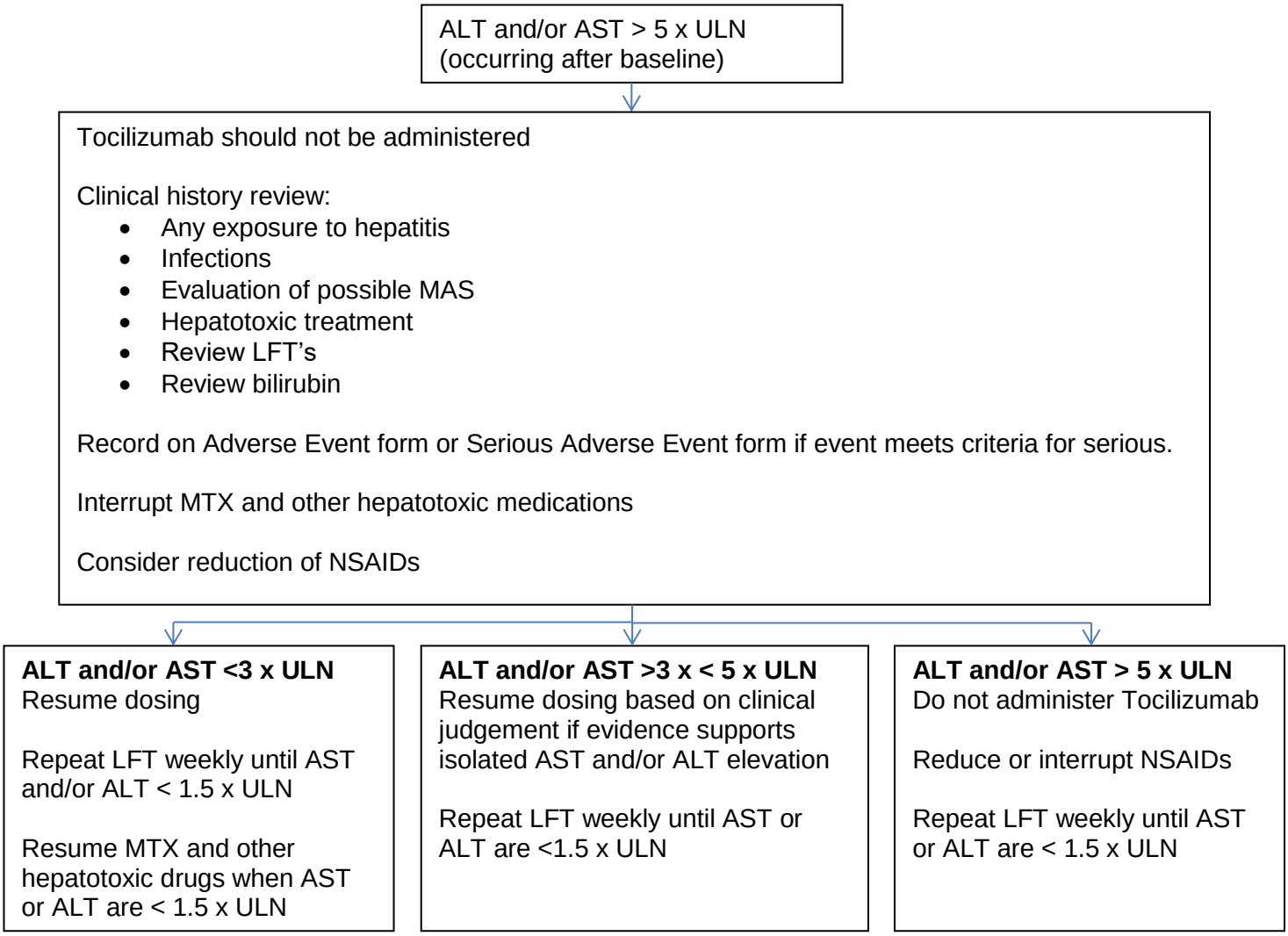
21 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

Documents referenced within the protocol that are separately maintained and version controlled are listed in the 'APTITUDE Documents Supplementary to protocol' log. Any of the supplementary documents subject to ethical review are submitted as separate version controlled documents.

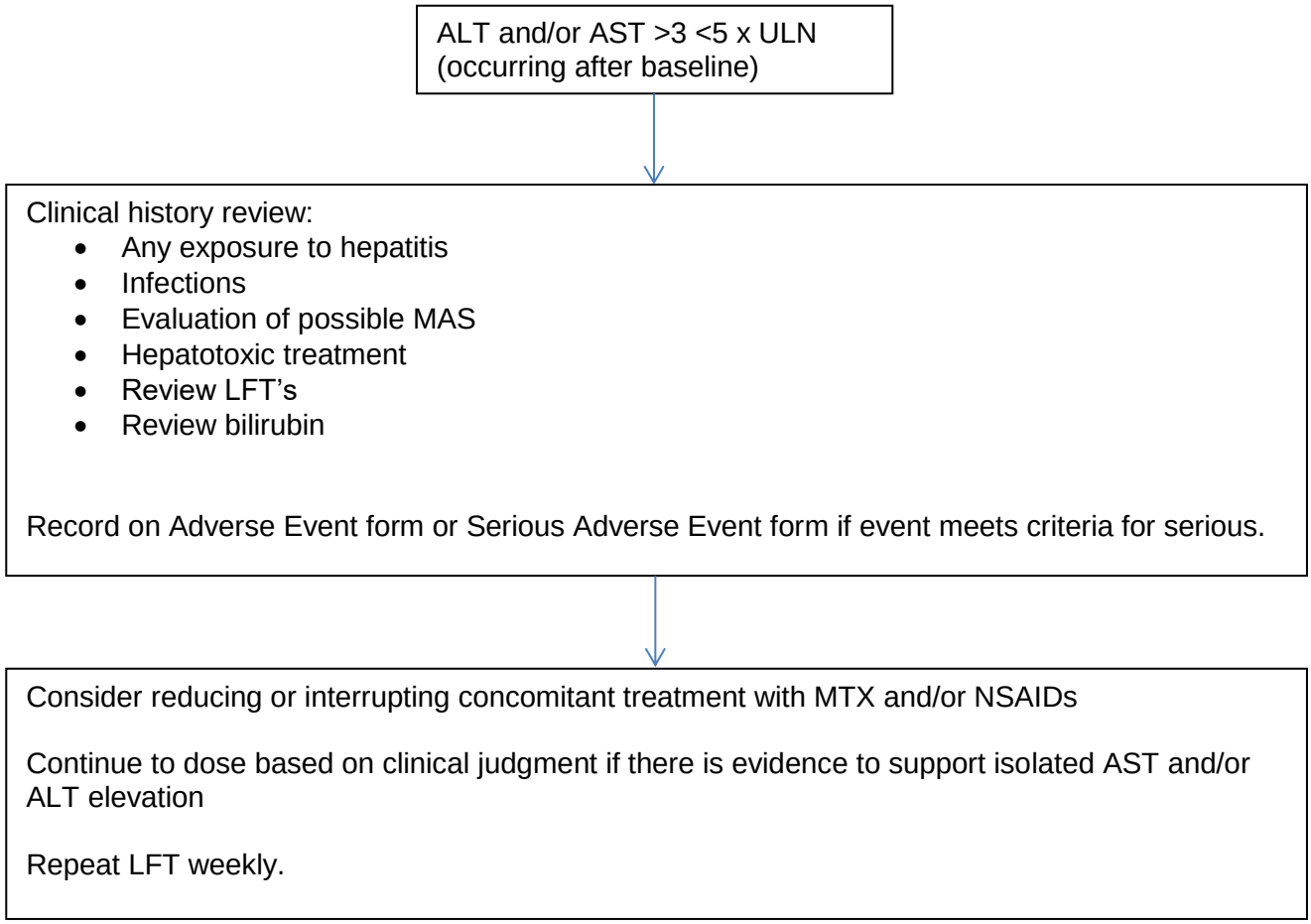
- Parent/Guardian information sheet and consent form
- Adult information sheet and consent form
- 11-15 years information sheet and assent form
- 6-10 years information sheet and assent form
- Under 5 years information sheet
- CHAQ
- CHQ
- List of participating centres
- Investigator Brochure
- Patient treatment diary
- Centre/site inclusion criteria
- Pharmacovigilance reporting guideline
- Publication policy

22 APPENDICES

Appendix A – Liver Function Test Guidance



Appendix A – Liver Function Test Guidance (continued)



ALT= alanine transaminase
AST =aspartate transaminase
LFT = liver function test
MAS= macrophage activation syndrome;
MTX= methotrexate
NSAID= nonsteroidal anti-inflammatory drug
ULN= upper limit of normal.