ISRCTN12427150 https://doi.org/10.1186/ISRCTN12427150

A study to see whether adalimumab or secukinumab is better for treating children and young people with juvenile idiopathic arthritis (JIA) associated uveitis or chronic anterior uveitis

Submission date 21/10/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 14/02/2023	**Overall study status** Ongoing	[_] Statistical analysis plan [X] Results
Last Edited 20/05/2025	**Condition category** Eye Diseases	[_] Individual participant data

Plain English summary of protocol

Background and study aims
The aim of the study is to see which treatment (Adalimumab or Secukinumab) is better for treating patients who suffer with Juvenile Idiopathic Arthritis (JIA) and Uveitis or chronic anterior Uveitis. JIA is the most common rheumatic disease in children. Around 1 in 1000 children in the UK develops JIA per year. Of these, 15-25% are at risk of inflammation of the uvea in the eye (known as uveitis). The majority of children with JIA are treated with a medication called methotrexate but over 40% need more medication to control uveitis. Adalimumab has shown to work together with methotrexate for controlling uveitis in JIA patients but for 27% of patients it didn't work. Secukinumab has shown to work in treating adults with uveitis.

Who can participate?
The study will aim to recruit 50 patients with JIA associated uveitis or chronic anterior uveitis aged 2-18 years old from around 12 hospitals across the UK.

What does the study involve?
Participants will be involved in the study for 24 weeks of treatment and then 72 weeks follow up, if they are getting better with study treatment at 24 weeks then they may be able to carry on taking study treatment in follow-up. Patients will receive an ophthalmology and rheumatology review, be asked to complete some questionnaires, complete routine assessments (pregnancy test, urinalysis, physical examination, vital signs, height and weight, routine blood samples), complete a treatment diary and provide optional biobank samples.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration

Risks:
Adalimumab has effects on the immune system and may cause the patient to develop infections and patients will be asked to notify their doctor immediately if they develop any of the following: sore throat, a fever, chicken pox, any other symptoms of infection or if the child hasn't had chicken pox and comes into contact with someone who has chicken pox or shingles. Chicken pox and shingles can be very severe in people who are treated with adalimumab and therefore an antiviral treatment may be required. Very rarely patients may develop a condition called "drug-induced lupus" while taking adalimumab, and would need to withdraw from the study treatment.

There may be a slightly increased risk of certain types of cancer in patients using an anti-TNF drug. Whilst this has not been proven it is the subject of current research.

Some patients may experience allergic reaction to either study drugs. Most reactions occur within two hours after the drug is given. Adalimumb may cause a reaction at the injection site i.e redness, swelling or pain. None of these are serious reactions. Secukinumab may make the patient more likely to develop infections and patients who develop the following should notify their doctor immediately: fever/flu-like symptoms/night sweats, tiredness/shortness of breath /cough which won't go away, warm & red painful skin/painful skin rash with blisters, burning sensation while urinating. Serious allergic reactions to Secukinumab may include: difficulty breathing or swallowing, low blood pressure causing dizziness or light-headedness, swelling of face/lips/tongue/throat, severe itching of skin with a red rash or raised bumps. Most other side effects of Secukinumab are mild to moderate and common side effects include: upper respiratory tract infections, cold sores, diarrhoea, runny nose, athlete's foot, headache, nausea, fatigue.

Both treatments have side effects, however, they are outweighed by the benefits. Both treatments have been shown to improve symptoms of JIA uveitis but it cannot be guaranteed and it is also unknown which treatment is best.

Participants and their family will be given details on who to contact if they experience any side effects, all safety events will be monitored by the research team throughout trial participant and reviewed at each trial visit.

Where is the study run from?
University Hospitals Bristol and Weston NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
October 2022 to August 2027

Who is funding the study?
Novartis (Switzerland)

Who is the main contact?
Dr Sian Drake, turtle.trial@liverpool.ac.uk
Dr Athimalaipet Ramanan, avramanan@hotmail.com

Contact information

Type(s)
Scientific

Contact name
Dr Sian Drake

Contact details
LCTC, UoL, 2nd Floor
Institute in the Park
Alder Hey Children's NHS Foundation Trust
Eaton Road
Liverpool
United Kingdom
L12 2AP
+ 44 151 794 0627
turtle.trial@liverpool.ac.uk

Type(s)
Principal investigator

Contact name
Prof Athimalaipet Ramanan

Contact details
Upper Maudlin Street
Bristol
United Kingdom
BS2 8BJ
+44 117 342 0149
avramanan@hotmail.com

Additional identifiers

Clinical Trials Information System (CTIS)
2022-003068-26

Integrated Research Application System (IRAS)
1006319

Central Portfolio Management System (CPMS)
55025

Protocol serial number
CH/2020/7101

Study information

Scientific Title
A randomised controlled trial of secukinumab versus adalimumab for the treatment of juvenile idiopathic arthritis (JIA) associated uveitis or chronic anterior uveitis using a Bayesian design

Acronym

TURTLE

Study objectives
Primary objectives:
For both stages of the trial the primary objective is to determine the response rate at 12 weeks of Secukinumab with methotrexate or mycophenolate for participants who have active uveitis. Stage 1 solely focuses on this whilst stage 2 of the trial compares Secukinumab with methotrexate or mycophenolate to Adalimumab with methotrexate or mycophenolate with regards to response rate.

Secondary objective:
To evaluate the short-term safety and tolerability of secukinumab in combination with methotrexate or mycophenolate versus adalimumab in combination with methotrexate, with regards to optic complications of treatment, adverse events and laboratory assessments.

The exploratory objective is to collect fully consented serum, DNA and RNA samples for donation to a tissue bank to be available for use for future ethically approved work.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 18/01/2023, North West - Liverpool Central Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8340; liverpoolcentral.rec@hra.nhs.uk), ref: 22/NW/0366

Primary study design
Interventional

Study design
Interventional randomized parallel group controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Juvenile Idiopathic Arthritis (JIA) Associated Uveitis or chronic anterior uveitis

Interventions
Eligible patients in the first stage (biologic refractory patients) will be registered to receive secukinumab. Patients will receive weekly secukinumab injections (75mg if weighing less than 25kg, 150mg if weighing between 25kg and less than or equal to 50kg or 300mg if weighing more 50kg for the first month then every 4 weeks thereafter. Participants who receive 150mg and 300mg of secukinumab will be administered with auto injector formulation of secukinumab. Those participants who receive 75mg of secukinumab will be administered with a pre-filled syringe.

Eligible patients in the second stage (randomised controlled trial) will be randomised between arm A – adalimumab and arm B - secukinumab. Patients in arm A will receive adalimumab (20mg /0.8ml for patients <30kg or 40mg/0.8ml for patients weighing ≥30kg, s/c injection every 2 weeks based on body weight). Patients in arm B will receive weekly secukinumab injections

(75mg if weighing less than 25kg, 150mg if weighing between 25kg and less than or equal to 50kg or 300mg if weighing more than 50kg for the first month then every 4 weeks thereafter. Participants who receive 150mg and 300mg of secukinumab will be administered with auto injector formulation of secukinumab. Those participants who receive 75mg of secukinumab will be administered with a pre-filled syringe.

Participants in arm A will receive adalimumab (20mg/0.8ml for patients <30kg or 40mg/0.8ml for patients weighing ≥30kg, s/c injection every 2 weeks based on body weight).

Participants in arm B will receive weekly secukinumab injections (75mg if weighing less than 25kg, 150mg if weighing between 25kg and less than or equal to 50kg or 300mg if weighing more than 50kg for the first month then every 4 weeks thereafter.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Secukinumab, adalimumab

Primary outcome(s)
For stage 1 the primary outcome is to determine the response rate of secukinumab at 12 weeks in combination with methotrexate or mycophenolate with regards to controlling disease activity in participants who are refractory* to adalimumab treatment. Each participant will have an assessment of treatment response after 12 weeks of trial treatment. If 3 or more participants show a 2-step improvement in the SUN grade score then the trial will progress to stage 2.

For stage 2, we want to determine the response rate at 12 weeks of secukinumab in combination with methotrexate or mycophenolate versus adalimumab in combination with methotrexate or mycophenolate with regard to controlling disease activity in refractory* uveitis associated with juvenile idiopathic arthritis. 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

*refractory refers to active uveitis with SUN ≥1+ despite treatment with MTX or MMF

Key secondary outcome(s)
1. Safety, tolerability and compliance at baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 24 weeks, 36 weeks, 48 weeks, 60 weeks, 72 weeks, 84 weeks and 96 weeks:
1.1. Adverse events (AEs), serious adverse events (SAEs) and Adverse Events of Special Interest (AESI)
1.2. Laboratory parameters (haematological and biochemical analysis and urinalysis)
1.3. Participant diaries and dosing records will determine tolerability and compliance throughout the trial treatment period
2. Response Rate
Determine the response rate at 24 weeks with regard to controlling disease activity in refractory uveitis associated with juvenile idiopathic arthritis
3. Use of Corticosteroids over duration of study period and throughout follow up (at baseline, 4

weeks, 8 weeks, 12 weeks, 16 weeks, 24 weeks, 36 weeks, 48 weeks, 60 weeks, 72 weeks, 84 weeks and 96 weeks):
3.1. Total oral corticosteroid dose
3.2. Reduction in and rate of systemic corticosteroid dose from entry dose
3.3. Topical corticosteroid use (frequency) compared to usage at randomisation.
4. Optic and Ocular at baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 24 weeks:
4.1. Visual acuity measured by Age-appropriate LogMAR assessment
4.2. Number of participants with resolution of associated optic nerve oedema (as assessed by slit lamp biomicroscopy) or macular oedema (as assessed by optical coherence tomography (OCT).
4.3. Number of patients who are able to reduce topical or systemic agents for ocular hypertension.
4.4. Number of participants with disease control (defined as zero cells, with topical treatment at 12 weeks treatment visit and 24 weeks treatment visit.)
4.5. Number of participants entering disease remission (defined as zero cells, without topical treatment at 12 and 24 weeks treatment visit)
4.6. Duration of sustaining inactive disease (zero cells, with or without topical treatment.)
4.7. Failure to reduce topical steroid eye drops to 2 drops/day by or at the 12 weeks visit
5. Quality of life at baseline, 12 weeks and 24 weeks:
Quality of Life assessment (Childhood Health Questionnaire (CHQ), (Childhood Health Assessment Questionnaire (CHAQ))
6. Rheumatology assessment at baseline, 12 weeks, 24 weeks:
American College of Rheumatology (ACR) Pedi core set criteria: at ACR30, ACR50, ACR70, ACR90 and ACR100 levels. JIA inactive disease
7. Other treatments
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.
8. Flare of arthritis at baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 24 weeks:
Number of participants undergoing flare of arthritis, in remissions on and off medication of their JIA and with minimum disease activity
9. Juvenile Arthritis Disease Activity Score at baseline, 4 weeks, 8 weeks, 12 weeks, 16 weeks, 24 weeks:
Participants score of the Juvenile Arthritis Disease Activity Score (JADAS 27). 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. Exploratory at Baseline, 12 and 24 weeks:
To collect fully consented serum, DNA and RNA samples for donation to a tissue bank. The objective is to store tissue bank samples available for use by researchers for future ethically approved work
Collection of serum, DNA and RNA samples from consented patients. The objective is to have tissue bank samples ready for future ethically approved work to take place

Completion date
18/08/2027

Eligibility

Key inclusion criteria
Stage 1
1. Children and young people aged ≥ 2 and <18 years fulfilling ILAR diagnostic criteria for JIA (all

subgroups that have uveitis) with associated uveitis, or chronic anterior uveitis with no known associated autoimmune disease
2. SUN grade ≥1+ or more for two clinic visits during the preceding 12 weeks' therapy despite MTX or MMF, adalimumab and corticosteroid therapy (both systemic and topical). The latest date of SUN grade score must be the date of the screening visit.
3. They must have failed adalimumab ((< 30kg 20mg every 2 weeks, > 30 kgs 40mg every 2 weeks).) during the 12 weeks prior to screening. The participant must have been on MTX or MMF for at least 12 weeks* and have been on a stable dose for 4 weeks prior to screening visit.
4. No Disease modifying immunosuppressive drugs, other than MTX or MMF, in the 4 weeks prior to screening
5. Participant and parent/legal guardian willing and able to comply with protocol requirements and provide written informed consent, and assent where appropriate.
6. For participants of reproductive potential (males and females), use of a reliable means of contraception throughout their trial participation. Post pubertal females must have a negative serum pregnancy test within 10 days before the first dose of trial drug.
7. Able to be registered and commence trial treatment within 2 weeks of the screening visit.

Stage 2
1. Children and young people aged ≥ 2 and <18 years fulfilling ILAR diagnostic criteria for JIA (all subgroups that have uveitis) with associated uveitis, or chronic anterior uveitis with no known systemic autoimmune disease .
2. SUN grade ≥1+ or more for two clinic visits during the preceding 12 weeks' therapy despite MTX and corticosteroid (both systemic and topical) therapy". The latest date of SUN grade score must be the date of the screening visit.
3. They must have failed MTX (minimum dose of 10-20mg/m2, with a maximum dose of 25mg /participant) or MMF (minimum dose of 300/m2 twice a day to maximum dose 600/m2 twice a day). The participant must have been on MTX or MMF for at least 12 weeks* and have been on a stable dose for 4 weeks prior to screening visit.
4. No Disease modifying immunosuppressive drugs, other than MTX or MMF, in the 4 weeks prior to screening
5. Participant and parent/legal guardian willing and able to comply with protocol requirements and provide written informed consent, and assent where appropriate.
6. For participants of reproductive potential (males and females), use of a reliable means of contraception throughout their trial participation. Post pubertal females must have a negative serum pregnancy test within 10 days before the first dose of trial drug.
7. Able to be randomised and commence trial treatment within 2 weeks of the screening visit.

* Omission of a maximum of 2 weeks MTX or MMF treatment within the 12 weeks is acceptable and will not render the patient ineligible unless they have missed 2 weeks of treatment in the 4 weeks prior to the screening visit.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Child

Lower age limit

2 Years

Upper age limit
18 Years

Sex
All

Key exclusion criteria
Eligibility Criteria for Biologic Refractory Participants (stage 1)
1. Uveitis associated with infection, or history of ocular herpetic disease
2. Active inflammatory disease other than JIA and Uveitis
3. Currently on a biologic agent or has previously received any other biologic agent (other than adalimumab.)
4. Have been on adalimumab within previous 4 weeks
5. Currently on more than 1 disease-modifying anti-rheumatic drug (DMARD)
6. Chronic uncontrolled JIA and/or uveitis for more than 52 weeks
7. More than 6 topical steroid eye drops per eye, per day prior to screening (this dose must have been stable for at least 4 weeks prior to registration)
8. For patients on Prednisone or Prednisone equivalent, dose >0.2mg/kg per day or change of dose within 4 weeks prior to registration
9. Intra-articular joint injections within 4 weeks prior to registration
10. History or current diagnosis of Electrocardiogram (ECG) abnormalities indicating significant risk of safety for patients participating in the study such as:
10.1. Concomitant clinically significant cardiac arrhythmias, e.g., sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
10.2. History of familial long QT syndrome or known family history of Torsades de Pointes.
11. Underlying metabolic, hematologic, renal, hepatic, pulmonary, neurologic, endocrine, cardiac, infectious or gastrointestinal conditions which in the opinion of the Investigator immunocompromises the subject and/or places the subject at unacceptable risk for participation in a study with an immunomodulatory treatment.
12. History of active tuberculosis of less than 24 weeks treatment or untreated latent TB or evidence of Latent TB (positive QuantiFERON or PPD at screening) but unwilling or unable to complete a minimum of 4 weeks of latent TB treatment before initiating treatment with secukinumab
13. Participant has history of central nervous system (CNS) neoplasm, active CNS infection, demyelinating disease, or any progressive or degenerative neurological disease
14. Poorly controlled diabetes or persistently poorly controlled severe hypertension (>95th percentile for height / age) as deemed by the treating physician
15. Previous history of malignancy
16. Intraocular surgery within the 12 weeks prior to screening (cataract/ glaucoma/ vitrectomy)
17. Peri-ocular corticosteroids within 4 weeks prior to screening or intraocular steroid at any time.
18. Pregnant or nursing female
19. Demonstrations of clinically significant deviations in any of the following laboratory parameters:
19.1. Screening total white blood cell (WBC) count < 3,000/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL or haemoglobin < 8.5 g/dL (85 g/L). Any single parameter may not exceed 2 x upper limit of normal (ULN). A single parameter elevated up to and including 2 x ULN should be re-checked once more as soon as possible, and in all cases, at least prior to baseline, to rule out lab error.

19.2. Serum bilirubin exceeding the value of 1.6 mg/dL (27 µmol/L).
20. Having been administered a live or attenuated vaccine within 12 weeks prior to screening
21. Previous entry into either arm of the trial or first stage of the trial.
22. Intra-ocular pressure <6mm Hg , Intra-ocular pressure > 25mm Hg or intraocular pressure requiring systemic acetazolamide
23. Participated in a trial of a medicinal product within 4 weeks prior to screening visit.
24. History of hepatitis B virus
25. Any contraindications to secukinumab
Exclusion criteria in stage 2 allows participants who have taken another biologic to be included, stage 1 is just looking for participants who have taken adalimumab only previously.

Date of first enrolment
01/03/2023

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
University Hospitals Bristol NHS Foundation Trust
Trust Headquarters
Marlborough Street
Bristol
United Kingdom
BS1 3NU

Study participating centre
Alder Hey Children's NHS Foundation Trust
Eaton Road
Liverpool
United Kingdom
L12 2AP

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Queen Victoria Road
Newcastle upon Tyne

United Kingdom
NE1 4LP

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Sheffield Children's NHS Foundation Trust
Clarkson Street
Sheffield
United Kingdom
S10 2TQ

Study participating centre
University Hospitals of Leicester NHS Trust
Groby Road
Leicester
United Kingdom
LE3 9QP

Study participating centre
Manchester University NHS Foundation Trust
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Royal Hospital for Children and Young People, Edinburgh NHS Lothian
50 Little France Crescent
Edinburgh bio Quarter
Edinburgh
United Kingdom
EH16 4TJ

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
The Old Schools
Trinity Lane
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Great Ormond Street Hospital for Children NHS Foundation Trust
Great Ormond Street
London
United Kingdom
WC1N 3JH

Study participating centre
The Leeds Teaching Hospitals NHS Trust
Leeds General Infirmary
Leeds
United Kingdom
LS1 3EX

Sponsor information

Organisation
University Hospitals Bristol and Weston NHS Foundation Trust

Funder(s)

Funder type
Industry

Funder Name
Novartis

Alternative Name(s)
Novartis AG, Novartis International AG

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
Access to the anonymised datasets can be requested by contacting the Chief Investigator avramanan@hotmail.com

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		19/05/2025	20/05/2025	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes