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Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness—a protocol for a randomised controlled trial (ASTUTE trial)

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ABSTRACT

Introduction Adalimumab is an effective treatment for autoimmune non-infectious uveitis (ANIU), but it is currently only funded for a minority of patients with ANIU in the UK as it is restricted by the National Institute for Health and Care Excellence guidance. Ophthalmologists believe that adalimumab may be effective in a wider range of patients. The Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness (ASTUTE) trial will recruit patients with ANIU who do and do not meet funding criteria and will evaluate the effectiveness and cost-effectiveness of adalimumab versus placebo as an add-on therapy to standard care.

Methods and analysis The ASTUTE trial is a multicentre, parallel-group, placebo-controlled, pragmatic randomised controlled trial with a 16-week treatment run-in (TRI). At the end of the TRI, only responders will be randomised (1:1) to 40 mg adalimumab or placebo (both are the study investigational medicinal product) self-administered fortnightly by subcutaneous injection. The target sample size is 174 randomised participants. The primary outcome is time to treatment failure (TF), a composite of signs indicative of active ANIU. Secondary outcomes include individual TF components, retinal morphology, adverse events, health-related quality of life, patient-reported side effects and visual function, best-corrected visual acuity, employment status and resource use. In the event of TF, open-label drug treatment will be restarted as per TRI for 16 weeks, and if a participant responds again, allocation will be switched without unmasking and treatment with investigational medicinal product restarted.

Ethics and dissemination The trial received Research Ethics Committee (REC) approval from South Central – Oxford B REC in June 2020. The findings will be presented at international meetings, by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The trial population evaluates adalimumab in a range of patients instead of those for whom the National Institute for Health and Care Excellence (NICE) currently recommends its use and reflects the views of experts regarding the population in whom it is likely to have benefit.
⇒ The trial is pragmatic using standard National Health Service logistics with patients self-administering the investigational medicine product as they would in usual care.
⇒ The treatment run-in (TRI) feature means only responders will be randomised.
⇒ Being able to repeat the TRI and switch allocation after treatment failure provides reassurance to responders about having access to adalimumab in the event of being randomised to placebo.
⇒ The follow-up schedule mirrors the usual care pathway; this is familiar, efficient and reassuring to patients.

Trial registration ISRCTN31474800. Registered 14 April 2020.

INTRODUCTION

Autoimmune non-infectious uveitis (ANIU) is a group of inflammatory conditions that can affect both the anterior chamber (iris and ciliary body) and posterior segment (vitreous, retina and choroid) of the eye. It has been reported to affect 115.3/100 000 patients with an incidence of 52.4/100 000.[1] For about 20% of patients, ANIU is sight threatening, and although rare, ANIU is estimated to be

the third leading cause of blindness in high-income countries.[2] Usual care is immunomodulatory treatment (IMT) aiming to maintain remission with low-dose or no corticosteroids (CS).[3 4] However, IMT fails for 40% of patients with sight-threatening ANIU,[5–7] that is, 8% of all patients, who are usually treated with long-term high-dose oral CS but at the cost of significant morbidity; ≥7.5 mg CS/day increases the risk of heart attack, stroke and other systemic and ocular comorbidities.[8–11] In one UK cross-sectional study, 61% of patients with sight-threatening ANIU were taking 40 mg CS/day.[12] Another UK study found that 33% of patients with uveitis were prescribed high-dose CS in the previous 12 months.[13] Intravitreal steroid is an alternative but is not suitable for many patients with ANIU because of side effects or failure to treat systemic disease.[14]

Systematic reviews of drugs inhibiting tumour necrosis factor alpha (TNFa) conclude that adalimumab is beneficial for ANIU refractory to IMT.[15 16] Two multicentre randomised controlled trials (RCTs) reported that adalimumab delays treatment failure (TF).[17 18] The applicability of these results to patients in the UK is uncertain. The trials had selective inclusion criteria and did not study adalimumab as an add-on therapy, and the most important sight-threatening complication of uveitis, cystoid macular oedema, was not an eligibility criterion or a primary outcome event. Furthermore, the presence of anterior chamber inflammation was a primary outcome event, whereas this can be treated with an adjunctive topical CS and is not considered as TF. The National Institute for Health and Care Excellence (NICE) only recommends treatment for patients who meet the eligibility criteria for the Efficacy and Safety of Adalimumab in Patients with Active Uveitis (VISUAL1) trial.[17 19]

The Adalimumab vs placebo as add-on to Standard Therapy for autoimmune Uveitis: Tolerability, Effectiveness and cost-effectiveness (ASTUTE) trial was set up because ophthalmologists consider that adalimumab is effective in a wider range of patients with ANIU than eligible for inclusion in the VISUAL1 trial.[17] The ASTUTE trial will compare the effectiveness and cost-effectiveness of adalimumab with placebo when used to treat ANIU in either or both eyes in patients taking ≤5 mg oral CS/day and other IMT drugs, as required.

Specific objectives are to estimate (1) the effectiveness of adalimumab in reducing the hazard of TF between groups, (2) differences between groups for a range of secondary outcomes, (3) the cost-effectiveness of adalimumab compared with usual care in a National Health Service (NHS) setting and (4) associations between patient factors and ocular and retinal signs on enrolment with responder status and emerging participant phenotypes associated with TF.

METHODS AND ANALYSIS

Trial design and population

The ASTUTE trial is a multicentre, parallel-group, placebo-controlled, pragmatic RCT with a treatment run-in (TRI). In the TRI, eligible participants will receive open-label adalimumab for 16 weeks. At 16 weeks, participants will be assessed, and only those classified as having a therapeutic response will be randomised. The study schema is shown in figure 1.

The target population is adults with active or controlled ANIU. To inform future coverage by health systems and insurers for all patients in whom add-on adalimumab may be indicated, we will recruit patients to the TRI who are and are not covered by NICE guidelines.[19] When approached, both new patients and existing patients may be receiving a range of non-biological IMT including CS, at the discretion of their clinicians.

The study opened to recruitment, 7 months behind target, on 25 June 2021 following delays experienced as a result of the COVID-19 pandemic. Recruitment is due to end on 31 November 2024 and full study completion including the reporting of results on 31 June 2026.

Eligibility criteria

A patient may take part in the study if all of the following apply:

1. 18 years or over.
2. Has (a) 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 >5.0 mg CS/day or (b) has controlled ANIU and is being prescribed >5.0 mg CS/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 postmenopausal for >12 months.
4. Able to provide informed consent.

A patient is ineligible if any of the following apply:

1. ANIU is controlled, and a patient is maintained on ≤5.0 mg CS/day at the time of screening.
2. Systemic disease (whether associated with ANIU or not) that is being treated with steroids and requires >5 mg CS/day.
3. Untreated or active tuberculosis.
4. Severe infection, sepsis or opportunistic infection.
5. Uncontrolled glaucoma.
6. Multiple sclerosis.
7. HIV positive.
8. Hepatitis B or hepatitis C.
9. Syphilis.
10. Lyme disease.
11. Behcet's disease.
12. Toxoplasmosis chorioretinitis
13. Heart failure (New York Heart Association class III/IV).
14. Been diagnosed with cancer <5 years ago.

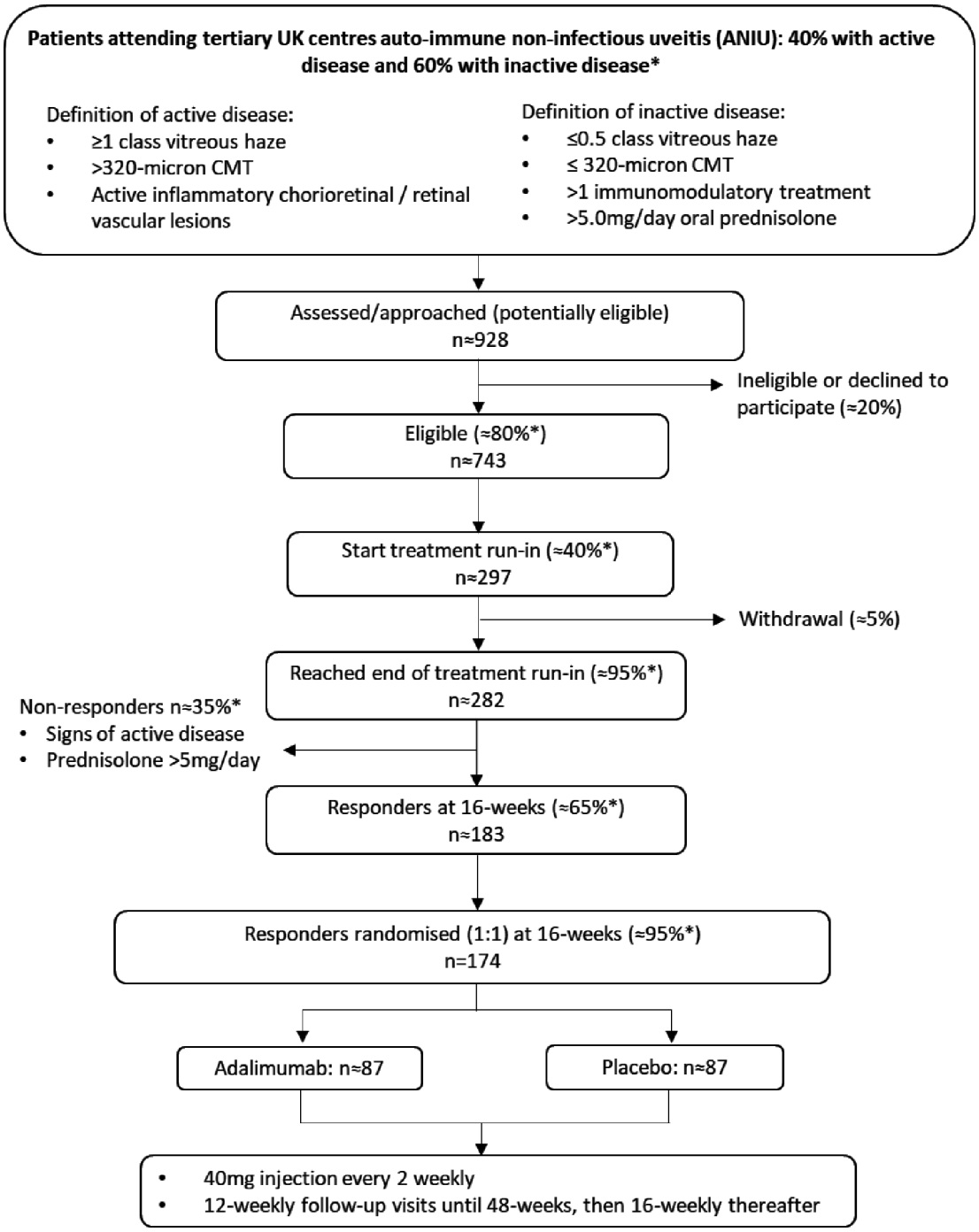


Figure 1 Trial schema. *Percentages uncertain at the beginning of the trial. These numbers have been revised since the original funding application, taking into account new information.

15. Being monitored for recurrence of cancer/tumour growth where their oncologist has a concern that a TNFa inhibitor would be contraindicated.
16. Taking another biological drug (anakinra and abatacept are contraindicated).
17. Taken an anti-TNFa drug within the previous 90 days.
18. Had an Iluvien implant within the previous 18 months and has controlled ANIU, or had an Iluvien implant within the previous 12 weeks regardless of whether ANIU is active or controlled.
19. Had an Ozurdex implant, an intravitreal steroid injection or periocular steroid within the previous 12 weeks.
20. Pregnant.
21. Known allergy or hypersensitivity to adalimumab or any of its excipients.
22. Taking part in another interventional study.
23. An epiretinal membrane likely to prevent an eye from meeting response criterion at 16 weeks of CMT <320 µm.

Patient approach and consent

New patients with ANIU and existing patients with ANIU who are having ongoing treatment and who present to, and are managed by, ophthalmologists who staff clinics in tertiary UK hospitals treating ANIU will be approached. Patients will be screened using their medical records. Eligible patients will be given or sent an invitation letter and a patient information leaflet describing the study and the potential risks and benefits of study participation, provided with detailed study information and the opportunity to ask questions before written informed consent is sought. Participants will be consented to both the TRI and RCT using one form (online supplemental file 1), by an authorised member of the research team. Consent is required before full screening assessments can be done because some exclusion criteria involve tests not always required for usual care.

Interventions

The intervention is fortnightly 40 mg subcutaneous injection of Imraldi, a licensed biosimilar for adalimumab manufactured by Biogen International GmBH (Switzerland). The comparator intervention is subcutaneous injections of placebo which contains all excipients used in the commercially available devices, also manufactured by Biogen GmBH and unconditionally donated to the study. The investigational medicinal product (IMP), whether adalimumab or placebo, is prefilled in a pen device identical to the commercially available Imraldi devices. A manufacturing pharmacy prepares the IMP, attaching non-removable labels describing the devices as IMP for the ASTUTE trial (figure 2) over all commercial labelling.

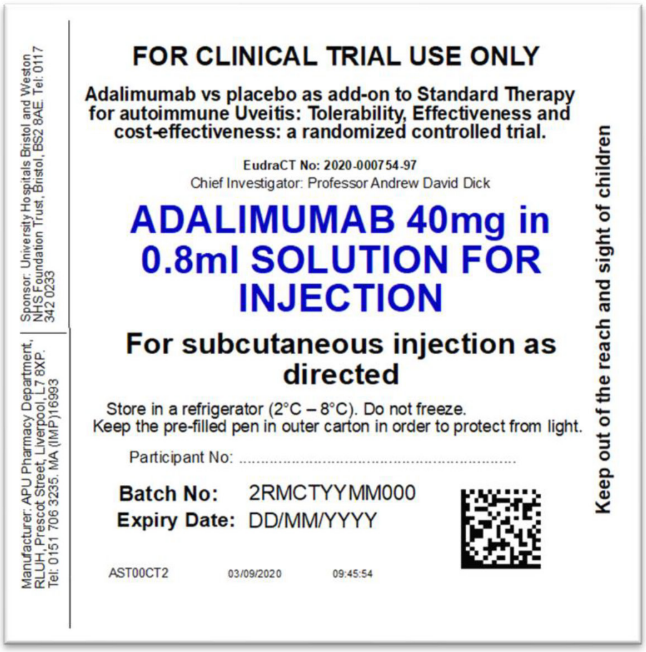
All patients enrolled in TRI will be treated with open-label adalimumab for 16 weeks. TRI will commence with an 80 mg subcutaneous dose of adalimumab and continue 1 week after the initial 80 mg dose with fortnightly 40 mg injections (weeks 1, 3, 5, 7, 9, 11, 13 and 15). After 16 weeks (time window of 112–119 days), the participants' response will be assessed. A participant is defined as having responded if all of the following criteria apply:

1. No evidence of active or new inflammatory chorioretinal lesions.[17]
2. CMT ≤320 µm.[20] On any optical coherence tomography (OCT) device.
3. No evidence of active retinal vasculitis.[17]
4. ≤0.5+ vitreous haze (binocular indirect ophthalmoscopy score).[20]
5. Prescription of ≤5.0 mg CS/day; a participant is also defined as a responder if prescribed >5.0 mg CS/day for a comorbidity (eg, rheumatological disease) where all of the items from 1 to 4 are met.

Responders who remain eligible and reconfirm consent at 16 weeks will be randomly allocated to adalimumab or placebo (the IMP). Starting from 1 week after randomisation, participants self-administer the allocated IMP, that is, 40 mg injections of adalimumab or placebo, fortnightly to the end of the trial or TF. The trial ends when the last participant has completed the 48-week visit. In the event of TF in either or both eyes, open-label drug will be restarted as for the TRI for 16 weeks, and if a participant is again assessed as having responded after 16 weeks, IMP will be restarted but with the allocation switched (up to two TFs), maintaining masking.

Each participant can withdraw at any time. The clinician may withdraw the participant from treatment if continuation is considered not in the best interests of the participant.

A



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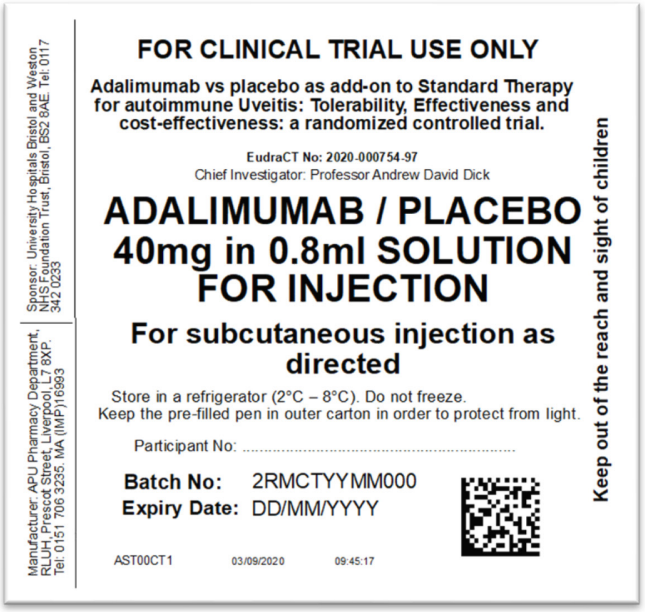

Figure 2 IMP labels. IMP labels for open-label adalimumab in treatment run-in (A) and blinded adalimumab/placebo in 7 the randomised controlled trial (B).

All study medications (open-label adalimumab and blinded IMP) will be stored by a central pharmacy in accordance with Good Clinical Practice (GCP) and the pharmacy's standard operating procedures (SOPs). Study medication will be transferred from the central pharmacy to a third-party organisation (Sciensus) to deliver study medication to participants' homes. Sciensus will also use their network of trained nurses to train participants to self-inject. Participants will return empty packaging to site staff for IMP accountability.

Randomisation

At the 16-week TRI visit after confirming eligibility, responders will reconfirm verbal consent before randomisation. Randomisation is performed using a secure internet-based randomisation system ensuring allocation concealment by an authorised member of the local research team. Participants will be allocated in a 1:1 ratio to either adalimumab or placebo.

The random allocations were computer generated by a statistician in the clinical trial unit in blocks of varying sizes (unknown to trial personnel) and stratified by a site before the trial started to recruit. The allocations are embedded in the trial database and concealed from all clinical and research personnel until key data to characterise a participant's current clinical status are recorded.

Masking

In the TRI, all participants will receive open-label adalimumab. In RCT, participants, their clinical care team and the research nurse(s) responsible for participant follow-up will all be masked to allocation. Except for the study statistician, clinical trial staff managing the trial will also be masked to allocation. Participants will be made aware before consenting that they will not be told which treatment they will receive during RCT. Doctors will prescribe the IMP, and the randomisation system will provide a unique code which the study pharmacy (Sciensus) will use to identify the injectable pens to be dispensed.

The prefilled devices look identical, and we are not aware of any sensation when self-injecting that will differ between adalimumab and placebo. Adalimumab may induce side effects in some patients that will inadvertently unmask participants.

If clinically indicated (eg, in the event of a serious adverse event (SAE), requiring knowledge of the allocation for treatment), the allocation can be unmasked. Unmasking will be done by authorised personnel. Instances of unmasking will be monitored throughout the trial.

Outcomes

The primary outcome is TF in either eye. If any of the following criteria (assessed by a masked staff member) apply, in one or both eyes, the patient will be classified as having experienced TF:

1. Decrease in best-corrected visual acuity (BCVA) of 15 letters or more, assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) charts, compared with BCVA measured at the 16-week TRI visit
2. New active inflammatory chorioretinal lesions
3. >20% increase in CMT, compared with CMT at the 16-week TRI timepoint
4. Onset or worsening of retinal vasculitis
5. Two-step worsening of vitreous haze compared with the score at the 16-week TRI visit
6. Prescription of >5 mg CS/day, unless a participant is prescribed >5.0 mg CS/day for a comorbidity (eg, rheumatological disease) where ALL of the items from 1 to 4 are met

Secondary outcomes, assessed at visits as shown in table 1, comprise the following:

1. Individual TF components
2. Retinal morphology (macular and retinal nerve fibre layer assessed from OCT)
3. Adverse events (AEs) and SAEs
4. BCVA assessed using the ETDRS charts.
5. Health-related quality of life (HRQoL) measured using the EuroQol 5-dimension 5-level (EQ-5D-5L) questionnaire[21 22]
6. Patient-reported symptoms of side effects (also recorded at unscheduled attendances if prompted by an AE)
7. Patient-reported visual function[23]
8. Employment status
9. NHS resource use

Data collection

Data will be collected on the number of patients screened and eligible before and after consent and when starting the TRI, including reasons for declining participation. The schedule of data collection for consented patients is shown in the Standard Protocol Items: Recommendations for Interventional Trials diagram (table 1).

Data will be collected using bespoke questionnaires and trial case report forms (CRFs) and entered into a purpose-designed secure database, with 'real-time' validation. Participants starting the TRI will be seen at 4 and 16 weeks in a hospital and contacted by telephone at 8 weeks. This visit frequency approximates usual care when a patient starts treatment with adalimumab. Follow-up visits will be scheduled at 12 weekly intervals up to 48 weeks after randomisation and 16 weekly thereafter, consistent with usual care for patients with ANIU. AEs and SAEs will be collected from the date of induction dose in the TRI until the end of the trial and will be recorded and reported in accordance with GCP guidelines and SOPs of the Bristol Trials Centre and Sponsor.

In addition, optional research blood samples will be taken as indicated in table 1 and serum and DNA prepared and stored. These samples, and retinal images taken as part of the study, will be collected and stored for objective (iv).

Table 1 Schedule of data collection

		TRI			RCT				
Data item to be collected	**Screen/baseline**	**4 w**	**8 w**	**16w /Rx**	**12 w**	**24 w**	**36 w**	**48 w**	**Then:**
Confirm eligibility	✓			✓					
Consent confirmed	✓			✓*					
Medical history	✓								
Baseline characteristics	✓								
Vital signs	✓			✓	✓	✓	✓	✓	16 w+
Weight	✓			✓		✓		✓	16 w+
History-directed medical exam	✓			✓	✓	✓	✓	✓	16 w+
Full blood count	✓	✓		✓	✓	✓	✓	✓	16 w+
Liver function tests	✓	✓		✓	✓	✓	✓	✓	16 w+
Electrolyte profile	✓	✓		✓	✓	✓	✓	✓	16 w+
Glucose test	✓	✓							
TB IGRA test	✓								
Chest X-ray	✓								
12-lead ECG	✓†								
MRI	✓								
Syphilis test, HIV test, hep B/hep C test	✓								
Lyme IgG/IgM antibody serology	✓								
Varicella history	✓								
Pregnancy test (women only)	✓								
BCVA	✓	✓		✓	✓	✓	✓	✓	16 w+
OCT	✓			✓	✓	✓	✓	✓	16 w+
Fundus colour imaging	✓			✓	✓	✓	✓	✓	16 w+
Autofluorescence imaging	✓‡			✓‡	✓‡	✓‡	✓‡	✓‡	16 w+‡
Fundus fluorescein angiogram	✓‡			✓‡	✓‡	✓‡	✓‡	✓‡	16 w+‡
Clinical exam (including slit-lamp examination and indirect ophthalmoscopy)	✓	✓		✓	✓	✓	✓	✓	16 w+
Telephone well-being review			✓						
Adverse events		✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D-5L, VCM1, symptoms of side effects, WPAI-SHP questionnaire	✓			✓	✓	✓	✓	✓	16 w+
Blood sample (for serum)*§	✓			✓	✓§	✓§	✓§	✓	48 w+§
Blood sample (for DNA)	✓								
Resource use				✓	✓	✓	✓	✓	16 w+

*Written informed consent will be obtained at the start of the TRI; this consent will be confirmed among responders at the start of RCT.
†Only required if clinically indicated.
‡Only required if clinically indicated to support decision about TF.
§A blood sample for serum will also be taken in the event of TF at a postrandomisation visit.
BCVA, best corrected visual acuity; hep B/hep C, hepatitis B/hepatitis C; IGRA, interferon gamma release assay; OCT, optical coherence tomogram; RCT, randomised controlled trial; Rx, Randomisation; TB, Tuberculosis; TF, treatment failure; TRI, treatment run-in; VCM1, Visual Function Questionnaire 1; w, weekly; w+, weekly thereafter; WPAI-SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem Questionnaire.

Sample size

A total of 174 participants will be randomised to either adalimumab or placebo. In estimating the sample size, we have considered the results of previous studies (hazard ratios (HRs) for time to first TF in two previous trials were 0.50 and 0.57).[17 18] Since ASTUTE will only randomise participants who are found to respond to treatment in the TRI, we anticipate that we will observe a greater benefit than in these trials and have set the target HR at 0.5. Assuming that 27% of participants in the placebo group survive free from TF at 12 months (estimated from placebo groups of the two trials with 40:60 active/

inactive disease), 174 participants will allow HR ≤0.5 (27% vs 52% survival free from TF at 12 months) to be detected with 90% power with 5% two-sided significance, allowing for 10% loss to follow-up in the first 12 months. The required number of participants enrolled into the TRI will depend on the percentage of participants being classified as a responder at the end of the TRI. Assuming a 65% response rate and that 8% of responders in the TRI withdraw consent for randomisation, we will need to enrol approximately 290 participants into the TRI to randomise 174 responders.

Statistical analysis

The data will be analysed according to intention-to-treat (ITT) principles and follow Consolidated Standards of Reporting Trials reporting guidelines. Analyses will be adjusted for centre. The primary outcome will be compared using survival methods, allowing for censoring of participants lost to follow-up. Secondary outcomes up to the time of TF will be compared using a mixed linear or logistic regression model as appropriate, adjusted for baseline measures when available. These outcomes will be modelled jointly with the time to first TF. Changes in treatment effect with time will be assessed by adding a treatment × time interaction to the model and comparing models using a likelihood ratio test. Model fit will be assessed, and alternative models and/or transformations (eg, to induce normality) will be explored where appropriate. Frequencies of AEs will be described. Treatment differences will be reported with 95% CIs.

A secondary analysis will include follow-up time after the first TF. The time when an individual restarts IMP in the RCT will become the time origin for the second period of follow-up. This process can be repeated another time, in the event of a second TF, generating up to three discrete 'disconnected' periods of follow-up for an individual in the RCT. Follow-up will cease after a third TF.

The allocation group (and other important covariates) will be updated when IMP (adalimumab or placebo) is restarted in the RCT. We will analyse multiple periods of treatment exposure within participants with survival models. The primary analysis, that is, time to first TF, will be unbiased. Analyses of subsequent follow-up periods must be considered non-randomised, and potentially biased because participants' characteristics are likely to predict TF, and will be adjusted for important covariates. Nevertheless, switches will provide a within-subject comparison of survival free from TF between intervention and placebo.

Health economic evaluation

A within-trial cost-effectiveness analysis of the intervention compared with placebo will be undertaken from the perspective of the UK NHS and personal social services. The main outcome measure for the economic evaluation will be HRQoL using quality-adjusted life years (QALYs) estimated from the EQ-5D-5L questionnaire, completed at baseline by participants and other time points (table 1). Questionnaire responses will be assigned valuations from published UK population tariffs, in line with NICE recommendations.[24–26] Analyses will be performed on an intention-to-treat basis. Costs and effects will be discounted as our time horizon is over 12 months. Resource use data will be collected on relevant NHS care resource episodes for trial participants at the time points in table 1. Unit costs to attach to healthcare resource use will be mainly from national sources, such as the National Schedule of Reference Costs for MRI and Unit Costs of Health and Social Care for community costs. Resources will be valued in 2023/2024 pounds sterling. Missing data for resource use and outcomes (EQ-5D scores) will be handled using multiple imputation.[27] The incremental cost-effectiveness ratio (ICER) will be calculated as the incremental change (difference) in costs between groups divided by the incremental change in health outcome. Our ICER will be derived from the average costs and QALYs (outcome) gained in each trial arm, producing an incremental cost per QALY gained from the intervention compared with placebo. Sensitivity analyses will examine the impact on costs and cost-effectiveness results of variation in key variables and major cost drivers.

Risk of bias

Concealed randomisation will protect against bias arising from the randomisation process. Placebo control will protect against bias due to deviations from intended interventions and bias in the measurement of outcomes, since participants, staff caring for participants and members of the research team will be masked to participants' allocations. The allocation will be stratified by centre to minimise confounding due to centre-specific factors. In the event of instances of unmasking, applying standard protocols, predefining procedures for participant follow-up/data collection and applying the procedures to all participants in the same way will minimise bias due to deviations from intended interventions and measurement of outcomes. Adherence to all aspects of the protocol will be monitored.

Bias due to missing outcome data, that is, systematic differences in withdrawals between the groups, will be minimised by (1) the offer of a switch in allocation in the event of TF and (ii) maintaining regular contact with participants throughout the duration of the RCT to maximise the proportion of participants for whom all outcome data are available. The Data Monitoring and Safety Committee (DMSC) will monitor attrition by trial group.

Data management

Data will be entered into a purpose-designed database hosted on the NHS server. Information capable of identifying individuals and the nature of treatment received will be held in the password-restricted database and will not be made available in any form to those outside the study. The database and randomisation system will be designed to protect patient information in line with data protection legislation. Trial staff will ensure that the

participants' anonymity is maintained through protective and secure handling and storage of patient information at participating sites and in accordance with Research Ethics Committee (REC) approval. All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with data protection legislation.

Data will be entered promptly from paper CRFs, and data validation and cleaning will be carried out throughout the trial. All study documentation will be retained in a secure location during the conduct of the study and for 15 years after the end of the study. All patient-identifiable records will be destroyed by confidential means.

Data monitoring

The trial coordinating centre will carry out regular monitoring and audit compliance of centres with GCP and data collection procedures. The trial management group will review accumulating data in the form of central monitoring reports generated approximately monthly. An independent Trial Steering Committee (TSC) will be established to oversee the conduct of the study.

The primary analysis will take place when follow-up is complete for all recruited participants. No interim analysis is planned. Safety data will be reported to the independent DMSC at least annually, together with any additional analyses the committee requests. In these reports, the data will be presented by group, but the allocation will remain masked.

Patient and public involvement (PPI)

Patients have been involved in the trial from an early stage. The acceptability of the design features of the trial emerged from an active collaboration with patients and representatives of the Birdshot Uveitis Society and Fight for Sight. Patient and public colleagues consider the TRI design feature to be equitable and welcome the broad eligibility criteria and the offer to switch to the alternative treatment in the case of TF. A PPI member is a coauthor, and two PPI members are part of the TSC.

Ethics and dissemination

The trial received REC approval from South Central – Oxford B REC in June 2020, Medicines and Healthcare Regulatory Agency (MHRA) approval in October 2020 and Health Research Authority (HRA) approval in October 2020.

The ASTUTE trial is sponsored by the University Hospitals Bristol and Western NHS Foundation Trust and managed by the Bristol Trials Centre. The study will be conducted in accordance with GCP guidelines, The Medicines for Human Use (Clinical Trials) Regulations 2004, the Data Protection Act, General Data Protection Regulation UK and the UK Policy Framework for Health and Social Care Research.

The findings will be disseminated by usual academic channels, that is, presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

Changes to the protocol since first regulatory approvals

Since initial approval, four substantial amendments to the trial protocol (online supplemental file 2) have been approved by the REC, MHRA and HRA and implemented by all sites. The current version is V.8.0 dated 29 July 2022. Amendments have (1) updated the inclusion and exclusion criteria; (2) implemented the updated summary of product characteristics with two additional AEs; (3) clarified responder and TF criteria; (4) clarified pharmacy arrangements; (5) clarified the injection schedule, imaging and follow-up visit windows; (6) clarified AE/SAE reporting window; (7) added an 8-week telephone follow-up contact in the TRI; and (9) specified BCVA as a secondary outcome.

Protocol amendments are circulated to investigators on submission and once regulatory approvals are received. Participants are informed of any relevant changes at their next follow-up visit.

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