Clinical trial results:
A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab as Maintenance Therapy in Subjects Requiring High Dose Corticosteroids for Active Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese Patients

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2009-016095-68
Trial protocol	FR ES BE PT GB NL DE DK AT IT CZ GR
Global end of trial date	29 August 2014

Results information

Result version number	v1 (current)
This version publication date	24 July 2016
First version publication date	24 July 2016

Trial information

Trial identification

Sponsor protocol code	M10-877

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01138657
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbvie Deutschland GmbH & Co.KG
Sponsor organisation address	AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Information, Abbvie, 001 800-633-9110,
Scientific contact	Andrew Payne, AbbVie, andy.payne@abbvie.com

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	29 August 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study was to evaluate the efficacy and safety of adalimumab 80 mg loading dose followed by 40 mg dose given every other week (eow) subcutaneously (SC) starting at Week 1 compared with placebo as maintenance therapy in subjects requiring high dose corticosteroids for active non-infectious intermediate uveitis, posterior uveitis, or panuveitis.

Protection of trial subjects:

The study was conducted in accordance with the protocol, ICH guidelines, applicable regulations and guidelines governing clinical study conduct, and the ethical principles that have their origin in the Declaration of Helsinki and all applicable local regulations.
The investigator or his/her representative explained the nature of the study to the subject, and answered all questions regarding the study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement was reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 August 2010
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	Australia: 14
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Japan: 16
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	United States: 85
Country: Number of subjects enrolled	Argentina: 3
Country: Number of subjects enrolled	Poland: 4
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 14
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 3

Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Greece: 1
Country: Number of subjects enrolled	Italy: 12
Worldwide total number of subjects	239
EEA total number of subjects	90

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)	0
Adults (18-64 years)	213
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study includes a Japan sub-study. 239 subjects with active non-infectious intermediate uveitis, posterior uveitis, or panuveitis were randomized worldwide, including 223 participants at 67 sites in Australia, Europe, Israel, Latin America, and North America (Main Study), and 16 participants randomized at 7 sites in Japan (Japan sub-study).

Pre-assignment

Screening details:

Subjects were randomized in a 1:1 ratio double-masked fashion using baseline immunosuppressant usage as the stratification factor. Subjects recruited in the Japan sub-study were randomized in a separate stratum with no stratification by baseline IMM usage.
Study completion is defined as meeting treatment failure or reaching study Week 80.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo subcutaneous injection at Baseline followed by every other week (eow) dosing starting at Week 1 for up to 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection

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

Dosage and administration details:

Administered orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper schedule in which all subjects continuing in the study were to discontinue prednisone no later than Week 15.

Arm title	Adalimumab

Arm description:

Subjects received adalimumab 80 mg subcutaneous loading dose at Baseline followed by 40 mg doses eow starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Arm type	Experimental

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	Humira
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered SC as an 80 mg loading dose (2 syringes) at Baseline followed by a 40 mg dose eow starting at Week 1.

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

Dosage and administration details:

Administered orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper schedule in which all subjects continuing in the study were to discontinue prednisone no later than Week 15.

Number of subjects in period 1	Placebo	Adalimumab
Started	120	119
Enrolled in Main Study	112	111
Enrolled in Japan Sub-study	8 [1]	8 [2]
Completed	112	101
Not completed	8	18
Other	3	4
Adverse event	3	10
Lost to follow-up	-	3
Lack of efficacy	2	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only includes subjects who enrolled in Japan

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only includes subjects who enrolled in Japan

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo subcutaneous injection at Baseline followed by every other week (eow) dosing starting at Week 1 for up to 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.	
Reporting group title	Adalimumab
Reporting group description:	
Subjects received adalimumab 80 mg subcutaneous loading dose at Baseline followed by 40 mg doses eow starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.	

Reporting group values	Placebo	Adalimumab	Total
Number of subjects	120	119	239
Age categorical Units: Subjects			
< 40 years	56	47	103
40 - 64 years	54	56	110
≥ 65 years	10	16	26
Age continuous Units: years			
arithmetic mean	43.19	43.46	
standard deviation	± 14.331	± 15.458	-
Gender categorical Units: Subjects			
Female	73	66	139
Male	47	53	100
Race Units: Subjects			
White	91	89	180
Black	12	11	23
Asian	10	12	22
American Indian/Alaskan Native	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Other	5	6	11
Multi Race	1	1	2
Type of Uveitis Units: Subjects			
Intermediate	24	25	49
Posterior	38	38	76
Panuveitis	58	56	114
Diagnosis Units: Subjects			
Idiopathic	50	40	90
Birdshot Choroidopathy	21	24	45
Multifocal Choroiditis And Panuveitis	5	8	13

Vogt Koyanagi Harada	14	12	26
Sarcoid	12	12	24
Behcet's	4	14	18
Other	14	9	23
Eye Affected Units: Subjects			
Left	5	6	11
Right	4	7	11
Both	111	106	217
Duration of Uveitis Units: months			
arithmetic mean	58.56	41.18	
standard deviation	± 85.308	± 53.53	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo subcutaneous injection at Baseline followed by every other week (eow) dosing starting at Week 1 for up to 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Reporting group title	Adalimumab

Reporting group description:

Subjects received adalimumab 80 mg subcutaneous loading dose at Baseline followed by 40 mg doses eow starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Subject analysis set title	Main Study: Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects, excluding those enrolled in the Japan sub-study, received placebo subcutaneous injection at Baseline followed by eow dosing starting at Week 1 for up to 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Subject analysis set title	Main Study: Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects, excluding those enrolled in the Japan sub-study, received adalimumab 80 mg subcutaneous loading dose at Baseline followed by 40 mg doses every other week (eow) starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Subject analysis set title	Integrated Study (Main + Japan Sub-study): Placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects, including those enrolled in the Main Study and the Japan Sub-study, received placebo subcutaneous injection at Baseline followed by eow dosing starting at Week 1 for up to 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Subject analysis set title	integrated Study (Main + Japan Sub-study): Adalimumab
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects, including those enrolled in the Main Study and the Japan Sub-study, received adalimumab 80 mg subcutaneous loading dose at Baseline followed by 40 mg doses eow starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Primary: Time to Treatment Failure on or After Week 6

End point title	Time to Treatment Failure on or After Week 6

End point description:

Time to treatment failure was analyzed using Kaplan-Meier methods. Treatment failures on or after Week 6 were counted as events. Dropouts for reasons other than treatment failure at any time during the study were censored at the drop out date. To be considered a treatment failure, ≥ 1 of these criteria had to be present in at least 1 eye:
• New active, inflammatory chorioretinal or retinal vascular lesions relative to Baseline
• Inability to achieve ≤ 0.5+ at Week 6 or a 2-step increase relative to best state achieved at all visits after Week 6 in anterior chamber cell grade or vitreous haze grade
• Worsening of best corrected visual acuity by ≥ 15 letters relative to best state achieved.

The primary analysis was performed in the intent-to-treat (ITT) population which included all randomized subjects recruited outside Japan; 6 subjects at 2 sites were excluded from the ITT due to

incomplete efficacy source data and compliance issues. "99999" indicates values not estimable.

End point type	Primary

End point timeframe:

From Baseline until end of study (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	107	110	115	118
Units: months				
median (inter-quartile range (Q1-Q3))	3 (1.5 to 5.6)	5.6 (3 to 99999)	3 (1.5 to 5.6)	4.8 (2.8 to 99999)

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The primary analysis of the primary endpoint was performed on Main Study data, excluding the Japanese sub-study. The statistical test was performed at a 2-sided significance level of 0.05. The hazard ratio of adalimumab versus placebo was calculated using proportional hazards regression with treatment as factor.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.7

Notes:

[1] - Difference

Statistical analysis title	Additional Analysis – Integrated Study

Statistical analysis description:

An additional analysis of the primary endpoint was performed using the Integrated Study data (Main Study + Japan sub-study). The statistical test was performed at a 2-sided significance level of 0.05. The hazard ratio of adalimumab versus placebo was calculated using proportional hazards regression with treatment and race (Japanese versus non-Japanese) as factors.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab

Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.76

Notes:

[2] - Difference

Secondary: Change in Anterior Chamber (AC) Cell Grade in Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change in Anterior Chamber (AC) Cell Grade in Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

Slit lamp examinations were conducted at each visit to assess AC cell count. The number of AC cells observed within a 1 mm × 1 mm slit beam was used to determine the grade according to the Standardization of Uveitis Nomenclature (SUN) criteria:
Grade 0 = < 1 cell
Grade 0.5+ = 1-5 cells
Grade 1+ = 6-15 cells
Grade 2+ = 16-25 cells
Grade 3+ = 26-50 cells
Grade 4+ = > 50 cells.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used; subjects with no values after Week 6 were excluded.

End point type	Secondary

End point timeframe:

From Baseline to Week 6 and at the Final/Early Termination Visit (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[3]	101[4]	110[5]	109[6]
Units: units on a scale				
arithmetic mean (standard deviation)				
Left Eye	0.59 (± 0.935)	0.35 (± 0.763)	0.56 (± 0.913)	0.35 (± 0.744)
Right Eye	0.69 (± 1.067)	0.36 (± 0.746)	0.65 (± 1.039)	0.36 (± 0.727)

Notes:

[3] - Subjects with values at both timepoints

[4] - Subjects with values at both timepoints

[5] - Subjects with values at both timepoints

[6] - Subjects with values at both timepoints

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.011 [8]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.51
upper limit	-0.07

Notes:

[7] - Difference

[8] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as factor adjusted for clustered observations (i.e., observations from each of the subject's eyes).

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.019 [10]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.46
upper limit	-0.04

Notes:

[9] - Difference

[10] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors adjusted for clustered observations (i.e., observations from each of the subject's eyes).

Secondary: Change in Vitreous Haze (VH) Grade in Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change in Vitreous Haze (VH) Grade in Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

Vitreous haze was measured using dilated indirect ophthalmoscopy (DIO) and assessed by the Investigator according to National Eye Institute (NEI) and SUN criteria:
Grade 0: No evident vitreous haze;
Grade 0.5+: Slight blurring of the optic disc margin because of the haze; normal striations and reflex of the nerve fiber layer cannot be visualized;
Grade 1+: Permits a better definition of both the optic nerve head and the retinal vessels (compared to higher grades);
Grade 2+: Permits better visualization of the retinal vessels (compared to higher grades);
Grade 3+: Permits the observer to see the optic nerve head, but the borders are quite blurry;
Grade 4+: Optic nerve head is obscured.

This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used; subjects with no values after Week 6 were excluded.

End point type	Secondary

End point timeframe:

From Baseline to Week 6 and Final/Early Termination Visit (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103[11]	101[12]	111[13]	109[14]
Units: units on a scale				
arithmetic mean (standard deviation)				
Left eye	0.33 (± 0.666)	0.11 (± 0.559)	0.34 (± 0.675)	0.11 (± 0.547)
Right eye	0.45 (± 0.781)	0.13 (± 0.648)	0.49 (± 0.815)	0.16 (± 0.648)

Notes:

[11] - Subjects with values at both time points

[12] - Subjects with values at both time points

[13] - Subjects with values at both time points

[14] - Subjects with values at both time points

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	< 0.001 [16]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.11

Notes:

[15] - Difference

[16] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as factor adjusted for clustered observations.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	< 0.001 [18]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.43
upper limit	-0.12

Notes:

[17] - Difference

[18] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors adjusted for clustered observations.

Secondary: Change In Logarithm of the Minimum Angle of Resolution (LogMAR) Best Corrected Visual Acuity (BCVA) In Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change In Logarithm of the Minimum Angle of Resolution (LogMAR) Best Corrected Visual Acuity (BCVA) In Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

Using corrective lenses based on that visit's refraction testing, subject's best corrected visual acuity was measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) logMAR chart.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used; subjects with no values after Week 6 were excluded.

End point type	Secondary

End point timeframe:

From Baseline to Week 6 and Final/Early Termination Visit (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	103[19]	101[20]	111[21]	109[22]
Units: logMAR				
arithmetic mean (standard deviation)				
Left eye	0.12 (± 0.169)	0.07 (± 0.16)	0.11 (± 0.179)	0.07 (± 0.164)

Right eye	0.13 (± 0.32)	0.04 (± 0.143)	0.13 (± 0.328)	0.05 (± 0.145)

Notes:

[19] - Subjects with values at both timepoints

[20] - Subjects with values at both timepoints

[21] - Subjects with values at both timepoints

[22] - Subjects with values at both timepoints

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Adalimumab v Main Study: Placebo
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.003 [24]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	-0.02

Notes:

[23] - Difference

[24] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as factor adjusted for clustered observations.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.008 [26]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	-0.02

Notes:

[25] - Difference

[26] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors adjusted for clustered observations.

Secondary: Time to Optical Coherence Tomography (OCT) Evidence of Macular Edema in At Least 1 Eye On or After Week 6

End point title	Time to Optical Coherence Tomography (OCT) Evidence of Macular Edema in At Least 1 Eye On or After Week 6

End point description:

Optical coherence tomography was performed at every visit using 1 of 3 approved machines. Images were evaluated by a central reader. Macular edema was defined as cystoid macular edema.
OCT evidence of macular edema on or after Week 6 was to be counted as an event. Dropouts due to reasons other than OCT evidence of macular edema were to be considered as censored observations at the time of dropping out.
This endpoint was only analyzed in subjects without macular edema at Baseline. "99999" indicates values not estimable.

End point type	Secondary

End point timeframe:

From Baseline until the Final Visit (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	45[27]	55[28]	47[29]	57[30]
Units: months				
median (inter-quartile range (Q1-Q3))	6.2 (1.4 to 99999)	11.1 (2.6 to 15.9)	3.7 (1.4 to 99999)	9.2 (2.7 to 15.9)

Notes:

[27] - Subjects without macular edema at Baseline

[28] - Subjects without macular edema at Baseline

[29] - Subjects without macular edema at Baseline

[30] - Subjects without macular edema at Baseline

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%. The hazard ratio of adalimumab versus placebo was calculated using proportional hazards regression with treatment as factor.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.231
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.26

Notes:
[31] - Difference

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%. The hazard ratio of adalimumab versus placebo was calculated using proportional hazards regression with treatment and race (Japanese versus non-Japanese) as factors.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab
Number of subjects included in analysis	104
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.191
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.21

Notes:
[32] - Difference

Secondary: Percent Change in Central Retinal Thickness in Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Percent Change in Central Retinal Thickness in Each Eye From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

Central retinal thickness was measured using OCT and assessed by a central reader.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used; subjects with no values after Week 6 were excluded.

End point type	Secondary

End point timeframe:

Baseline to Week 6 and Final/Early Termination Visit (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[33]	101[34]	108[35]	109[36]
Units: percent change				
arithmetic mean (standard deviation)				
Left eye (n=100, 100, 107, 108)	20.2 (± 52.01)	9.6 (± 29.76)	19 (± 50.57)	13.9 (± 53.95)
Right eye (n=102, 101, 108, 109)	22 (± 62.48)	8.2 (± 25.78)	21.7 (± 60.75)	14.5 (± 57.05)

Notes:

[33] - Subjects with values at both timepoints

[34] - Subjects with values at both timepoints

[35] - Subjects with values at both timepoints

[36] - Subjects with values at both timepoints

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.02 [38]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	-1.8

Notes:

[37] - Difference

[38] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and OCT machine as factors adjusted for clustered observations.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	integrated Study (Main + Japan Sub-study): Adalimumab v Integrated Study (Main + Japan Sub-study): Placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	other[39]
P-value	= 0.428 [40]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.7
upper limit	7.5

Notes:

[39] - Difference

[40] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment, race (Japanese versus non-Japanese) and OCT machine as factors adjusted for

clustered observations.

Secondary: Change in Visual Functioning Questionnaire 25 (VFQ-25) Composite Score From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change in Visual Functioning Questionnaire 25 (VFQ-25) Composite Score From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

The National Eye Institute VFQ-25 is an ocular disease-specific survey that measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning.
The VFQ-25 consists of a base set of 25 vision-targeted questions plus an additional single-item general health rating question.
The overall composite score ranges from 0 to 100, where higher scores or increases in score indicate better vision-related functioning.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used; subjects with no values after Week 6 were excluded.

End point type	Secondary

End point timeframe:

Baseline to Week 6 and Final/Early Termination Visit (up 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[41]	101[42]	110[43]	109[44]
Units: units on a scale				
arithmetic mean (standard deviation)	-5.5 (± 11.968)	-1.3 (± 10.98)	-5.34 (± 11.899)	-1.68 (± 10.924)

Notes:

[41] - Subjects with values at both timepoints

[42] - Subjects with values at both timepoints

[43] - Subjects with values at both timepoints

[44] - Subjects with values at both timepoints

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.01 [46]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	4.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	7.38

Notes:

[45] - Difference

[46] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as a factor.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	integrated Study (Main + Japan Sub-study): Adalimumab v Integrated Study (Main + Japan Sub-study): Placebo
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.019 [48]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	3.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	6.71

Notes:

[47] - Difference

[48] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Secondary: Change in VFQ-25 Distance Vision Subscore From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change in VFQ-25 Distance Vision Subscore From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

The National Eye Institute VFQ-25 is an ocular disease-specific survey that measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning.
The VFQ-25 consists of a base set of 25 vision-targeted questions plus an additional single-item general health rating question.
The distance vision subscore is calculated from the answers to 3 distance vision-related questions and ranges from 0 to 100, where higher scores or increases in score indicate better vision-related functioning.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used.

End point type	Secondary

End point timeframe:

From Baseline to Week 6 and at the Final/Early Termination Visit (up to 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[49]	101[50]	110[51]	109[52]
Units: units on a scale				
arithmetic mean (standard deviation)	-5.64 (± 14.654)	-3.77 (± 13.414)	-5.72 (± 14.531)	-4.42 (± 13.871)

Notes:

[49] - Participants with values at both time points

[50] - Participants with values at both time points

[51] - Participants with values at both time points

[52] - Participants with values at both time points

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.346 [54]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.03
upper limit	5.75

Notes:

[53] - Difference

[54] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as a factor.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	= 0.496 [56]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	1.31

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.47
upper limit	5.09

Notes:

[55] - Difference

[56] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Secondary: Change in VFQ-25 Near Vision Subscore From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change in VFQ-25 Near Vision Subscore From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

The National Eye Institute VFQ-25 is an ocular disease-specific survey that measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning.
The VFQ-25 consists of a base set of 25 vision-targeted questions plus an additional single-item general health rating question.
The near vision subscore is calculated from the answers to 3 near vision-related questions and ranges from 0 to 100, where higher scores or increases in score indicate better vision-related functioning.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used.

End point type	Secondary

End point timeframe:

Baseline to Week 6 and Final/Early Termination Visit (up 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[57]	101[58]	110[59]	109[60]
Units: units on a scale				
arithmetic mean (standard deviation)	-8.09 (± 17.754)	-2.97 (± 16.784)	-7.65 (± 17.808)	-3.52 (± 16.494)

Notes:

[57] - Subjects with values at both timepoints

[58] - Subjects with values at both timepoints

[59] - Subjects with values at both timepoints

[60] - Subjects with values at both timepoints

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab

Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	= 0.036 [62]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	5.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	9.9

Notes:

[61] - Difference

[62] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as a factor.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab
Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.077 [64]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	4.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.45
upper limit	8.72

Notes:

[63] - Difference

[64] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Secondary: Change in VFQ-25 Ocular Pain Subscore From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point title	Change in VFQ-25 Ocular Pain Subscore From Best State Achieved Prior to Week 6 to the Final/Early Termination Visit

End point description:

The National Eye Institute VFQ-25 is an ocular disease-specific survey that measures the influence of visual disability and visual symptoms on generic health domains such as emotional well-being and social functioning, in addition to task-oriented domains related to daily visual functioning.
The VFQ-25 consists of a base set of 25 vision-targeted questions plus an additional single-item general health rating question.
The ocular pain subscore is calculated from the answers to 2 eye pain questions and ranges from 0 to 100, where higher scores or increases in score indicate less pain.
This endpoint was analyzed in the intent-to-treat population; last observation carried forward (LOCF) imputation was used.

End point type	Secondary

End point timeframe:

Baseline to Week 6 and Final/Early Termination Visit (up 80 weeks)

End point values	Main Study: Placebo	Main Study: Adalimumab	Integrated Study (Main + Japan Sub-study): Placebo	integrated Study (Main + Japan Sub-study): Adalimumab
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	102[65]	101[66]	110[67]	109[68]
Units: units on a scale				
arithmetic mean (standard deviation)	-12.62 (± 21.435)	-2.6 (± 15.342)	-12.39 (± 20.841)	-3.56 (± 16.056)

Notes:

[65] - Subjects with values at both timepoints

[66] - Subjects with values at both timepoints

[67] - Subjects with values at both timepoints

[68] - Subjects with values at both timepoints

Statistical analyses

Statistical analysis title	Primary Analysis - Main Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Main Study: Placebo v Main Study: Adalimumab
Number of subjects included in analysis	203
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	< 0.001 [70]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	10.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.86
upper limit	15.19

Notes:

[69] - Difference

[70] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment as a factor.

Statistical analysis title	Additional Analysis - Integrated Study

Statistical analysis description:

The statistical test for the ranked secondary variables was carried out in hierarchical order at the significance level of 5%.

Comparison groups	Integrated Study (Main + Japan Sub-study): Placebo v integrated Study (Main + Japan Sub-study): Adalimumab

Number of subjects included in analysis	219
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	< 0.001 [72]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	8.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.88
upper limit	13.79

Notes:

[71] - Difference

[72] - From ANOVA of change from best state achieved prior to Week 6 to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first study drug administration until 70 days following the last study drug administration or until rollover into the extension study. Median duration of treatment was 91 days in the placebo arm and 129 days in the adalimumab arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects received placebo subcutaneous injection at Baseline followed by eow dosing starting at Week 1 for up to 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Reporting group title	Adalimumab

Reporting group description:

Subjects received adalimumab 80 mg subcutaneous loading dose at Baseline followed by 40 mg doses eow starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 60 mg/day at study entry followed by a protocol-defined mandatory taper until Week 15.

Serious adverse events	Placebo	Adalimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 120 (4.17%)	16 / 119 (13.45%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Carcinoid Tumour Of The Gastrointestinal Tract			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma Multiforme			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Neovascularisation			

subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Abortion Induced			
subjects affected / exposed	1 / 120 (0.83%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic Reaction			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental Overdose			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament Rupture			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon Rupture			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist Fracture			
subjects affected / exposed	1 / 120 (0.83%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Demyelination			

subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Angle Closure Glaucoma			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis Acute			
subjects affected / exposed	1 / 120 (0.83%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Calculus Ureteric			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal Failure Chronic			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Lupus-Like Syndrome			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis Viral			

subjects affected / exposed	1 / 120 (0.83%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pilonidal Cyst			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis Acute			
subjects affected / exposed	1 / 120 (0.83%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 120 (0.83%)	0 / 119 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper Respiratory Tract Infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid Overload			

subjects affected / exposed	0 / 120 (0.00%)	1 / 119 (0.84%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Adalimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	61 / 120 (50.83%)	71 / 119 (59.66%)	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 120 (13.33%)	13 / 119 (10.92%)	
occurrences (all)	17	21	
Paraesthesia			
subjects affected / exposed	0 / 120 (0.00%)	6 / 119 (5.04%)	
occurrences (all)	0	6	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	7 / 120 (5.83%)	12 / 119 (10.08%)	
occurrences (all)	7	12	
Eye disorders			
Cystoid Macular Oedema			
subjects affected / exposed	6 / 120 (5.00%)	3 / 119 (2.52%)	
occurrences (all)	6	3	
Eye Pain			
subjects affected / exposed	2 / 120 (1.67%)	9 / 119 (7.56%)	
occurrences (all)	4	10	
Uveitis			
subjects affected / exposed	8 / 120 (6.67%)	12 / 119 (10.08%)	
occurrences (all)	8	13	
Vision Blurred			
subjects affected / exposed	2 / 120 (1.67%)	8 / 119 (6.72%)	
occurrences (all)	2	8	
Gastrointestinal disorders			
Dry Mouth			

subjects affected / exposed	1 / 120 (0.83%)	6 / 119 (5.04%)	
occurrences (all)	1	6	
Nausea			
subjects affected / exposed	7 / 120 (5.83%)	6 / 119 (5.04%)	
occurrences (all)	8	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 120 (3.33%)	7 / 119 (5.88%)	
occurrences (all)	5	9	
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	3 / 120 (2.50%)	7 / 119 (5.88%)	
occurrences (all)	3	8	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 120 (0.00%)	6 / 119 (5.04%)	
occurrences (all)	0	7	
Insomnia			
subjects affected / exposed	8 / 120 (6.67%)	9 / 119 (7.56%)	
occurrences (all)	8	12	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 120 (10.00%)	10 / 119 (8.40%)	
occurrences (all)	14	13	
Back Pain			
subjects affected / exposed	3 / 120 (2.50%)	9 / 119 (7.56%)	
occurrences (all)	3	10	
Muscle Spasms			
subjects affected / exposed	4 / 120 (3.33%)	7 / 119 (5.88%)	
occurrences (all)	4	8	
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 120 (3.33%)	7 / 119 (5.88%)	
occurrences (all)	5	8	
Influenza			

subjects affected / exposed	6 / 120 (5.00%)	1 / 119 (0.84%)	
occurrences (all)	6	1	
Nasopharyngitis			
subjects affected / exposed	11 / 120 (9.17%)	21 / 119 (17.65%)	
occurrences (all)	13	27	
Urinary Tract Infection			
subjects affected / exposed	0 / 120 (0.00%)	6 / 119 (5.04%)	
occurrences (all)	0	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2010	Substantial changes included: ● Revised treatment failure parameters and efficacy variables where referenced throughout the document to reflect updated scientific approach and statistical analyses. ● Exclusion Criteria: changed BCVA worse than 20/400 to 20/200 and logMar from "> 1.34" to "> 1.0." ● Exclusion Criteria: added "All subjects with intermediate uveitis must have had a prior brain MRI at time of or after diagnosis of intermediate uveitis" to ensure that patients with intermediate uveitis do not have demyelinating disease such as multiple sclerosis, an appropriate diagnostic work up should include a brain MRI. ● Concomitant Therapy: added text regarding the use of topical or systemic corticosteroids.
23 April 2010	Substantial changes included: ● Revised the description of primary endpoint with regard to fundus visualization and to make editorial changes. ● Exclusion criteria: Added exclusion of subjects with severe vitreous haze that precludes visualization of the fundus to ensure the appropriate subject population is studied. ● Best Corrected Visual Acuity Testing: Removed the requirement that the individual performing refraction and BCVA testing not be the Principal Investigator nor the same person entering data on the eCRFs; there are no restrictions on who the BCVA examiners are for this study; however, they must be proficient in ETDRS refraction and ETDRS visual acuity measurement, and they must be certified by standardization vendor in both those study tasks. ● Study Procedures/Oral Prednisone Taper: Added text regarding oral prednisone taper to clarify that no deviations from the oral prednisone taper are allowed.
10 June 2010	Substantial changes included: ● Inclusion Criterion: Added "Subject with prior adequate response to corticosteroids (equivalent of prednisone up to 1 mg/kg/day)" to clarify the intent of Exclusion Criterion No. 2 which defines the appropriate subject population for this trial. ● Exclusion Criterion: Added Human T-Lymphotropic Virus Type 1 (HTLV-1), Whipple's disease, HZV (herpes zoster virus) as examples of potential infectious causes of uveitis. ● Exclusion Criterion: Revised to read "Subject has previous exposure to anti-TNF therapy and any biologic [including anti vascular endothelial growth factor (VEGF) therapy with a potential therapeutic impact on non-infectious uveitis" to provide clarification that prior anti VEGF therapy is also considered exclusionary for this clinical trial. ● Prohibited Therapy: Added "anti-VEGF therapy" and "periocular, intraocular or intravitreal injections" to clarify that anti-VEGF therapy, periocular, intraocular or intravitreal injections are not allowed during the study. ● Study Activities Table: Added Magnetic Resonance Imaging (MRI) to ensure the appropriate subject population is studied. ● Study Procedures: Indicated the correct order the eye exams are to be performed to ensure that the tests are done in the correct order to maximize the result of these procedures. ● Secondary Variables: Addition of change in Anterior Chamber (AC) cells to indicate that information collected on AC cell count/grade would not only be a component of the primary endpoint but also be evaluated as a secondary efficacy variable. ● Added Human Immunodeficiency Virus (HIV) testing Screening visit for Japanese subjects to satisfy local requirements in Japan.

11 February 2011	Substantial changes included: ● Inclusion Criteria and Study Procedures: - Added option to use QuantiFERON®-TB Gold for tuberculosis screening. - Added instruction that subjects with positive PPD and or QuantiFERON® TB Gold, history of active or latent tuberculosis [TB] or chest x-ray indicative of latent TB will be required to initiate and take at least 2 weeks of an ongoing course of prophylaxis prior to starting study therapy. ● Exclusion Criterion: - Changed to exclude subjects with 1 immunosuppressive therapy with dose increase within previous 28 days or who are on a dose outside of the allowed range listed and clarified that the dose of 1 allowable concomitant immunosuppressive therapy must be in the allowable range at Baseline. - Added text to exclude subjects with macular edema due to diabetic retinopathy. - Added Ozurdex® (dexamethasone implant) and intravitreal methotrexate (MTX) as prohibited therapy. - Added exclusion criterion that allows the prior use of intravitreal anti-VEGF therapy provided a 3 month washout period from Baseline is observed. - Added text to exclude use of marijuana in the previous 12 months. - Exclude hepatitis B surface antigen (HBsAg) positive subjects or subjects who are positive for either hepatitis surface antibodies (HBsAb) and/or core antibodies (HBcAb, Total), and HBV DNA PCR result that meets or exceeds detection sensitivity. ● Added requirement if at Week 52, a subject has a positive TB test subjects will undergo a standard Chest X-ray. ● Discontinuation of Individual Subjects: added dysplasia of the gastrointestinal tract, diagnosis of lupus like syndrome, multiple sclerosis or demyelinating disease and non-compliance with TB therapy.
21 March 2011	Substantial changes included: ● Added text to exclude use of systemic carbonic anhydrase inhibitor within 1 week prior to Screening visit and as prohibited therapy. ● Added instruction to evaluate subjects for treatment failure criteria at Unscheduled visits (as applicable) and complete Unscheduled visit activities per the investigator's clinical judgment. ● Added instruction to use the same fundus camera throughout the study per subject.
24 August 2011	Substantial changes included: ● Limited the maximum corticosteroid dose at study start to ≤ 60 mg/day. ● Removed allowance for subjects with positive TB tests except where a subject received a BCG vaccination or has a history of an ulcerative reaction to a PPD skin test. If the PPD test is positive, the QuantiFERON®-TB Gold test (or equivalent) must be performed. If the QuantiFERON®-TB Gold test (or equivalent) is negative, the subject is eligible. ● Changed BCVA score to < 34 letters. ● Added exclusion for those subjects who have had Retisert® (glucocorticosteroid implant) removed less than 90 days before Baseline or had complications related to the removal of the device. ● Changed exclusion of subjects with macular edema due to diabetic retinopathy to subjects with clinically significant macular edema due to diabetic retinopathy. ● Modified that both Fluorescent Treponemal Antibody (FTA) and Rapid Plasma Reagin (RPR) must be tested. If RPR or FTA is positive, the subject is excluded. ● Added criterion to exclude subjects with macular edema as the only sign of uveitis. ● Added criterion to exclude subjects with a history of scleritis. ● Added criterion to exclude subjects who require TB-prophylaxis. ● Added "Retisert® (glucocorticosteroid implant)" to list of prohibited medications. ● Changed secondary efficacy variable analysis to be percent change in central retinal thickness. ● Added hypotony to the list of uveitis related events.

15 March 2012	Substantial changes included: ● Revised language to include subjects with either negative PPD (< 5 mm of induration) or negative QuantiFERON®-TB Gold test (or Interferon-Gamma Release Assay [IGRA] equivalent) as eligible. ● Added that subjects with "previous" TB are also not eligible for this study. ● Reduced the number of letters a subject must read for BCVA to 20 letters. ● Added tacrolimus as an acceptable concomitant immunosuppressant ● Allow prior use of cyclophosphamide provided a 30 day washout prior to Baseline is observed. Added chlorambucil and cyclophosphamide to prohibited concomitant medication list. ● Reduced the washout period for intraocular or periocular corticosteroids to 30 days. ● Reduced intravitreal anti-VEGF therapy washout periods for Lucentis® (ranibizumab) or Avastin® (bevacizumab) to 45 days of the Baseline visit or for anti-VEGF Trap (Aflibercept) for 60 days of the Baseline visit. ● Allow refractive laser surgery, retinal laser photocoagulation or Nd:YAG capsulotomy (neodymium-doped yttrium aluminium garnet (YAG)) laser ≥ 30 days prior to Baseline visit. ● Removed Rapid Plasma Reagin testing. Syphillis testing will consist of Fluorescent Treponemal Antibody (FTA) testing only. ● Added that each vaccine administered to the subject should be listed as a concomitant medication on the Other Medications eCRF. Live vaccines may not be given concurrently while on study drug or for 70 days after the last dose of adalimumab. ● Changed reporting of uveitis-related events such that standard adverse reporting procedures apply for all adverse events regardless of the relationship to uveitis.
21 December 2012	Substantial changes included: ● Reordered ranking of secondary variables: The Anterior Chamber (AC) Cell grade and Vitreous Haze grade ranking were changed based on observed reasons for treatment failure in the blinded data. ● Removed interim analyses and reduced the total number of treatment failures to complete the study. ● Added language and new requirements regarding malignancy in patients who are 30 years old or younger. ● Adverse Event Reporting changed to require non-serious events of malignancy in subjects 30 or younger to be reported to Abbvie within 24 hours of site awareness.
24 June 2013	Substantial changes included: ● Added Rituxan® (rituximab) as prohibited therapy. ● Subjects with optic neuritis are exclusionary. ● Added Stelara® (ustekinumab), Benlysta® (belimumab), and corticosteroids with the exceptions of protocol specified prednisone taper and the protocol specified corticosteroid eye drop taper as prohibited medications.
19 November 2013	Substantial changes included: ● Increased overall sample size to 266 subjects (including 32 Japanese subjects) and increased the number of required treatment failures to 138 events and 19 events in subjects enrolled in Japan in order to maintain a power of 90%. ● Changed the definition of secondary endpoints to be able to include those subjects in the analysis that have a treatment failure at Week 6.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported