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Treatment of inflammation inside the eye caused by an overactive immune system (autoimmune uveitis) using adalimumab

Submission date 25/03/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 14/04/2020	**Overall study status** Ongoing	
Last Edited 25/03/2025	**Condition category** Eye Diseases	

Plain English summary of protocol

Background and study aims

Autoimmune uveitis is a term for several rare eye diseases in which the body's own immune system causes sight-threatening damage to the light sensitive retina at the back of the eye. Uveitis causes sight loss from inflammation inside the eye, damage to blood vessels in the retina or leakage of fluid into the central, most sensitive area of the retina. Two in 10,000 people are at risk of serious sight loss from uveitis. Usual treatment for autoimmune uveitis involves low dose steroids and one or two other drugs to reduce inflammation. Unfortunately, many patients do not respond to or tolerate usual treatment, or they need high dose steroids to control the uveitis. Long term high dose steroids increase the risk of heart attack, stroke, and infection and affect physical and mental health. Adalimumab is a drug that targets chemicals released by inflamed tissue, neutralising their damage to the body. This study aims, first, to identify patients who are most likely to benefit from adalimumab. Then, in patients who are successfully treated with adalimumab and low dose steroids, a randomised controlled trial will be conducted to compare adalimumab and placebo.

Who can participate?

Adults over 18 years, with sight-threatening autoimmune non-infectious uveitis and is prescribed corticosteroids greater than 5.0 mg/day.

What does the study involve?

All eligible patients who consent will be given adalimumab for a 16-week trial period, if necessary in combination with low dose of steroids; these patients will include those with impaired vision due to uveitis, requiring high dose steroids to bring the disease under control, and those with better vision but who require high dose steroids to keep the uveitis under control. Over the 16 weeks, doctors will aim to reduce the steroid dose to a low level that should not cause side effects.

Then, patients who are successfully treated with adalimumab and low dose steroids will enter the main study. They will be given adalimumab or a dummy treatment, in combination with their other medications (including low dose steroids). Chance will determine who receives which treatment and neither patients nor their eye doctors will know. Regular eye examinations, tests

and questionnaires will be used to assess how well patients are doing. This part of the study, which will treat and follow up patients for 12 to 30 months, will find out whether adalimumab is better at preventing recurrence of uveitis than the dummy treatment and whether adalimumab is cost-effective compared to the dummy treatment.

What are the possible benefits and risks of participating?
The study cannot promise any benefits to participants but the information we get from this study will help improve the treatment of people with uveitis. Patients who are currently not eligible for adalimumab on the NHS could benefit from being prescribed it as part of this study. Participants might be able to reduce their dose of corticosteroids if taking adalimumab. It is possible, but cannot be guaranteed, that participants will eventually be able to stop taking at least one of their other immunosuppression medications.
There is a small risk of permanent eye damage from uveitis if participants are allocated to the placebo group, although the risk is the same as if they were receiving normal NHS care and not taking adalimumab. To minimise this risk, participants will be closely monitored with frequent enough hospital visits that if their condition relapses it should be picked up by their eye doctor before permanent uveitis damage occurs. In both group, injections under the skin can be mildly sore, and participants can get a reaction at the injection site. Adalimumab can cause side effects, although not everybody gets them. Most side effects are mild to moderate. However, some may be serious and require treatment. Side effects may occur up to four months or more after the last adalimumab injection.

Patient and public involvement
Patients with uveitis have contributed to the study from the start, helping to: design the protocol to ensure it applies to uveitis patients who may benefit; co-authoring the lay summary; helping to draft the application, providing feedback on the trial design and participating in a national survey to assess support for the study. They will continue to contribute in these ways and provide support to patients. The research team includes eye doctors and researchers with expertise in doing eye studies.

Where is the study run from?
Bristol Trials Centre (UK)

When is the study starting and how long is it expected to run for?
November 2020 to June 2026

Who is funding the study?
National Institute for Health Research (UK)

Who is the main contact?
Kirsty Lanyon, astute-trial@bristol.ac.uk

Study website
https://www.bristol-trials-centre.bristol.ac.uk/studies/astute/

Contact information

Type(s)
Public

Contact name

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Additional identifiers

EudraCT/CTIS number
2020-000754-97

IRAS number
271051

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
IRAS 271051, CPMS 45139

Study information

Scientific Title
The ASTUTE trial: Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness: a randomized controlled trial

Acronym
ASTUTE

Study objectives
The trial hypothesises that adalimumab reduces the hazard of treatment failure in patients with autoimmune non-infectious uveitis (ANIU), after weaning of corticosteroids (CS) to less than or equal to 5 mg/day in a treatment run-in period.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 03/06/2020, South Central - Oxford B Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, United Kingdom; +44 (0)2071048046; oxfordb.rec@hra.nhs.uk), ref: 20/SC/0153

Study design

Double-blind parallel multi-centre randomized placebo-controlled trial with open-label treatment run-in period

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Autoimmune non-infectious uveitis

Interventions
Current interventions as of 25/03/2025:
All participants start on open-label adalimumab for 16 weeks.

Participants who respond to adalimumab are randomised to adalimumab or placebo for up to 128 weeks.

Randomisation is concealed and done by an online computer program after data to confirm eligibility is recorded.

Adalimumab (Imraldi) and placebo
Dose: 80mg followed by 40mg every 2 weeks, starting 1 week after the initial dose.

During the treatment run-in phase, data are collected at week 4, week 8, and week 16.
During the RCT phase, data is collected at 12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, 128 weeks, 144 weeks and 160 weeks.

Open-Label Extension: active patients were approached to consent to being unmasked to their current allocation. Patients allocated to placebo no longer receive the study drug, and patients allocated to adalimumab will continue to receive the study drug until the end of the follow-up period. Patients who did not consent to transition to the Open-Label Extension were withdrawn from the study.

Previous interventions:
All participants start on open-label adalimumab for 16 weeks.

Participants who respond to adalimumab are randomised to adalimumab or placebo for up to 128 weeks.

Randomisation is concealed and done by an online computer program after data to confirm eligibility is recorded.

Adalimumab (Imraldi) and placebo
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During the RCT phase, data is collected at 12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, and 128 weeks.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Adalimumab

Primary outcome measure
Current primary outcome measure as of 25/03/2025:
Time to the first treatment failure (TF) assessed at each visit after randomisation (12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, 128 weeks, 144 weeks and 160 weeks)
i.e. TF may occur in either eye and may be triggered by incident ANIU in an eye that did not previously have ANIU. TF is defined as a composite of standard criteria reflecting clinical decision-making, including visual acuity and clinical signs of active inflammation, which have been used successfully in other ANIU trials. Participants will be assessed for TF at each visit after randomisation. Any of the following criteria in one or both eyes, where applicable, will constitute TF:
1. greater than or equal to 15 letter decrease in best-corrected visual acuity (BCVA), compared to BCVA measured by an optometrist masked to treatment allocation at the 16-week treatment run-in (TRI) visit
2. new active inflammatory chorioretinal lesions
3. greater than 20% increase in central macular thickness (CMT), compared to CMT at the 16-week TRI timepoint
4. onset or worsening of retinal vasculitis
5. 2-step worsening of vitreous haze cf. compared to best score at either the 8- or 16-week TRI visit
vi. prescription by a masked clinician of greater than 5mg/day corticosteroids to maintain disease remission (i.e. to avert relapse before any of the above criteria for manifest active disease (i-v))

Previous primary outcome measures:
Time to the first treatment failure (TF) assessed at each visit after randomisation (12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, and 128 weeks)
i.e. TF may occur in either eye and may be triggered by incident ANIU in an eye that did not previously have ANIU. TF is defined as a composite of standard criteria reflecting clinical decision-making, including visual acuity and clinical signs of active inflammation, which have been used successfully in other ANIU trials. Participants will be assessed for TF at each visit after randomisation. Any of the following criteria in one or both eyes, where applicable, will

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1. greater than or equal to 15 letter decrease in best-corrected visual acuity (BCVA), compared to BCVA measured by an optometrist masked to treatment allocation at the 16-week treatment run-in (TRI) visit
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5. 2-step worsening of vitreous haze cf. compared to best score at either the 8- or 16-week TRI visit
vi. prescription by a masked clinician of greater than 5mg/day corticosteroids to maintain disease remission (i.e. to avert relapse before any of the above criteria for manifest active disease (i-v))

Secondary outcome measures

Current primary outcome measure as of 25/03/2025:
At 12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, 128 weeks, 144 weeks and 160 weeks, unless otherwise noted.
1. Individual treatment failure (TF) components, assessed at each trial visit
2. Retinal morphology (OCT; macular and retinal nerve fibre layer), assessed at each trial visit
3. Adverse events, assessed at each trial visit
4. Health-related quality of life measured using the EQ-5D-5L questionnaire at the start of treatment run-in (TRI), at 16 weeks immediately before randomisation, then 12-weekly after randomisation up to week 48 and 16-weekly thereafter
5. Patient-reported symptoms of side-effects at each trial visit after starting the TRI and at any interim attendance prompted by an adverse event
6. Patient-reported visual function at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter
7. Best corrected visual acuity (BCVA) assessed at each trial visit
8. Employment status at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter
9. Resource use during follow-up after randomisation, at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter

Previous secondary outcome measures as of 13/12/2023 to 25/03/2025:
At 12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, and 128 weeks unless otherwise noted.
1. Individual treatment failure (TF) components, assessed at each trial visit
2. Retinal morphology (OCT; macular and retinal nerve fibre layer), assessed at each trial visit
3. Adverse events, assessed at each trial visit
4. Health-related quality of life measured using the EQ-5D-5L questionnaire at the start of treatment run-in (TRI), at 16 weeks immediately before randomisation, then 12-weekly after randomisation up to week 48 and 16-weekly thereafter
5. Patient-reported symptoms of side-effects at each trial visit after starting the TRI and at any interim attendance prompted by an adverse event
6. Patient-reported visual function at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter
7. Best corrected visual acuity (BCVA) assessed at each trial visit
8. Employment status at the start of TRI, at 16 weeks immediately before randomisation, 12-

weekly up to week 48 and 16 weekly thereafter
9. Resource use during follow-up after randomisation, at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter

Previous secondary outcome measures:
At 12 weeks, 24 weeks, 36 weeks, 48 weeks, 64 weeks, 80 weeks, 96 weeks, 112 weeks, and 128 weeks unless otherwise noted.
1. Individual treatment failure (TF) components, assessed at each trial visit
2. Retinal morphology (OCT; macular and retinal nerve fibre layer), assessed at each trial visit
3. Adverse events, assessed at each trial visit
4. Health-related quality of life measured using the EQ-5D-5L questionnaire at the start of treatment run-in (TRI), at 16 weeks immediately before randomisation, then 12-weekly after randomisation up to week 48 and 16-weekly thereafter
5. Patient-reported symptoms of side-effects at each trial visit after starting the TRI and at any interim attendance prompted by an adverse event
6. Patient-reported visual function at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter
7. Employment status at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter
8. Resource use during follow-up after randomisation, at the start of TRI, at 16 weeks immediately before randomisation, 12-weekly up to week 48 and 16 weekly thereafter

Overall study start date
01/04/2020

Completion date
30/06/2026

Eligibility

Key inclusion criteria
Current inclusion criteria as of 21/11/2023:
1. Aged 18 years or over
2. Participant has:
2.1. Active sight-threatening ANIU (active inflammatory chorioretinal lesions OR abnormal central macular thickness (CMT) OR evidence of retinal vasculitis OR vitreous haze >0.5) and is being prescribed (already taking or being started on, if newly presenting with ANIU) oral prednisolone >5.0 mg/day; OR
2.2. Has controlled ANIU and is being prescribed oral prednisolone >5.0 mg/day.
3. Women must have a negative pregnancy test and be willing to use effective contraception for the duration of the participation in the trial and for 5 months after, or be surgically sterile or post-menopausal for >12 months
4. Able to provide informed consent

Previous inclusion criteria:
1. Aged 18 years or over
2. Sight-threatening ANIU and is prescribed CS greater than 5.0 mg/day
3. Women must have a negative pregnancy test and be willing to use effective contraception for the duration of the participation in the trial and for 5 months after, or be surgically sterile or post-menopausal for >12 months
4. Able to provide informed consent

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
174

Total final enrolment
115

Key exclusion criteria
Current participant exclusion criteria as of 06/07/2022:
1. Participant has controlled ANIU and is maintained on oral prednisolone ≤5.0mg/day at the time of screening
2. Participant has systemic disease (whether associated with ANIU or not) that is being treated with steroids and requires >5mg/day oral prednisolone
3. Participant has untreated or active tuberculosis
4. Participant has severe infection, sepsis, or opportunistic infection
5. Participant has uncontrolled glaucoma
6. Participant has multiple sclerosis
7. Participant is HIV positive
8. Participant has hepatitis B or hepatitis C
9. Participant has syphilis
10. Participant has Lyme disease
11. Participant has Behcet's disease
12. Participant has toxoplasmosis chorioretinitis
13. Participant has heart failure (NYHA III/IV)
14. Participant has been diagnosed with cancer <5 years ago
15. Participant is undergoing monitoring for recurrence of cancer/tumour growth where their oncologist has concern that a TNFalpha inhibitor would be contraindicated
16. Participant is taking another biologic drug
17. Participant has taken an anti-TNF drug within the previous 90 days (anakinra and abatacept are contraindicated);
18. Participant has had an Iluvien® implant within the previous 18 months and has controlled ANIU, or has had an Iluvien® implant within the previous 12 weeks regardless of whether ANIU is active or controlled
19. Participant has had an Ozurdex® implant, or an intravitreal steroid injection, or periocular steroid within the previous 12 weeks regardless of whether ANIU is active or controlled
20. Participant is pregnant
21. Participant has a known allergy or hypersensitivity to adalimumab or any of its excipients

22. Participant is taking part in another interventional study
23. Participant has an epiretinal membrane likely to prevent an eye meeting response criterion at 16 weeks of central macular thickness <320um

Previous exclusion criteria as of 08/06/2020:
1. Participant has controlled ANIU and is maintained on CS ≤5.0mg/day at the time of screening
2. Participant has untreated or active tuberculosis
3. Participant has severe infection, sepsis or opportunistic infection
4. Participant has uncontrolled glaucoma
5. Participant has multiple sclerosis
6. Participant is HIV positive
7. Participant has hepatitis B or hepatitis C
8. Participant has syphilis
9. Participant has Lyme disease
10. Participant has Behcet's disease
11. Participant has heart failure (NYHA III/IV;
12. Participant has been diagnosed with cancer <5 years ago
13. Participant is undergoing monitoring for recurrence of cancer/tumour growth where their oncologist has concern that a TNFalpha inhibitor would be contraindicated
14. Participant is taking another biologic drug
15. Participant has taken an anti-TNF drug within the previous 90 days (anakinra and abatacept are contraindicated)
16. Participant has an ocular CS implant within the previous 12 months or an intravitreal steroid injection within the previous 3 months
17. Participant is pregnant
18. Participant has a known allergy or hypersensitivity to adalimumab or any of its excipients
19. Participant is taking part in another interventional study

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Previous exclusion criteria:
1. Controlled ANIU and is maintained on CS less than or equal to 5.0 mg/day at the time of screening
2. Untreated or active tuberculosis
3. Severe infection, sepsis or opportunistic infection
4. Uncontrolled glaucoma
5. Multiple sclerosis
6. HIV positive
7. Hepatitis B or hepatitis C
8. Behcet’s disease
9. Heart failure (NYHA III/IV)
10. No history of varicella or does not have varicella antibodies
11. Taking another biologic drug
12. Taken an anti-TNF drug within the previous 90 days (anakinra and abatacept are contraindicated)
13. Ocular CS implant within the previous 12 months or an intravitreal steroid injection within the previous 3 months
14. Pregnant
15. Known allergy or hypersensitivity to adalimumab or any of its excipients
16. Taking part in another interventional study

Date of first enrolment

01/12/2020

Date of final enrolment
07/06/2024

Locations

Countries of recruitment
England

United Kingdom

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

Study participating centre
John Radcliffe Hopsital
Oxford University Hospitals NHS Foundation Trust
Headley Way
Oxford
United Kingdom
OX3 9DU

Study participating centre
Royal Liverpool Hospital
Royal Liverpool and Broadgreen University Hospitals NHS Trust
Prescot Street
Liverpool
United Kingdom
L7 8XP

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

Study participating centre
York Hospital
York Teaching Hospital NHS Foundation Trust
Wigginton Road
York
United Kingdom
YO31 8HE

Study participating centre
Leicester Royal Infirmary
University Hospitals of Leicester NHS Trust
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Queen Elizabeth Hospital
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Edgbaston
Birmingham
United Kingdom
B15 2GW

Study participating centre
Addenbrookes Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge
United Kingdom
CB2 0QQ

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

Study participating centre
Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
St. James's University Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Moorfields Eye Hospital
Moorfields Eye Hospital NHS Foundation Trust
162 City Rd
London
United Kingdom
EC1V 2PD

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
St Thomas' Hospital
Guy’s and St Thomas’ NHS Foundation Trust
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Royal Hallamshire Hospital
Sheffield Teaching Hospitals NHS Foundation Trust
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Maidstone and Tunbridge Wells NHS Trust
The Maidstone Hospital
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
The James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Sussex Eye Hospital
Royal Sussex County Hospital
University Hospitals Sussex NHS Foundation Trust
Eastern Road
Brighton
United Kingdom
BN2 5BF

Sponsor information

Organisation
University Hospitals Bristol and Weston NHS Foundation Trust

Sponsor details
Marlborough Street
Bristol
England

United Kingdom
BS1 3NU
+44 (0)1173420233
research@uhbw.nhs.uk

Sponsor type
Hospital/treatment centre

Website
https://www.uhbw.nhs.uk/

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Results will be published in peer-reviewed medical journals and presented at professional conferences. Results will be disseminated via patient groups, on the trial web-page and publicised on social media. A summary of the results will be sent to participants who specify that they would like to receive them.

Intention to publish date
01/07/2026

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. (Contact the chief investigator Prof Andrew Dick; Email: a.dick@bristol.ac.uk. Data will be made available after the trial outcomes paper is published in a peer-reviewed journal; applicants must provide an as a minimum a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research; de-identified data will be available indefinitely; consent from participants for secondary use of data will be obtained; patient identifiable data will never be shared with third parties.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	version v3.0	20/05/2020	06/11/2020	No	No
Protocol file	version V4.0	15/10/2020	19/11/2020	No	No
Protocol file	version 6.0	11/11/2021	21/03/2022	No	No
Protocol file	version 7.0	25/04/2022	06/07/2022	No	No
Protocol file	version 8.0	29/07/2022	23/01/2023	No	No
HRA research summary			28/06/2023	No	No
Protocol article		24/01/2024	25/01/2024	Yes	No
Protocol file	version 9.0	31/10/2023	25/03/2025	No	No
Protocol file	version 10.0	12/07/2024	25/03/2025	No	No
Protocol file	version 11.0	10/09/2024	25/03/2025	No	No