



Clinical trial results: ADalimumab Vs. conventional ImmunoSupprESSION for uveitis (ADVISE)Trial

Summary

EudraCT number	2019-002366-12
Trial protocol	GB
Global end of trial date	09 September 2024

Results information

Result version number	v1 (current)
This version publication date	06 June 2025
First version publication date	06 June 2025

Trial information

Trial identification

Sponsor protocol code	Protocolversion1.0
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03828019
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Johns Hopkins Bloomberg SPH
Sponsor organisation address	410 N Washington Street, Baltimore, United States, 21231
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 September 2024
Global end of trial reached?	Yes
Global end of trial date	09 September 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The ADVISE Trial is a randomized, parallel-treatment, comparative effectiveness trial, comparing adalimumab to conventional immunosuppression for the treatment of non-infectious, intermediate, posterior, and panuveitides.

Based on the preliminary data we assume that adalimumab will be superior to conventional immunosuppression for successful corticosteroid-sparing with no clinically important increase in uveitis symptoms namely inactive uveitis and prednisone <7.5 mg/day for 2 visits >28 days apart by 6 months of follow-up.

Protection of trial subjects:

The protocol and consent were approved by the IRB/Ethics of participating centers before beginning recruitment of patients. All participants signed a consent statement and medical record release form as well as HIPAA – complaint privacy practices acknowledgment prior to participation in the study.

Surveillance of uveitis and treatment complications is conducted throughout the study; any such complications encountered are managed by the best medical judgment of the treating ophthalmologist. These events are recorded on study data forms and are submitted to the CC. Summaries of these data are reviewed by the DSMC at each meeting. Important, serious, or unusual adverse events require expedited reporting to the CC and are reviewed by the CC Safety Officer, who makes the determination as to whether the event meets the criteria for a safety report and whether expedited review by DSMC Safety Officer is warranted. The CC Safety Officer follows all serious adverse events through resolution. All serious and unexpected events possibly related to uveitis treatment will be reported as safety reports to the NEI project officer, the FDA, the pharmaceutical supplier (where appropriate), and all clinical centers in accordance with FDA regulations. The CC and clinical centers will submit all safety reports as expedited reports to their IRBs. Reports of serious events not deemed to be unexpected will be submitted to the CC IRB, to the IRB of the clinical center in which the event was reported, as well as to any other study center IRBs, which require such reports.

Confidentiality of patient data will be maintained in accordance with legal regulations. Protected health information (PHI) not be transmitted to the CO, CC, RC, or to other ADVISE sites. PHI collected for study purposes, possibly including name, social security number, address, and other such personal data will be kept sole

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 August 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 12
Country: Number of subjects enrolled	Australia: 23

Country: Number of subjects enrolled	United States: 192
Worldwide total number of subjects	227
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	3
Adults (18-64 years)	199
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial was conducted at 27 clinical centers in the United States (19), the United Kingdom (5), Australia (2), and Canada (1). Eligible patients were adults or adolescents >13 years age, with active or recently-active (within 60 days) non-infectious, intermediate, posterior, or panuveitis for whom immunosuppression was indicated.

Pre-assignment

Screening details:

Screening details:

338 screened, 227 randomized

111 Excluded

Major reasons for exclusion were;

Patient preference (20%)

inactive Uveitis (7%)

Medication issues (29%)

Medical condition (23%)

Period 1

Period 1 title	Overall study 12 months (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Visual acuity and ophthalmic reading center graders were masked as to treatment assignment

Arms

Are arms mutually exclusive?	Yes
Arm title	Adalimumab (ADA)

Arm description:

Adalimumab administered by subcutaneous injection at dosage and frequency specified below; total duration of treatment is 12 months.

Adults (≥ 18 years of age) and adolescents ≥ 30 kg: 80 mg as initial dose; one week later by 40 mg then 40 mg every two weeks. Adolescents < 30 kg: 40 mg as initial dose; one week later 20 mg then 20 mg every 2 weeks.

Arm type	Experimental
Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

Adalimumab administered by subcutaneous injection at dosage and frequency specified below; total duration of treatment is 12 months.

Adults (≥ 18 years of age) and adolescents ≥ 30 kg: 80 mg as initial dose; one week later by 40 mg then 40 mg every two weeks. Adolescents < 30 kg: 40 mg as initial dose; one week later 20 mg then 20 mg every 2 weeks. Adalimumab (ADA): Adalimumab is a fully-human monoclonal antibody to tumor necrosis factor (TNF- α), which is approved by the U.S. FDA for the treatment of non-infectious intermediate, posterior, and panuveitis in adults and children 2 years of age and older

Arm title	Conventional Immunosuppression (CID)
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Arm description:

Conventional immunosuppressive agents selected by study ophthalmologist at dose and frequency specified below; 12 month treatment duration.

Azathioprine: initially 2 mg/kg/day; max dose 200 mg/day. Methotrexate initially 15 mg/wk; max dose 25 mg/wk. Mycophenolate initially 1 gm twice a day (BID); max dose 1.5 gm BID. Cyclosporine (Sandimmune - dose 2.5 mg/kg BID and Neoral dose 2 mg/kg BID. Tacrolimus initially 1 mg BID; max dose 3 mg BID.

Arm type	Active comparator
Investigational medicinal product name	Azathioprine:
Investigational medicinal product code	
Other name	Imuran
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

initially 2mg/kg/day; max dose 200mg/day.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Injection
Routes of administration	Oral use, Injection

Dosage and administration details:

Methotrexate initially 15mg/wk; max dose 25 mg/wk.

Investigational medicinal product name	Mycophenolate
Investigational medicinal product code	
Other name	CellCept
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Mycophenolate initially 1 gm twice a day (BID); max dose 1.5 gm BID

Investigational medicinal product name	Cyclosporine
Investigational medicinal product code	
Other name	Sandimmune, Neoral
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

dose 2.5mg/kg BID

Investigational medicinal product name	Tacrolimus
Investigational medicinal product code	
Other name	Prograf
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

initially 1 mg BID; max dose 3 mg BID.

Number of subjects in period 1	Adalimumab (ADA)	Conventional Immunosuppression (CID)
Started	114	113
Completed	109	98
Not completed	5	15
Physician decision	1	-
Consent withdrawn by subject	2	6
Incarcerated	1	-
Lost to follow-up	1	9

Baseline characteristics

Reporting groups

Reporting group title	Adalimumab (ADA)
Reporting group description:	
Adalimumab administered by subcutaneous injection at dosage and frequency specified below; total duration of treatment is 12 months.	
Adults (≥ 18 years of age) and adolescents ≥ 30 kg: 80 mg as initial dose; one week later by 40 mg then 40 mg every two weeks. Adolescents < 30 kg: 40 mg as initial dose; one week later 20 mg then 20 mg every 2 weeks.	
Reporting group title	Conventional Immunosuppression (CID)
Reporting group description:	
Conventional immunosuppressive agents selected by study ophthalmologist at dose and frequency specified below; 12 month treatment duration.	
Azathioprine: initially 2 mg/kg/day; max dose 200 mg/day. Methotrexate initially 15 mg/wk; max dose 25 mg/wk. Mycophenolate initially 1 gm twice a day (BID); max dose 1.5 gm BID. Cyclosporine (Sandimmune - dose 2.5 mg/kg BID and Neoral dose 2 mg/kg BID. Tacrolimus initially 1 mg BID; max dose 3 mg BID.	

Reporting group values	Adalimumab (ADA)	Conventional Immunosuppression (CID)	Total
Number of subjects	114	113	227
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	44	44	
inter-quartile range (Q1-Q3)	34 to 55	34 to 59	-
Gender categorical Units: Subjects			
Female	75	78	153
Male	39	35	74
Race			
Race			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	8	4	12
Black	21	20	41
White	81	82	163
More than 1 race	1	2	3
Unknow	3	4	7
Type of uveitis			

Units: Subjects			
Intermediate	8	10	18
Anterior and intermediate birdshot	20	12	32
Multifocalchoroiditis with panuveitis	23	26	49
Serpiginouschoroiditis	10	9	19
Punctate innerchoroiditis	2	4	6
Sympatheticophthalmia	3	2	5
Vogt-Koyanagi-Harada diseaseearly stage	2	2	4
Vogt-Koyanagi-Harada diseaselate stage	7	6	13
Isolated retinalvasculitis orpanuveitis withretina	1	4	5
Isolatedchoroiditis orpanuveitis withchoroiditis	28	23	51
	10	15	25
On immunotherapy at baseline			
Was the patient taking an immunotherapy medication (methotrexate, azathioprine, mycophenolate, cyclosporine, tacrolimus) at baseline. Randomization was stratified by whether the participant was receiving no or 1 immunosuppressive drug at baseline.			
Units: Subjects			
No Immunotherapy	90	88	178
On immunotherapy	24	25	49
Starting trial corticosteroid dose			
Indicates whether patient was to begin the trial on a daily dose of corticosteroid ≥ 30 mg or less than 30 mg.			
Units: Subjects			
steroid dose < 30 mg	29	28	57
steroid dose ≥ 30 mg	85	85	170
Best corrected visual acuity			
Participants' visual acuity was measured by certified examiners with best refractive correction in place. Participants were challenged with reading letters on lines of the standard ETDRS eye chart(5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart.Participants read down the chart until no more meaningful readings could be made and were scored by how many letters could be correctly identified. More letters read is associated with higher visual acuity. (85 standard letters =20/20 vision)			
Units: Standard lettersEDTRS eyechart			
median			
inter-quartile range (Q1-Q3)			-
Retinal thickness at the center subfield			
Measure Description: Central subfield thickness asmeasured by OCT at a fundus photograph reading center.Values > 300 are indicative of macular edema.			
Units: um retinal thickness			
median			
inter-quartile range (Q1-Q3)			-

Subject analysis sets

Subject analysis set title	Eyes with uveitis from Arm 1 (ADA)
Subject analysis set type	Per protocol
Subject analysis set description:	
Eyes with uveitis from participants assigned to ADAL. Each patient can contribute one or both eyes to the analysis set. Randomization was per person.	
Subject analysis set title	Eyes with uveitis from Arm 2 (CID)
Subject analysis set type	Per protocol

Subject analysis set description:

Eyes with uveitis from participants assigned to ADAL. Each patient can contribute one or both eyes to the analysis set. Randomization was per person.

Reporting group values	Eyes with uveitis from Arm 1 (ADA)	Eyes with uveitis from Arm 2 (CID)	
Number of subjects	214	220	
Age categorical			
Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)			
Gender categorical			
Units: Subjects			
Female			
Male			
Race			
Race			
Units: Subjects			
American Indian or Alaska Native Asian Black White More than 1 race Unknow			
Type of uveitis			
Units: Subjects			
Intermediate Anterior and intermediate birdshot Multifocalchoroiditis with panuveitis Serpiginouschoroiditis Punctate innerchoroiditis Sympatheticophthalmia Vogt-Koyanagi-Harada diseaseearly stage Vogt-Koyanagi-Harada diseaselate stage Isolated retinalvasculitis orpanuveitis withretina Isolatedchoroiditis orpanuveitis withchoroiditis			

On immunotherapy at baseline			
Was the patient taking an immunotherapy medication (methotrexate, azathioprine, mycophenolate, cyclosporine, tacrolimus) at baseline. Randomization was stratified by whether the participant was receiving no or 1 immunosuppressive drug at baseline.			
Units: Subjects			
No Immunotherapy			
On immunotherapy			
Starting trial corticosteroid dose			
Indicates whether patient was to begin the trial on a daily dose of corticosteroid ≥ 30 mg or less than 30 mg.			
Units: Subjects			
steroid dose < 30 mg			
steroid dose ≥ 30 mg			
Best corrected visual acuity			
Participants' visual acuity was measured by certified examiners with best refractive correction in place. Participants were challenged with reading letters on lines of the standard ETDRS eye chart(5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart.Participants read down the chart until no more meaningful readings could be made and were scored by how many letters could be correctly identified. More letters read is associated with higher visual acuity. (85 standard letters =20/20 vision)			
Units: Standard lettersEDTRS eyechart			
median	81	81	
inter-quartile range (Q1-Q3)	71 to 87	71 to 86	
Retinal thickness at the center subfield			
Measure Description: Central subfield thickness asmeasured by OCT at a fundus photograph reading center.Values > 300 are indicative of macular edema.			
Units: um retinal thickness			
median	255	247	
inter-quartile range (Q1-Q3)	229 to 318	219 to 282	

End points

End points reporting groups

Reporting group title	Adalimumab (ADA)
Reporting group description: Adalimumab administered by subcutaneous injection at dosage and frequency specified below; total duration of treatment is 12 months. Adults (≥ 18 years of age) and adolescents ≥ 30 kg: 80 mg as initial dose; one week later by 40 mg then 40 mg every two weeks. Adolescents < 30 kg: 40 mg as initial dose; one week later 20 mg then 20 mg every 2 weeks.	
Reporting group title	Conventional Immunosuppression (CID)
Reporting group description: Conventional immunosuppressive agents selected by study ophthalmologist at dose and frequency specified below; 12 month treatment duration. Azathioprine: initially 2 mg/kg/day; max dose 200 mg/day. Methotrexate initially 15 mg/wk; max dose 25 mg/wk. Mycophenolate initially 1 gm twice a day (BID); max dose 1.5 gm BID. Cyclosporine (Sandimmune) - dose 2.5 mg/kg BID and Neoral dose 2 mg/kg BID. Tacrolimus initially 1 mg BID; max dose 3 mg BID.	
Subject analysis set title	Eyes with uveitis from Arm 1 (ADA)
Subject analysis set type	Per protocol
Subject analysis set description: Eyes with uveitis from participants assigned to ADAL. Each patient can contribute one or both eyes to the analysis set. Randomization was per person.	
Subject analysis set title	Eyes with uveitis from Arm 2 (CID)
Subject analysis set type	Per protocol
Subject analysis set description: Eyes with uveitis from participants assigned to ADAL. Each patient can contribute one or both eyes to the analysis set. Randomization was per person.	

Primary: Corticosteroid-sparing Treatment Success Within the First 6 Months After Randomization

End point title	Corticosteroid-sparing Treatment Success Within the First 6 Months After Randomization
End point description: Corticosteroid-sparing success is defined as achieving inactive uveitis for two consecutive visits ≥ 28 days apart while on ≤ 7.5 mg/day of corticosteroids. Uveitis status (active vs inactive) is determined by the study ophthalmologist after reviewing the eye exam and imaging. Steroid dose and uveitis activity from visit months 6, 8, 10 and 12 were included in the analysis. Generalized estimating equations were used to fit logistic regression models to compare the cumulative proportion of corticosteroid sparing between the two treatment groups over time while accounting for correlation between replicate measurements on the same individual with an unstructured covariance matrix. Results were reported at 6 months (primary outcome) and 12 months (secondary outcome).	
End point type	Primary
End point timeframe: At 6 months	

End point values	Adalimumab (ADA)	Conventional Immunosuppression (CID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	105		
Units: Proportion with corticosteroid sparing				
number (confidence interval 5%)	0.69 (0.60 to 0.77)	0.54 (0.44 to 0.64)		

Statistical analyses

Statistical analysis title	Treatment effect Odds ratio ADA/CID
Statistical analysis description:	
Odds ratio ADA / CID	
Generalized estimating equations were used to fit logistic regression models to compare the cumulative proportion of corticosteroid outcomes (sparing and cessation) between the two treatment groups over time while accounting for correlation between replicate measurements on the same individual with an unstructured covariance matrix	
Comparison groups	Adalimumab (ADA) v Conventional Immunosuppression (CID)
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	3.25

Secondary: Corticosteroid discontinuation at 6 months

End point title	Corticosteroid discontinuation at 6 months
End point description:	
Corticosteroid discontinuation success is defined as achieving inactive uveitis for two consecutive visits ≥ 28 days apart after discontinuing corticosteroids. Uveitis status (active vs inactive) is determined by the study ophthalmologist after reviewing the eye exam and imaging. Steroid dose and uveitis activity from visit months 6,8,10 and 12 were included in the analysis. Generalized estimating equations were used to fit logistic regression models to compare the cumulative proportion of corticosteroid discontinuation between the two treatment groups over time while accounting for correlation between replicate measurements on the same individual with an unstructured covariance matrix. Results were reported at 6 months and 12 months.	
End point type	Secondary
End point timeframe:	
6 months	

End point values	Adalimumab (ADA)	Conventional Immunosuppression (CID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	105		
Units: cumulative proportion				
number (confidence interval 95%)	0.15 (0.09 to 0.24)	0.11 (0.06 to 0.18)		

Statistical analyses

Statistical analysis title	Treatment effect Odds Ratio ADA/CID
Statistical analysis description:	
Greater than 1 indicates ADA was superior in participants achieving cessation of corticosteroid treatment	
Comparison groups	Adalimumab (ADA) v Conventional Immunosuppression (CID)
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	3.46

Secondary: Corticosteroid-sparing Treatment Success at 12 months

End point title	Corticosteroid-sparing Treatment Success at 12 months
End point description:	
on ≤ 7.5 mg/day of corticosteroids. Uveitis status (active vs inactive) is determined by the study ophthalmologist after reviewing the eye exam and imaging. Steroid dose and uveitis activity from visit months 6,8,10 and 12 were included in the analysis. Generalized estimating equations were used to fit logistic regression models to compare the cumulative proportion of corticosteroid sparing between the two treatment groups over time while accounting for correlation between replicate measurements on the same individual with an unstructured covariance matrix. Results were reported at 6 months (primary outcome) and 12 months (secondary outcome).	
End point type	Secondary
End point timeframe:	
At 12 months	

End point values	Adalimumab (ADA)	Conventional Immunosuppression (CID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Proportion with corticosteroid sparing				
number (confidence interval 95%)	0.86 (0.78 to 0.92)	0.77 (0.67 to 0.84)		

Statistical analyses

Statistical analysis title	Treatment effect Odds ratio ADA/CID
Statistical analysis description:	
Odds ratio ADA / CID	
Generalized estimating equations were used to fit logistic regression models to compare the cumulative proportion of corticosteroid outcomes (sparing and cessation) between the two treatment groups over time while accounting for correlation between replicate measurements on the same individual with an unstructured covariance matrix	
Comparison groups	Adalimumab (ADA) v Conventional Immunosuppression (CID)
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.077
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	3.83

Secondary: Corticosteroid discontinuation at 12 months

End point title	Corticosteroid discontinuation at 12 months
End point description:	
Corticosteroid discontinuation success is defined as achieving inactive uveitis for two consecutive visits >= 28 days apart after discontinuing corticosteroids. Uveitis status (active vs inactive) is determined by the study ophthalmologist after reviewing the eye exam and imaging. Steroid dose and uveitis activity from visit months 6,8,10 and 12 were included in the analysis. Generalized estimating equations were used to fit logistic regression models to compare the cumulative proportion of corticosteroid discontinuation between the two treatment groups over time while accounting for correlation between replicate measurements on the same individual with an unstructured covariance matrix. Results were reported at 6 months and 12 months.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Adalimumab (ADA)	Conventional Immunosuppression (CID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	98		
Units: Cumulative proportion				
number (confidence interval 95%)	0.55 (0.45 to 0.64)	0.40 (0.30 to 0.50)		

Statistical analyses

Statistical analysis title	Treatment effect Odds Ratio ADA/CID
Statistical analysis description:	
Greater than 1 indicates ADA was superior in participants achieving cessation of corticosteroid treatment	
Comparison groups	Conventional Immunosuppression (CID) v Adalimumab (ADA)
Number of subjects included in analysis	207
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.06
upper limit	3.19

Secondary: Best Corrected Visual Acuity Change at 12 Months

End point title	Best Corrected Visual Acuity Change at 12 Months
End point description:	
Mean change in best-corrected visual acuity from baseline to 12 months. Participants' visual acuity was measured by certified examiners with best refractive correction in place. Participants were challenged with reading letters on lines of the standard ETDRS eye chart (5 letters per line). Lines became smaller as participants progressed from the top to the bottom of the chart. Participants read down the chart until no more meaningful readings could be made and were scored by how many letters could be correctly identified. More letters read is associated with higher visual acuity (85 letters is 20/20 vision). Visual acuity data was collected at baseline and months 1,2,3,4,5,6,8,10, and 12 and estimated at 12 months with a mixed model.	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Adalimumab (ADA)	Conventional Immunosuppression (CID)	Eyes with uveitis from Arm 1 (ADA)	Eyes with uveitis from Arm 2 (CID)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	0 ^[1]	0 ^[2]	198	188
Units: Standard letters ETDRS				
number (confidence interval 95%)	(to)	(to)	3.6 (1.3 to 5.8)	3.2 (1.7 to 4.6)

Notes:

[1] - Analysis sets were eyes

[2] - Analysis sets were eyes

Statistical analyses

Statistical analysis title	VA Difference in change from baseline ADA - CID
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Statistical analysis description:

Mixed effects models were used with a linear link. The fixed effects included initial steroid dose and immunosuppression use at baseline. Additional visit indicators (months 1-12) and corresponding treatment by visit interaction terms. An unstructured correlation was used to model repeated measurements by eye . A person-level random intercept was added to account for between-eye correlations.

Comparison groups	Eyes with uveitis from Arm 1 (ADA) v Eyes with uveitis from Arm 2 (CID)
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.77
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.3
upper limit	3.1

Secondary: Macular Edema at 12 Months of Follow up

End point title	Macular Edema at 12 Months of Follow up
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End point description:

Macular edema is defined as central retinal thickness greater than or equal to 300 micrometers as measured by a masked grader's review of OCT images. Greater retinal thickness is associated with poorer vision. Outcome measure is the odds ratio comparing macular edema at 12 months to baseline macular edema. Macular edema was measured at baseline and months 3, 6, and 12. The odds ratio at 12 months was estimated with a mixed model.

End point type	Secondary
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End point timeframe:

12 months

End point values	Eyes with uveitis from Arm 1 (ADA)	Eyes with uveitis from Arm 2 (CID)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	198	188		
Units: odds ratio				
number (confidence interval 95%)	0.34 (0.23 to 0.51)	0.63 (0.42 to 0.94)		

Statistical analyses

Statistical analysis title	Treatment effect - ratio of odds ratios
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Statistical analysis description:

Mixed effects models with a log link were used to assess treatment differences . The outcome measure was the odds ratio of having macular edema (OCT central subfield thickness > 300 um) at 12 months compared to baseline (BL). The treatment effect was the ratio of Odds ratios (ADA/CID) at 12 months. Values less than one indicate improvement in macular edema for the ADA treatment group relative to the CID group. Decrease in subfield thickness is good

Comparison groups	Eyes with uveitis from Arm 1 (ADA) v Eyes with uveitis from Arm 2 (CID)
Number of subjects included in analysis	386
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.028
Method	Mixed models analysis
Parameter estimate	Ratio of odds ratios
Point estimate	0.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.31
upper limit	0.94

Secondary: Hepatotoxicity - elevated levels of AST or ALT by 12 months

End point title	Hepatotoxicity - elevated levels of AST or ALT by 12 months
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End point description:

Cumulative proportion of participants having elevated levels of aspartate aminotransferase (AST) or alanine transaminase (ALT) greater than twice the upper level of normal by 12 months. Elevated levels of AST and ALT may indicate decline in liver function. Lab values of AST and ALT were measured at baseline and months 1,2,3,4,5,6,8,10, and 12 and the cumulative proportion of participants with elevated lab values by 12 months was estimated by Kaplan Meier methods.

End point type	Secondary
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End point timeframe:

12 months

End point values	Adalimumab (ADA)	Conventional Immunosuppression (CID)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	111	110		
Units: Cumulative proportion of participants				
number (confidence interval 95%)	2 (0 to 5)	10 (4 to 16)		

Statistical analyses

Statistical analysis title	Treatment effect hazard ratio ADA/CID
Statistical analysis description:	
Kaplan Meier techniques and Cox proportional hazards models were used to evaluate this outcome	
Comparison groups	Adalimumab (ADA) v Conventional Immunosuppression (CID)
Number of subjects included in analysis	221
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.014
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.7

Secondary: Cataract surgery by 12 months

End point title	Cataract surgery by 12 months
End point description:	
Cumulative proportion of uveitis eyes having cataract surgery by 12 months. Whether the patient had cataract surgery in the prior time period was determined at baseline and months 1,2,3,4,5,6,8,10,12 and the cumulative proportion of eyes having cataract surgery by 12 months was estimated by Kaplan-Meier methods	
End point type	Secondary
End point timeframe:	
12 months	

End point values	Eyes with uveitis from Arm 1 (ADA)	Eyes with uveitis from Arm 2 (CID)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	176	172		
Units: Cumulative proportion of participants				
number (confidence interval 95%)	2 (0 to 5)	11 (4 to 17)		

Statistical analyses

Statistical analysis title	Treatment effect hazard ratio ADA/CID
Comparison groups	Eyes with uveitis from Arm 1 (ADA) v Eyes with uveitis from Arm 2 (CID)
Number of subjects included in analysis	348
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.07
upper limit	0.67

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Over 12 months of study.

Adverse event reporting additional description:

Non serious events were collected in both systemic and non-systemic forms. Systematic collections was asking participants if they experienced any new occurrence of a specify diagnosis, event, or side effect symptom on the case report form at each clinic visit. Non-systemic data was collected by asking if the patient experienced any other events.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	4
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Reporting groups

Reporting group title	All participants in Arm 1 with follow up after baseline visit
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Reporting group description: -

Reporting group title	All participants in Arm 2 with follow up after baseline visit
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Reporting group description: -

Serious adverse events	All participants in Arm 1 with follow up after baseline visit	All participants in Arm 2 with follow up after baseline visit	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 113 (14.16%)	13 / 110 (11.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	1 / 113 (0.88%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
basal cell carcinoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ocular lymphoma			

subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
atrial fibrillation			
subjects affected / exposed	0 / 113 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
cardiovascular disorder			
subjects affected / exposed	0 / 113 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Miscarriage			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
iris bombe			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitic glaucoma			
subjects affected / exposed	2 / 113 (1.77%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced	Additional description: More than 6 lines of visual acuity loss		
subjects affected / exposed	5 / 113 (4.42%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cataract			
subjects affected / exposed	0 / 113 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: Hospitalized for evaluation		
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 113 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inflammatory bowel disease			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 113 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			

subjects affected / exposed	0 / 113 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 113 (0.00%)	2 / 110 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 110 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalemia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 110 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	All participants in Arm 1 with follow up after baseline visit	All participants in Arm 2 with follow up after baseline visit	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	108 / 113 (95.58%)	104 / 110 (94.55%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Appetite disorder subjects affected / exposed occurrences (all)	38 / 113 (33.63%) 38	46 / 110 (41.82%) 46	
Nervous system disorders			
dizziness subjects affected / exposed occurrences (all)	6 / 113 (5.31%) 6	5 / 110 (4.55%) 5	
Headache subjects affected / exposed occurrences (all)	76 / 113 (67.26%) 76	78 / 110 (70.91%) 78	
Tremor subjects affected / exposed occurrences (all)	43 / 113 (38.05%) 43	60 / 110 (54.55%) 60	
General disorders and administration site conditions			
Fatigue subjects affected / exposed occurrences (all)	76 / 113 (67.26%) 76	87 / 110 (79.09%) 87	
Impaired healing subjects affected / exposed occurrences (all)	28 / 113 (24.78%) 28	44 / 110 (40.00%) 44	
Eye disorders			
Epiretinal membrane subjects affected / exposed occurrences (all)	17 / 113 (15.04%) 17	20 / 110 (18.18%) 20	
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	46 / 113 (40.71%) 46	48 / 110 (43.64%) 48	
Diarrhea subjects affected / exposed occurrences (all)	42 / 113 (37.17%) 42	46 / 110 (41.82%) 46	
Gingival swelling subjects affected / exposed occurrences (all)	23 / 113 (20.35%) 23	24 / 110 (21.82%) 24	
Nausea			

subjects affected / exposed occurrences (all)	42 / 113 (37.17%) 42	52 / 110 (47.27%) 52	
Vomiting subjects affected / exposed occurrences (all)	15 / 113 (13.27%) 15	18 / 110 (16.36%) 18	
Mouth ulcer subjects affected / exposed occurrences (all)	21 / 113 (18.58%) 21	23 / 110 (20.91%) 23	
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	32 / 113 (28.32%) 32	36 / 110 (32.73%) 26	
Alopecia subjects affected / exposed occurrences (all)	38 / 113 (33.63%) 38	52 / 110 (47.27%) 52	
Easy bruising subjects affected / exposed occurrences (all)	55 / 113 (48.67%) 55	59 / 110 (53.64%) 59	
Hair growth abnormal subjects affected / exposed occurrences (all)	21 / 113 (18.58%) 21	23 / 110 (20.91%) 23	
Rash subjects affected / exposed occurrences (all)	34 / 113 (30.09%) 34	32 / 110 (29.09%) 32	
Swelling face subjects affected / exposed occurrences (all)	51 / 113 (45.13%) 51	67 / 110 (60.91%) 67	
Psychiatric disorders			
Depression subjects affected / exposed occurrences (all)	60 / 113 (53.10%) 60	67 / 110 (60.91%) 67	
Insomnia subjects affected / exposed occurrences (all)	77 / 113 (68.14%) 77	79 / 110 (71.82%) 79	
Musculoskeletal and connective tissue disorders			

Muscular weakness subjects affected / exposed occurrences (all)	44 / 113 (38.94%) 44	53 / 110 (48.18%) 53	
Myalgia subjects affected / exposed occurrences (all)	77 / 113 (68.14%) 77	84 / 110 (76.36%) 84	
Infections and infestations			
Covid-19 infection subjects affected / exposed occurrences (all)	11 / 113 (9.73%) 11	17 / 110 (15.45%) 17	
Upper respiratory infection subjects affected / exposed occurrences (all)	8 / 113 (7.08%) 8	2 / 110 (1.82%) 2	
Metabolism and nutrition disorders			
Fat redistribution subjects affected / exposed occurrences (all)	30 / 113 (26.55%) 30	30 / 110 (27.27%) 30	
Fluid retention subjects affected / exposed occurrences (all)	46 / 113 (40.71%) 46	51 / 110 (46.36%) 51	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported