Stopping of adalimumab in juvenile idiopathic arthritis-associated uveitis (ADJUST): a multicentre, double-masked, randomised controlled trial

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Summary

Background Adalimumab is an effective treatment for juvenile idiopathic arthritis-associated uveitis. Data are scarce on the effects of discontinuing adalimumab after control of the disease had been reached. We aimed to assess efficacy and safety of discontinuing treatment in patients with juvenile idiopathic arthritis-associated uveitis.

Methods We conducted a multicentre, double-masked, randomised, placebo-controlled trial at 20 ophthalmology and rheumatology clinics across the USA, the UK, and Australia. Patients aged at least 2 years who had controlled arthritis and uveitis for at least 1 year on adalimumab were randomly assigned in a 1:1 ratio using a web-based system to receive adalimumab or placebo, administered subcutaneously every 2 weeks until the 48-week visit or treatment failure. The primary outcome was the time to treatment failure, defined by recurrence of uveitis or arthritis; all participants were included in the primary and safety analysis. Unmasking occurred at treatment failure, and patients were offered open-label adalimumab through 48 weeks of follow-up. This trial was registered with ClinicalTrials.gov (NCT03816397).

Findings 87 patients were enrolled from March 3, 2020, to Feb 14, 2024, whereafter the prespecified interim stopping criteria were met and enrolment was stopped. One patient in each group dropped out but data were included in analyses. Six (14%) of 43 patients in the adalimumab group and 30 (68%) of 44 patients in the placebo group had treatment failure (hazard ratio 8·7, 95% CI 3·6–21·2; p<0·0001). The median time to treatment failure in the placebo group was 119 days (IQR 84–243). The median time to re-establishing sustained control of inflammation in the placebo group after restarting adalimumab was 105 days (63–196). 226 non-serious adverse events occurred in the adalimumab group (7·5 events per person-year, 95% CI 6·5–8·5), and 115 non-serious adverse events occurred in the placebo group (6·8 events per person-year, 5·6–8·1). Four serious adverse events were reported, all in the adalimumab group.

Interpretation Discontinuing adalimumab led to higher rates of recurrence of uveitis, arthritis, or both in patients with previously controlled juvenile idiopathic arthritis-associated uveitis. However, all patients who had treatment failure successfully regained control of inflammation by the end of the 48-week study period after restarting adalimumab.

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Introduction

Juvenile idiopathic arthritis-associated uveitis affects up to 20% of patients with juvenile idiopathic arthritis and constitutes nearly half of paediatric uveitis cases.[1,2] Active intraocular inflammation can cause morbidity, visual impairment, and blindness.[2–4]

Given the chronic nature of the uveitis, corticosteroid-sparing therapies are recommended to avoid the long-term complications of corticosteroids.[5–7] The disease-modifying, anti-rheumatic drug (DMARD) methotrexate is the first-line systemic treatment for juvenile idiopathic arthritis-associated uveitis.[5,7] If uveitis is refractory to methotrexate, adalimumab, a human monoclonal antibody to tumour necrosis factor (TNF), is recommended and is efficacious in treating both juvenile idiopathic arthritis and juvenile idiopathic arthritis-associated uveitis.[8,9] However, adalimumab has a high cost burden and a risk of adverse events, including opportunistic infections, malignancy, and demyelinating diseases.[10,11] Additionally, stopping and restarting anti-TNF therapy in patients with other autoimmune diseases has been associated with reduced responsiveness to the drug.[12,13]

There are scarce data on the discontinuation of immunosuppressive treatments in juvenile idiopathic

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See Online for appendix

Research in context

Evidence before this study

Tumour necrosis factor (TNF) is a cytokine that has a key role in regulating inflammatory responses and is involved in the pathogenesis of many inflammatory conditions, including juvenile idiopathic arthritis-associated uveitis. The TNF inhibitor, adalimumab, is the recommended treatment when patients with juvenile idiopathic arthritis-associated uveitis have persistent inflammation on conventional immunosuppressive therapies. Although adalimumab is highly effective, patients often desire to stop treatment after they enter disease remission because of the cost burden and risk of adverse events. There is a paucity of information available about the recurrence rates of arthritis and uveitis when adalimumab is stopped. We searched PubMed and ClinicalTrials.gov for English language publications available from database inception until July 14, 2024, with the search terms "JIA-associated uveitis" AND "discontinuing OR stopping" AND "adalimumab OR anti-TNF-α agent OR biologic OR Humira", inclusive of review articles, retrospective studies, and clinical trials. The small number of retrospective studies suggest a high relapse rate and a short time to recurrence of uveitis after stopping immunosuppressive therapies, including TNF inhibitors, but no randomised trial has evaluated the risks and benefits of stopping versus continuing adalimumab. Additionally, guidelines on the management of juvenile idiopathic arthritis-associated uveitis recommend 2 years of controlled disease before attempting to discontinue treatment but cite a low level of available evidence.

Added value of this study

To our knowledge, ADJUST is the first multicentre, randomised controlled trial comparing continuing versus discontinuing adalimumab therapy in patients with controlled juvenile idiopathic arthritis-associated uveitis. Our study showed that recurrence rates of inflammation were significantly higher in patients who stopped adalimumab compared with those who continued adalimumab. However, all patients who restarted drug treatment after recurrence were able to regain control of inflammation. Additionally, there was no difference in visual acuity or safety outcomes between groups. Follow-up and adherence were high, so this trial provides strong evidence for the outcomes reported.

Implications of all the available evidence

Results from this clinical trial can be used to guide counselling of patients and families who are considering discontinuing adalimumab for juvenile idiopathic arthritis-associated uveitis. Recommendations from the American College of Rheumatology and the Single Hub and Access Point for Paediatric Rheumatology in Europe that withdrawal of treatment can be attempted after 2 years of control should be considered with caution. If an attempt is made to withdraw therapy, patients should be closely monitored for recurrence, especially during the first 6 months. Patients can be reassured that disease control can be regained after restarting treatment. Future analyses will investigate whether clinical characteristics or laboratory biomarkers can be used to predict successful discontinuation of adalimumab.

arthritis-associated uveitis, and no clinical trial data are available to guide decision making on drug withdrawal.[14,15] Retrospective studies on patients with juvenile idiopathic arthritis-associated uveitis suggest that the relapse rate is high (although estimates vary) with therapy discontinuation, but longer duration of disease control and older age could be predictive of success in stopping treatment.[16–19] The American College of Rheumatology recommends 2 years of controlled inflammation on adalimumab before attempting to stop treatment for juvenile idiopathic arthritis-associated uveitis, but cites a low level of evidence to support this guideline.[5]

For more on the **National Eye Institute** see https://www.nei.nih.gov/

The Adalimumab in Juvenile Idiopathic Arthritis-associated Uveitis Stopping Trial (ADJUST) was designed to compare the efficacy and safety of stopping adalimumab treatment versus continuing treatment in patients who had reached clinical remission on the drug.

Methods

Study design

ADJUST was a multicentre, double-masked, randomised controlled trial conducted at 20 ophthalmology and rheumatology clinical sites across the USA, the UK, and Australia. The trial was approved by an institutional review board at the University of California San Francisco, CA, USA (number 17-23987) and conducted under a US Food and Drug Administration investigational new drug application (number 137674). The protocol and its amendments were approved by regulatory and ethics committees at each site (appendix pp 29–78). An independent data safety and monitoring committee was appointed by the National Eye Institute to review efficacy and safety outcomes on a semi-annual basis. This trial was registered with ClinicalTrials.gov (NCT03816397).

Patients

Eligible patients were aged 2 years or older with a history of chronic juvenile idiopathic arthritis-associated uveitis or chronic anterior uveitis diagnosed before the age of 16 years, with no other suspected disease association. The phenotype of idiopathic chronic anterior uveitis in children is identical to that of chronic juvenile idiopathic arthritis-associated uveitis, except for the absence of a history of arthritis.[20,21] The European Medicines Agency recommends that these patients are included in studies of juvenile idiopathic arthritis-associated uveitis.[22]

Inclusion criteria required corticosteroid-sparing control of uveitis (≤0·5+ anterior chamber cell, ≤0·5+ vitreous haze, no active retinal or choroidal inflammation or macular oedema) and inactive arthritis with adalimumab (originator product or biosimilar) for at least 12 consecutive months before enrolment. Also before enrolment, patients were required to be on a stable dose of adalimumab (at least 180 days of ≤40 mg every 2 weeks for patients ≥30 kg, or ≤20 mg every 2 weeks for patients <30 kg) and, if taken, stable doses of conventional DMARDs (for at least 90 days) and topical corticosteroids (at least 90 days of ≤2 drops prednisolone 1% per eye or equivalent per day).

Key exclusion criteria were a history of acute anterior uveitis characterised by redness and symptoms such as floaters, pain, and light sensitivity; intraocular surgery in the past 90 days or planned surgery in the next 12 months; and treatment with systemic, intraocular, or intra-articular corticosteroids within the past 12 months. Full eligibility criteria and definitions of controlled uveitis and arthritis are provided in the appendix (pp 6–7).

Patients were screened and recruited by investigators at established paediatric rheumatology–uveitis clinics. Written informed consent was obtained from all patients or guardians and each child gave assent when applicable. Sex was self-reported by the patients and recorded as a binary variable (male or female). Race and ethnicity were also self-reported. As per the National Institutes of Health guidelines, ethnicity options included "Hispanic", "non-Hispanic", "other", or "prefer not to answer".

Randomisation and masking

Patients were randomly assigned through a web-based system (the REDCap platform) to receive adalimumab or a dose-matching placebo in a 1:1 ratio using computer-generated permuted block sizes of two and four, stratified by country (USA, UK, or Australia) and conventional DMARD use (yes *vs* no). The trial biostatiscian and unmasked data analysts generated and uploaded the allocation sequence to the web-based system, where a local, unmasked treatment assigner performed the randomisation. An unmasked pharmacist or treatment assigner at the study site was responsible for dispensing the study drug or dose-matching placebo.

All personnel involved in patient care, including the patient and their parents or caregivers, were masked to the randomised treatment assignment. Prefilled syringes with either adalimumab or placebo were manufactured and donated by AbbVie (Ludwigshafen, Germany) and had identical labelling, packaging, and appearance to ensure masking.

Unmasking occurred at the primary endpoint, defined as the timepoint when treatment failure was declared, or at the 48-week visit if treatment failure did not occur. All ophthalmology and rheumatology assessments were performed before unmasking. Patients were also asked which randomised treatment they thought they had received. The investigator or coordinator then called the unmasked pharmacist or treatment assigner to unmask the site's research team, the patient, and the patient's parents or caregivers.

Procedures

All of the patients assigned to continue adalimumab received subcutaneous injections every 2 weeks (20 mg for patients weighing <30 kg or 40 mg for patients weighing ≥30 kg), whereas patients assigned to stop treatment received identical-looking, volume-matched, citrate-free placebo injections every 2 weeks. No dose reduction or change in the method of administration was allowed. In the case of a missed dose, patients were asked to administer the study medication as soon as possible and then resume the regular administration schedule of injections every 2 weeks. Conventional DMARDs or topical corticosteroid dose could not be changed from baseline regimens unless treatment failure was declared. For arthritis recurrence before treatment failure, rheumatologists were encouraged to use non-steroidal anti-inflammatory drugs or local corticosteroid injections.

After baseline (ie, week 0), trial visits were scheduled at 4, 8, 12, 16, 24, 32, 40, and 48 weeks. These were target timepoints, but data were still included if visits occurred before or after. If treatment failure was declared with fewer than 90 days remaining in the trial period, a final follow-up visit was scheduled 90 days after failure. Post-failure treatment plans were determined by the site's investigator, and open-label adalimumab was provided as needed from treatment failure until the end of the patients' 48-week follow-up period, regardless of their original randomisation.

Ophthalmic procedures to assess disease activity were measured at each visit using slit-lamp biomicroscopy and dilated fundoscopic examination, with inflammation measured according to the Standardization of Uveitis Nomenclature (SUN) criteria.[23] Electronic visual acuity, assessed with the EVA System (M&S Technologies, Niles, IL, USA), was used to measure best-corrected visual acuity (BCVA). Optical coherence tomography, a diagnostic imaging test used to evaluate posterior segment eye structures, was also performed at every study visit to monitor for macular oedema, which can occur with recurrence of uveitis. Rheumatological assessments were conducted at baseline, week 12, week 24, week 48, and, if applicable, treatment failure. Blood was taken to measure adalimumab and anti-adalimumab antibody concentrations, and a serum sample was taken to assess concentrations of the myeloid-related protein 8 (MRP8) and MRP14 protein complex. These samples were collected to study how these biomarkers are associated

with disease relapse or drug response, which could inform treatment decisions. Patients could also consent to optional assessments for future exploratory research: one for a blood biobank and one for a stool sample for microbiome testing.

Adverse event monitoring, including standard-of-care laboratory testing, was conducted per protocol. Patients who developed a fever of 38·3°C (101°F) or higher or an infection requiring antibiotics were asked to consult their physician and were allowed to stop taking the study medication or conventional DMARD at the physician's discretion. While preserving masking, these patients were to resume treatment once advised by the investigator. Additional details on trial procedures can be found in the protocol.

Outcomes

The primary outcome was time to treatment failure, with censoring at the 48-week study visit. Treatment failure was defined as having one or more of the following in at least one eye: two-step or greater increase from baseline in the anterior chamber cell grade at two consecutive visits at least 7 days apart; an anterior chamber cell grade higher than 0·5+ for at least 28 days; an anterior chamber cell grade of at least 3+, greater than 0·5+ vitreous haze, active retinal or choroidal lesions, or macular oedema at a single visit; or recurrence of joint inflammation persistent and severe enough to necessitate unmasking. Full criteria are available in the appendix (pp 8–11).

Secondary outcomes included the log of the minimum angle of resolution (logMAR) score for BCVA,[24] adalimumab and anti-adalimumab antibody concentrations, and the 27-joint Juvenile Arthritis Disease Activity Score (JADAS-27), defined as the sum of four components: a physician's global assessment of disease, the patient's or parent's global assessment of wellbeing, an erythrocyte sedimentation rate, and an active joint count assessed in 27 joints.[25] The schedule of assessments (p 12) and details on all secondary outcomes (pp 90–96) are available in the appendix.

Finally, in individuals who had treatment failure, we assessed time to re-establishment of initial and sustained control of uveitis through to the end of the patients' follow-up period (appendix p 7). Initial control was defined as the first instance where uveitis control was regained after the declaration of treatment failure, whereas sustained control was defined as the first instance of uveitis control that was then sustained through to the end of the 48-week follow-up period.

Adverse events were reported as detailed in the protocol. Additional clinical and laboratory outcomes outlined in the protocol were measured for future predictor analyses and will be reported in subsequent papers.

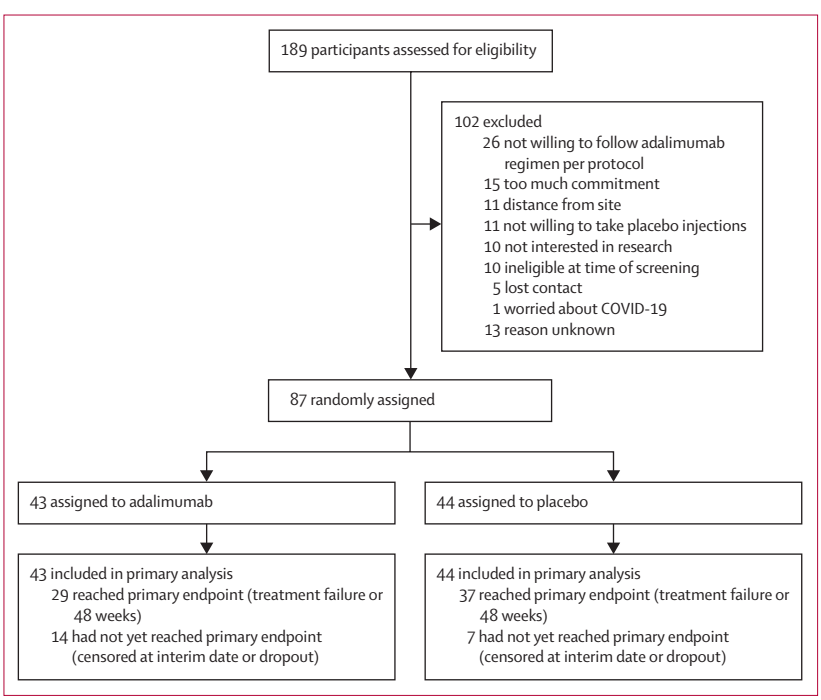

Figure 1: **Trial profile**
All patients assessed for eligibility at in-person clinic visits were first deemed eligible by chart review. Two patients dropped out of the trial before reaching the primary endpoint (one in each group). The length of time that these patients participated in the trial before dropout is included in the primary outcome analysis given the nature of survival analyses. Patients still in active follow-up who had not yet reached the primary endpoint (14 in the adalimumab group and seven in the placebo group) were censored at the interim analysis date, Feb 14, 2024. No patients were lost to follow-up and there were no withdrawals of consent.

Statistical analysis

In the intent-to-treat analysis of the primary outcome, a Cox proportional hazards regression was used to compare time to treatment failure between the adalimumab and placebo groups up to the primary endpoint of 48 weeks, with country and conventional DMARD use included as fixed effects in the model. Hypothesis testing was based on a permutation test of the log hazard ratio (100 000 replicates). The model was checked for the assumption of proportional hazards by assessing Schoenfeld residuals. Enrolment of 118 patients was estimated to provide 88% power to detect a hazard ratio (HR) of 2·0 for time to treatment failure between patients who discontinue versus continue adalimumab (appendix p 99).[18] A prespecified interim analysis was planned for when 34 (40%) of the anticipated treatment failures occurred using a Kim-DeMets alpha spending approach with stopping for interim efficacy specified at $p<0·01$ while maintaining a two-sided alpha of 0·05. For the interim analysis, data were censored at 48 weeks, or the interim analysis date if the patient had not reached the primary endpoint. A per-protocol analysis was prespecified to exclude patients who missed 20% or more of their study medication doses. All patients were included in the safety analyses. The statistical analysis plan includes the full details of sensitivity analyses (appendix pp 79–119). Three post-hoc subgroup analyses were

conducted for the primary outcome: first, by years of previous uveitis control (<2 years *vs* ≥2 years); second, by use of topical corticosteroids; and third, by age (≤12 years *vs* >12 years, the median patient age). In each case, main effects and interaction terms with treatment were included in the primary analysis Cox model.

Linear mixed-effects models were used to analyse longitudinal secondary outcomes (ie, BCVA, JADAS-27, and anti-adalimumab antibody and adalimumab concentrations) from baseline up to and including treatment failure or censoring at the 48-week visit, whichever occurred first. All mixed-effects models adjusted for baseline values and stratification variables. A Cox proportional hazards regression was used to measure the time to initial control and time to sustained control of ocular inflammation after treatment failure, with the index date defined as the date treatment failure was declared. Incidence rates of adverse events were calculated and summarised by treatment group. Participants who dropped out contributed person-time until their last study visit.

Fisher's exact testing was used to compare perceived treatment allocation between treatment groups before patient unmasking. This analysis was conducted separately for patients who were unmasked at treatment failure and patients who were unmasked at 48 weeks. Analyses were conducted using R version 4.3.2 (R project for statistical computing).

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

From March 3, 2020, to Feb 14, 2024, 189 patients across 20 sites in three countries were screened for eligibility. 102 patients were excluded and 87 patients were randomly assigned to receive either adalimumab (43 patients) or a placebo (44 patients; figure 1, table 1). One patient in each treatment group dropped out of the trial before reaching the primary endpoint; their patient time was included in the primary analysis. 11 doses of study medication were missed for nine patients on adalimumab. Seven of these were missed due to fever or infectious symptoms, one was missed due to a laboratory anomaly, one was missed due to a planned orthognathic surgery, and two were missed by accident. Six doses were missed for five patients on placebo, four of which were missed due to fever or infectious symptoms, and two of which were missed by accident. No patient missed more than 20% of the study medication doses, and thus no patients met prespecified criteria for exclusion from a per-protocol analysis.

The interim analysis was presented to the data safety and monitoring committee on Feb 14, 2024. For the primary outcome analysis, two treatment failures in

	Adalimumab group	Placebo group
Patient-level baseline characteristics		
Patients	43	44
Sex		
Female	32 (74%)	32 (73%)
Male	11 (26%)	12 (27%)
Age, years	12·56 (9·44–15·81)	12·26 (9·39–13·42)
Weight ≥30 kg		
No	12 (28%)	13 (30%)
Yes	31 (72%)	31 (70%)
Race		
Asian	4 (9%)	3 (7%)
Black	2 (5%)	2 (5%)
More than one	2 (5%)	2 (5%)
Other	1 (2%)	3 (7%)
White	34 (79%)	33 (75%)
Prefer not to answer	0	1 (2%)
Ethnicity		
Hispanic	6 (14%)	8 (18%)
Not of Hispanic, Latino, or Spanish origin	35 (81%)	28 (64%)
Other	2 (5%)	5 (11%)
Prefer not to answer	0	3 (7%)
Country		
Australia	2 (5%)	3 (7%)
UK	27 (63%)	27 (61%)
USA	14 (33%)	14 (32%)
Conventional DMARD use*		
Azathioprine	1 (2%)	3 (7%)
Leflunomide	2 (5%)	1 (2%)
Methotrexate (oral)	13 (30%)	9 (20%)
Methotrexate (subcutaneous)	14 (33%)	15 (34%)
Mycophenolate mofetil	1 (2%)	3 (7%)
None	12 (28%)	13 (30%)
Arthritis category		
None; chronic anterior uveitis	7 (16%)	7 (16%)
Oligoarthritis	29 (67%)	29 (66%)
Polyarthritis	7 (16%)	6 (14%)
Psoriatic arthritis	0	1 (2%)
Undifferentiated arthritis	0	1 (2%)
Age at diagnosis of juvenile idiopathic arthritis, years	2·77 (2·30–4·52)	3·71 (2·36–6·18)
Age at first uveitis diagnosis, years	5·06 (3·99–7·38)	5·51 (3·31–6·86)
Time since first diagnosis of uveitis, years	5·40 (3·53–7·98)	4·90 (3·40–9·00)
Presence of anti-nuclear antibody		
Chronic anterior uveitis, negative	3 (7%)	2 (5%)
Chronic anterior uveitis, positive	4 (9%)	5 (11%)
Juvenile idiopathic arthritis, negative	8 (19%)	12 (27%)
Juvenile idiopathic arthritis, not available†	6 (14%)	7 (16%)
Juvenile idiopathic arthritis, positive	22 (51%)	18 (41%)
Time since first starting adalimumab or biosimilar, years	3·40 (2·25–5·45)	3·70 (2·60–5·00)
Primary indication for starting adalimumab		
Uveitis	27 (63%)	31 (70%)
Arthritis	1 (2%)	1 (2%)
Both uveitis and arthritis	15 (35%)	12 (27%)

(Table 1 continues on next page)

	Adalimumab group	Placebo group
(Continued from previous page)		
Duration of corticosteroid-sparing control of uveitis, years	2·40 (1·90–3·70)	2·60 (1·78–3·53)
Corticosteroid-sparing control of ≥2 years		
No	12 (28%)	13 (30%)
Yes	31 (72%)	31 (70%)
Eye-level baseline characteristics‡		
Eyes assessed	73	82
Anterior chamber cell grade§		
0	64 (88%)	73 (89%)
0·5+	9 (12%)	9 (11%)
Visual acuity (logMAR¶)	–0·02 (–0·10 to 0·10)	0·00 (–0·06 to 0·10)
History of posterior synechiae	18 (25%)	26 (32%)
History of cataract	19 (26%)	10 (12%)
History of cataract surgery	8 (11%)	9 (11%)
History of ocular hypertension or glaucoma	27 (37%)	18 (22%)
History of glaucoma surgery	4 (5%)	5 (6%)
History of macular oedema	6 (8%)	6 (7%)
Eye pressure-lowering drops at baseline	2 (3%)	6 (7%)
Topical steroids at baseline‖	3 (4%)	8 (10%)

Data are n (%) or median (IQR). DMARD=disease-modifying antirheumatic drug. logMAR=logarithm of the minimum angle of resolution. *Conventional DMARD dosing details can be found in the appendix (p 13). †Anti-nuclear antibody results were collected but not required. ‡Only eyes affected by uveitis. §The anterior chamber cell grading was assessed according to the Standardization of Uveitis Nomenclature criteria.[37] Scores range from 0 to 4+, with higher scores indicating worse inflammation. Grade definitions are provided in the appendix (p 9). ¶Values for logMAR visual acuity are on a scale from –0·30 to 2·00, with higher values indicating poorer vision. A logMAR score of 0·00 has a Snellen equivalent of 20/20. ‖Two or fewer drops daily of 1% prednisolone or equivalent.

Table 1: **Baseline characteristics**

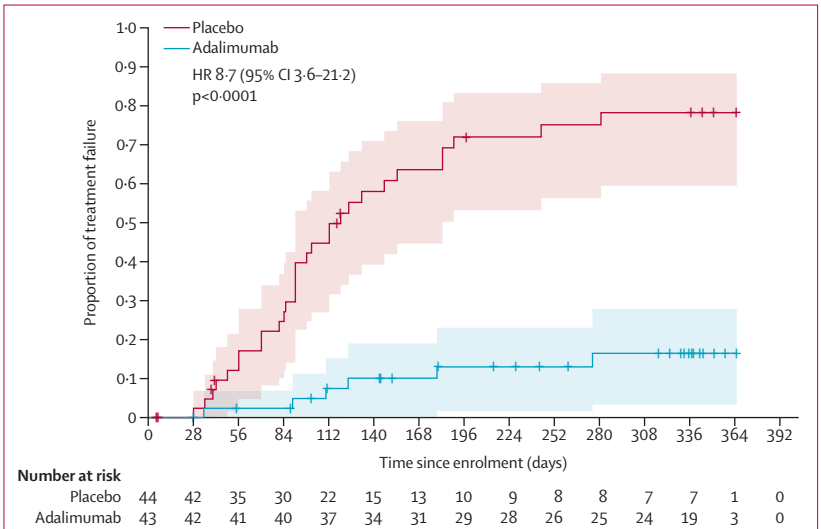

Figure 2: **Kaplan–Meier curves of cumulative proportion of treatment failure in adalimumab versus placebo groups**

Tick marks indicate censored data. One patient in each treatment group dropped out of the trial before reaching the primary endpoint. The length of time that these patients participated in the trial before dropout is included in the primary outcome analysis. Six (14%) of 43 patients in the adalimumab group and 30 (68%) of 44 patients in the placebo group had treatment failure. The median time to treatment failure for the placebo group was 119 days (IQR 84–243). HR is estimated from a Cox proportional hazards model (appendix p 14). HR=hazard ratio.

addition to the prespecified 34 were included as three occurred concurrently. The data were analysed in accordance with the prespecified analysis plan, and the results met stopping criteria. Thus, enrolment was suspended immediately. Per the data safety and monitoring committee's recommendation, patients still under follow-up on that date were given the option to unmask and encouraged to complete follow-up. The primary outcome analysis includes data from all patients, with censoring at the primary endpoint (treatment failure date or 48 weeks) or at the interim analysis date (Feb 14, 2024) if the primary endpoint was not yet reached.

Six (14%) of 43 patients in the adalimumab group and 30 (68%) of 44 patients in the placebo group had treatment failure. Of patients who had completed 48 weeks of follow-up by the interim analysis date, four (15%) of 27 patients in the adalimumab group and 21 (75%) of 28 patients in the placebo group had treatment failure. Patients who discontinued adalimumab were significantly more likely to have treatment failure than patients who continued adalimumab (HR 8·7, 95% CI 3·6–21·2; p<0·0001; figure 2). Most treatment failures occurred in the first 24 weeks of follow-up. The median time to treatment failure in the placebo group was 119 days (IQR 84–243). Conventional DMARD use did not protect against treatment failure (HR 1·1, 0·5–2·2; p=0·84; appendix p 14). The most common reason for treatment failure was a recurrence of ocular inflammation (appendix p 15). There was no difference in perceived treatment allocation between groups at the time of treatment failure (p=1·0) or at 48 weeks (p=0·26; appendix p 18).

Sensitivity analyses of the primary analysis were performed as prespecified in the protocol, all of which corroborated the results (appendix p 17). Post-hoc subgroup analyses were underpowered partly due to early stopping of the trial. Stratification by duration of previous uveitis control suggested stopping adalimumab led to higher treatment failure in patients with 2 or more years of previous control (HR 12·1, 95% CI 4·1–35·2) compared with patients with less than 2 years of control (3·6, 0·69–18·6), but the difference was not statistically significant ($p_{interaction}$=0·23). A subgroup analysis by topical corticosteroid use could not be conducted because only seven patients used topical steroids at enrolment, but an analysis restricted to the 80 patients without topical corticosteroid use yielded similar results to our primary analysis (HR 7·6, 3·1–18·9; p<0·0001). Stratification by age suggested higher risk of stopping adalimumab in patients younger than 12 years (20·7, 5·6–76·3) compared with patients aged 12 years or older (5·3, 1·5–18·9), but the difference was not statistically significant ($p_{interaction}$=0·15).

A summary of the secondary outcome analyses is provided in figure 3. BCVA did not significantly differ over time between treatment groups (p=0·68). Patients taking placebo injections developed higher concentrations of anti-adalimumab antibodies over time

compared with patients on masked adalimumab (p=0·01). Conventional DMARD use was associated with lower concentrations of anti-adalimumab antibodies (p=0·04; appendix p 19). Conventional DMARD use might have been associated with higher adalimumab drug concentrations (p=0·06; appendix p 19).

Patients in the placebo group had higher JADAS-27 scores than patients in the adalimumab group over time (p=0·03; figure 3). Arthritis recurrence occurred in 11 patients before or at the primary endpoint (four in the adalimumab group, seven in the placebo group). One patient in each group had treatment failure due to arthritis recurrence. Six patients in the placebo group had active arthritis but also developed ocular inflammation that led to treatment failure, five of whom had concurrent arthritis and uveitis recurrence and one who had arthritis preceding uveitis recurrence. Three patients in the adalimumab group had a recurrence of mild arthritis but did not have treatment failure. Eight patients treated the inflammation with oral non-steroidal anti-inflammatory drugs, two received corticosteroid injections, and all either eventually resumed or continued adalimumab.

All 30 patients in the placebo group who had treatment failure restarted adalimumab. Of the six who had treatment failure in the adalimumab group, four continued adalimumab as open-label treatment, one started infliximab, and one dropped out. Following treatment failure, the median time to initial control of ocular inflammation was 91 days (IQR 24–105) for the adalimumab group and 63 days (34–105) for the placebo group. The median time to achieving sustained control of ocular inflammation across both treatment groups was 105 days (63–196; figure 4). The median time to sustained control of ocular inflammation following treatment failure was 98 days (57–154) for the adalimumab group and 105 days (63–196) for the placebo group (appendix p 21).

226 non-serious adverse events occurred in the adalimumab group before or at the primary endpoint

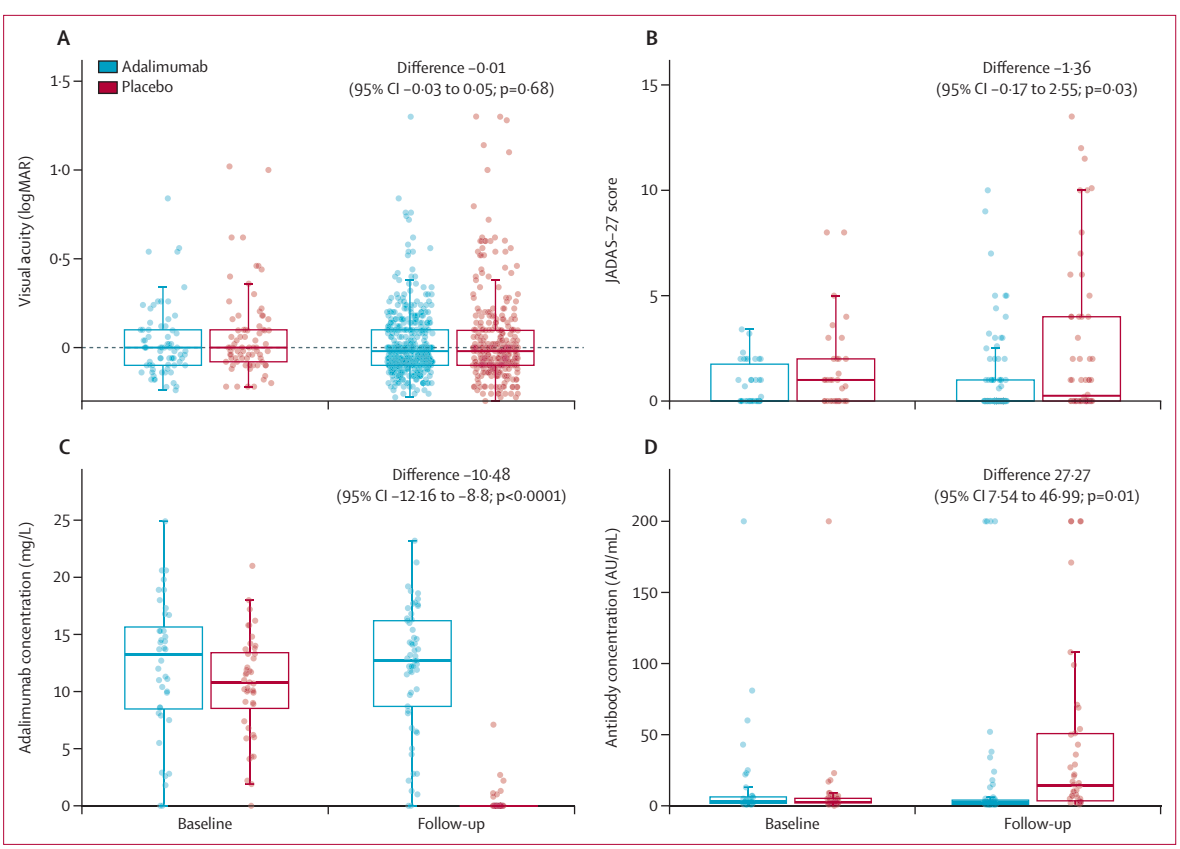

Figure 3: **Secondary outcomes at baseline and follow-up visits**
Values for logMAR visual acuity are on a scale from −0·30 to 2·00, with higher values indicating poorer vision. A logMAR score of 0·00 has a Snellen equivalent of 20/20. JADAS-27 is comprised of four components: the sum of 27 active joints, the erythrocyte sedimentation rate, the physician's global assessment of disease, and the patient's overall wellbeing score, with higher JADAS-27 scores corresponding to greater arthritis activity. Anti-adalimumab antibody concentrations were measured in AU. The follow-up plots include all longitudinal measures collected after baseline up to and including the primary endpoint. The primary endpoint was treatment failure, with censoring at 48 weeks or the interim date. The full secondary endpoint measurement schedule is available in the appendix (p 12). Estimated treatment effects, 95% CIs, and p values correspond to the effect of treatment assignment on longitudinal changes in each secondary endpoint and were derived from linear mixed-effects models, detailed in the appendix (p 19). All mixed-effects models adjusted for baseline values and stratification variables. Measures of secondary endpoints over time can be found in the appendix (p 20). AU=arbitrary units. JADAS-27=Juvenile Arthritis Disease Activity Score-27. logMAR=logarithm of the minimum angle of resolution.

(7·5 events per person-year, 95% CI 6·5–8·5), and 115 non-serious adverse events occurred in the placebo group before or at the primary endpoint (6·8 events per person-year, 5·6–8·1; table 2). The most reported adverse events were gastrointestinal-related events, headache, and fatigue. The rate of COVID-19 infections was higher in the adalimumab group compared with the placebo group (50 *vs* six events per 100 person-years). There were four serious adverse events that affected patients who were taking masked medication, all of whom were in the adalimumab group (table 3). One laboratory-related serious adverse event was considered possibly related to adalimumab.

Discussion

In this randomised, placebo-controlled trial of patients with juvenile idiopathic arthritis-associated uveitis and chronic anterior uveitis, stopping adalimumab led to a significantly shorter time to treatment failure than continuing adalimumab. Conventional DMARD use was not protective against treatment failure. Most treatment failures were due to recurrence of uveitis and occurred in the first 24 weeks after stopping treatment. The relapse rate was high, but one-quarter of the patients randomly assigned to the placebo group were able to remain in remission through the 48-week follow-up period, and all patients who had treatment failure were able to regain control after restarting the drug.

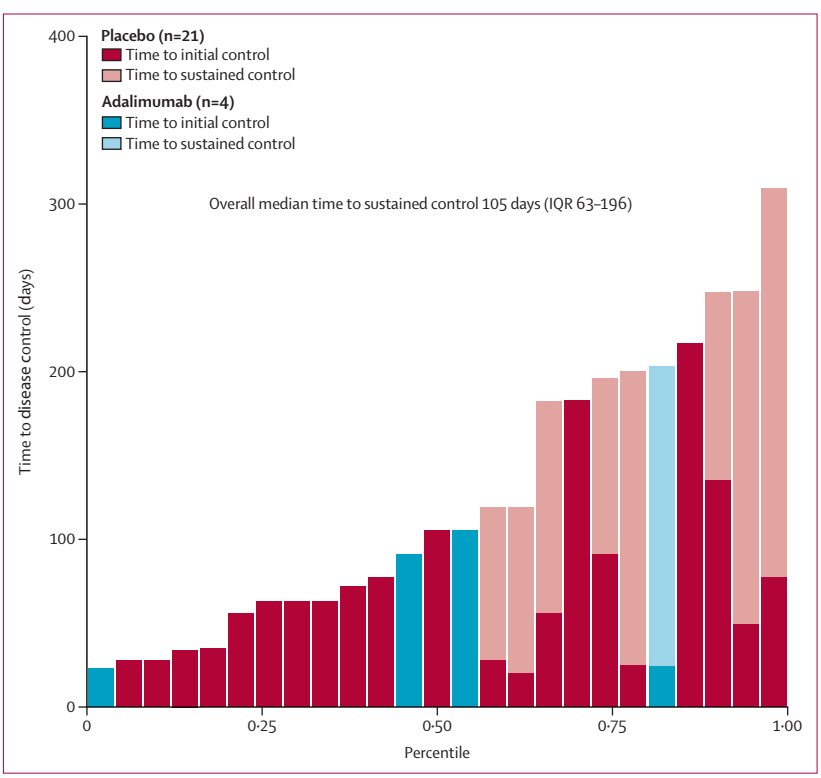

Figure 4: **Time to initial and sustained control of uveitis following treatment failure**
Time to initial control is defined as the first instance of meeting all control criteria (appendix p 7) following the declaration of treatment failure. Time to sustained control is defined as the first instance of meeting all control criteria whereafter control is maintained through to the end of the 48-week follow-up period. Only patients who had treatment failure and who completed 48 weeks of follow-up were included in the figure (n=25). The 11 additional patients who had treatment failure but had not completed their 48-week follow-up were not included in time to sustained control analyses. Each bar represents a patient and their time to control. Patients with only dark-shaded bars had initial control at the indicated timepoint, then maintained this control for the remainder of their 48-week follow-up period (n=16). Patients with a lightly shaded portion of the bar lost initial control after treatment failure but then regained control again for the remainder of the 48-week follow-up period at the timepoint indicated (n=9). All patients who had treatment failure and had completed their 48-week follow-up were able to regain sustained control of uveitis. The median time to sustained control overall was 105 days (IQR 63–196). Time to initial and sustained control Kaplan–Meier curves by treatment group and overall are available in the appendix (p 21).

Due to an absence of clinical trials on stopping therapy in juvenile idiopathic arthritis-associated uveitis, guidelines have been based on low levels of evidence.[2,5,26] In November, 2015, NHS England provided guidance that withdrawal of adalimumab can be attempted after 18 months of sustained control of uveitis in patients with juvenile idiopathic arthritis.[27] In 2019, the American College of Rheumatology and the Single Hub and Access point for Paediatric Rheumatology in Europe both recommended 2 years of control before trying to stop treatment for juvenile idiopathic arthritis-associated uveitis.[5,26,28] We elected to allow patients to enrol with at least 1 year of controlled uveitis given the paucity of available data supporting a specific timepoint. Our results show that the rate of recurrence of inflammation when stopping adalimumab is high, even when 62 (71%) of 87 patients had over 2 years of controlled uveitis. Furthermore, when a subgroup analysis of patients with at least 2 years of previous control was performed, the results indicated that the risk of recurrent disease was not decreased. The 2019 American College of Rheumatology guidelines also recommend against the use of chronic topical corticosteroid for juvenile idiopathic arthritis-associated uveitis. We allowed patients to use up to two drops daily of 1% prednisolone or equivalent, as literature before the study implementation suggested that low doses of topical corticosteroids were acceptable.[6] However, 80 (92%) of 87 patients in the trial were not using corticosteroid drops, and when restricting recurrence analysis to only these patients, those in the placebo group were still far more likely to relapse than those in the adalimumab group.

Our results also highlighted important secondary outcomes for patients attempting withdrawal. Visual acuity did not differ by treatment group. Loss of vision is usually due to uncontrolled uveitis over time.[29] In this study, close monitoring of patients for relapse and prompt restarting of adalimumab following treatment failure probably contributed to preventing vision loss. The JADAS-27 increased in the placebo group over time, but the magnitude of the rise was quite low. The adverse events seen in this study were as expected for adalimumab treatment, with higher rates of infection, such as COVID-19, in the adalimumab group probably a result of increased immunosuppression.[30] Overall,

these results are reassuring for patients who want to attempt stopping adalimumab.

There is little information on what happens to anti-adalimumab antibodies when adalimumab is stopped, and there is particular concern about the loss of therapeutic response on restarting the drug. Despite the increase in these antibodies in the placebo group, all patients who restarted adalimumab after treatment failure were able to regain control of their uveitis by 48 weeks, adding to the literature showing that anti-adalimumab antibody formation might not always result in loss of efficacy.[31,32] Assays that only detect freely circulating antidrug antibodies might show higher levels when drug concentrations decrease, but the assay used in our study measures both free and bound anti-adalimumab antibodies.[33,34] Additionally, there are few uveitis-specific studies on conventional DMARD use and anti-adalimumab antibody concentrations. Our results show that patients taking conventional DMARDs have lower concentrations of anti-adalimumab antibodies, which is in line with findings for other autoimmune conditions.[35–37] Further investigation into the effect of conventional DMARD use and antibody concentrations on recurrence of inflammation and re-establishment of control might be useful in risk stratification.

Additional secondary analyses to identify predictive factors that might aid in stratifying patients who could be able to successfully stop therapy in a state of stable disease remission are planned and will be reported in future papers. These factors include both clinical characteristics, such as weight, conventional DMARD type and dose, arthritis subtype, history or presence of ocular sequelae of uveitis at baseline, duration of uveitis control before enrolment, as well as biomarkers, including MRP8 and MRP14 complex serum concentrations, erythrocyte sedimentation rate, C-reactive protein, and adalimumab antibody concentrations. We will also evaluate transcriptome signatures in the peripheral blood and gut microbiome that could discriminate between disease control and active disease. Reports in the literature point to age as a possible predictor of successful medication withdrawal, so we conducted exploratory subgroup analyses by age and found that patients younger than 12 years who discontinued adalimumab were far more likely to relapse than patients older than 12 years, although the difference was not statistically significant due to limited power for tests of interaction in this stopped trial. Although older patients randomly allocated to the placebo group did also have treatment failure, clinicians might be more cautious when advising discontinuation of therapy in younger patients. A more thorough, comprehensive analysis on age as a clinical predictor of remission, in conjunction with other factors, will be explored in future analyses. Future trials could also explore the potential benefits of reduced-dose frequency or tapering regimens of adalimumab for treatment of uveitis.

	Patients		Events		Events per 100 person-years	
	Adalimumab (n=43)	Placebo (n=44)	Adalimumab (n=226)	Placebo (n=115)	Adalimumab (30 person-years)	Placebo (17 person-years)
Laboratory						
Atypical haemoglobin*	0	1	0	1	0	6
Atypical leukocyte count†	0	2	0	2	0	12
Atypical aspartate aminotransferase or alanine aminotransferase‡	2	0	3	0	10	0
Ocular						
Ocular hypertension§	1	2	1	4	3	24
Other ocular event¶	4	4	4	4	13	24
Systemic						
Allergic reaction||	5	1	10	1	33	6
COVID-19	12	1	15	1	50	6
Dyspnoea	4	3	8	4	26	24
Ear infection	0	2	0	2	0	12
Fatigue	15	8	28	12	93	71
Fever	8	2	8	2	26	12
Influenza	3	1	3	1	10	6
Gastrointestinal-related**	24	17	51	19	169	112
Headache	17	10	24	20	79	118
Mood changes	6	3	7	4	23	24
Muscle weakness	4	1	4	2	13	12
Impaired neurological function††	1	1	1	1	3	6
Other infection‡‡	4	4	5	5	17	30
Pneumonia	0	1	0	1	0	6
Sinus infection	1	1	2	1	7	6
Skin infection	4	3	5	4	17	24
Upper respiratory infection	9	7	16	8	53	47
Other						
Other event§§	14	9	31	16	103	94

Adverse events shown were reported before or at the primary endpoint (treatment failure or censoring at 48 weeks). Person-years were contributed by patients before primary endpoint. *Atypical haemoglobin or haematocrit is defined as haemoglobin <9 g/dL or haematocrit <27% (<0·27 L/L). †Atypical leukocyte (white blood cell) counts are defined as <2·5 cells × 10^9/L. ‡Atypical aspartate aminotransferase or alanine aminotransferase is defined as ≥2 times the upper limit of normal. §Intraocular pressure ≥24 mm Hg. ¶Other ocular events include allergic conjunctivitis related to hay fever, a chalazion, eyelid erythema from a mosquito bite, misty eye, and red or sore eyes. ||Allergic reactions for four of the six patients included slight swelling at injection site. Allergic reactions experienced by the other two patients were allergic reactions to food. **Diarrhoea, nausea, or vomiting. ††Numbness or tingling. ‡‡Other infections include strep throat, tonsilitis, scarlet fever, amoebiasis, *Heliobacter pylori*, a toenail infection, and chicken pox. §§Other events include anxiety, aphthous ulcers, bruising, eczema, epistaxis, fainting, finger or toe fractures, itchy skin, jaw dislocation, pain (ie, abdominal, ankle, back, chest, gastrointestinal, knee, leg, neck, or stomach), persistent cough, rash, Sever's disease, small nodular lesion, twitching, and vertigo.

Table 2: **Adverse events**

Limitations of the trial include the use of subjective grading of uveitis as a component of the primary endpoint. However, all study ophthalmologists were

	Original randomisation group	Medication at event
Surgery for torted cyst of Morgagni	Masked adalimumab	Masked adalimumab
Shortness of breath at rest; suspected to be anxiety related and unlikely to have been serious	Masked adalimumab	Masked adalimumab
Planned orthognathic surgery	Masked adalimumab	Masked adalimumab
Over 5 times the upper limit of normal for alanine aminotransferase; possibly related to study drug and probably related to methotrexate	Masked adalimumab	Masked adalimumab

Table 3: **Serious adverse events**

uveitis specialists experienced with using the SUN criteria for grading inflammation and were masked to the treatment assignment. The trial's smaller sample size due to the early stopping of enrolment might have resulted in a potential loss of power for secondary outcome analyses.

To our knowledge, our study is the first randomised controlled trial to assess the safety and efficacy of stopping adalimumab in patients with juvenile idiopathic arthritis-associated uveitis. The trial population was representative of patients with juvenile idiopathic arthritis-associated uveitis. The high rate of relapse after stopping adalimumab calls into question current recommendations regarding the timing for attempting withdrawal. Reassuringly, perhaps due to the close monitoring of patients throughout the trial follow-up, visual acuity was not compromised, and all patients who relapsed were able to regain control of inflammation after restarting adalimumab. Results from this study can be used to guide the counselling of patients and families who are considering discontinuing adalimumab.

Contributors

NRA and AVR conceptualised the study design and methodology. NRA acquired funding for the project. NRA and BFA wrote the statistical analysis plan. Overall trial management was done by KLD and EMR under the supervision of NRA. AVR facilitated project administration and oversight across clinical sites in the UK. BFA was the lead statistician with ABC, and SMW provided additional data management and statistical support, and all had access to all the data. ABC, SMW, and BFA conducted the formal statistical analyses, as well as data validation and data visualisation using computer code. NRA, ABC, KLD, EMR, SMW, and BFA prepared the first draft of the manuscript. NRA, AVR, ABC, KLD, EMR, SMW, CMG, EM, HJDP, KA, NP, JTC, and DPH participated in patient enrolment and carried out the trial. All authors critically reviewed the manuscript, and approved the final version. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

NRA declares receiving research funding from the National Eye Institute, under the National Institutes of Health, and a donation of study medication from AbbVie for the present study; consulting fees from Roche; and participation on an Advisory Board for the TURTLE trial. AVR declares speaker fees, honoraria, and consultancy work for AbbVie, Eli Lilly, Novartis, Roche, Swedish Orphan Biovitrum, AstraZeneca, and Union Chimique Belge; and participation on a Data Safety Monitoring Board or Advisory Board for Eli Lilly and AstraZeneca. CMG declares participation on a Data Safety Monitoring Board or Advisory Board for the TURTLE trial; and performs unpaid manuscript writing for the JUVE BRIGHT study sponsored by Eli Lilly. BFA declares receiving research funding from the National Eye Institute, under the National Institutes of Health; participation on a Data Safety Monitoring Board for the COAST Trial; and support for travel and accommodation expenses from the Bill & Melinda Gates Foundation. The University of California San Francisco Department of Ophthalmology is supported by a core grant from the National Eye Institute (EY06190) and an unrestricted grant from the Research to Prevent Blindness Foundation. All other authors declare no competing interests.

Data sharing

Data requests will be reviewed on a case-by-case basis by the corresponding author, NRA, and the ADJUST Coordinating Centre. Interested researchers should send an email request to the corresponding author along with the research proposal for consideration. Following approvals, de-identified patient data and a data dictionary defining each field in the set will be made available. The trial protocol and statistical analysis plan are provided in the appendix.

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