Clinical trial results:
A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Inactive Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis – Including a Sub-study in Japanese Patients

Summary

EudraCT number	2009-016008-22
Trial protocol	FR ES BE PT GB NL DE DK AT IT CZ GR
Global end of trial date	14 May 2015

Results information

Result version number	v1 (current)
This version publication date	29 May 2016
First version publication date	29 May 2016

Trial information

Trial identification

Sponsor protocol code	M10-880

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01124838
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, 011 800-633-9110,
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	14 May 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	14 May 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate the efficacy and safety of adalimumab 80 mg loading dose followed by 40 mg dose given every other week subcutaneously starting at Week 1 compared with placebo in patients with inactive 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	Netherlands: 4
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 31
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Greece: 2
Country: Number of subjects enrolled	Italy: 25
Country: Number of subjects enrolled	Argentina: 20
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Brazil: 3

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Japan: 32
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	United States: 61
Worldwide total number of subjects	261
EEA total number of subjects	116

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)	246
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study includes a Japan sub-study. A total of 261 subjects with inactive non-infectious intermediate uveitis, posterior uveitis or panuveitis were randomized at 72 study sites worldwide; 229 participants at 62 study sites in Australia, Israel, Latin America, North America, and Europe (Main Study), and 32 participants at 10 study sites in Japan.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio double-masked fashion using baseline immunosuppressant (IMM) usage as the stratification factor. Participants 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:

Participants 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. Participants continued to receive prednisone orally, 10 to 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion 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, 10 - 35 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 19.

Arm title	Adalimumab

Arm description:

Participants 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. Participants continued to receive prednisone orally, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

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 subcutaneously as an 80 mg loading dose (2 syringes) at Baseline followed by 40 mg 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, 10 - 35 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 19.

Number of subjects in period 1	Placebo	Adalimumab
Started	130	131
Enrolled in Main Study	114	115 [1]
Enrolled in Japan Sub-study	16 [2]	16 [3]
Completed	112	116
Not completed	18	15
Consent withdrawn by subject	3	2
Other	4	2
Adverse event	7	11
Lost to follow-up	2	-
Lack of efficacy	2	-

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 outside of 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

[3] - 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:	
Participants 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. Participants continued to receive prednisone orally, 10 to 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.	
Reporting group title	Adalimumab
Reporting group description:	
Participants 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. Participants continued to receive prednisone orally, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.	

Reporting group values	Placebo	Adalimumab	Total
Number of subjects			261

Vogt Koyanagi Harada	30	34	64
Sarcoid	20	22	42
Behcet's	7	10	17
Other	10	12	22
Eye Affected Units: Subjects			
Left	3	3	6
Right	5	2	7
Both	122	126	248
History of Infectious Uveitis Units: Subjects			
Yes	0	0	0
No	130	131	261
Duration of Uveitis Units: months			
arithmetic mean	59.36	58.35	
standard deviation	± 64.753	± 61.834	-

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

Participants 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. Participants continued to receive prednisone orally, 10 to 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

Reporting group title	Adalimumab

Reporting group description:

Participants 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. Participants continued to receive prednisone orally, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

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, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

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 eow starting at Week 1 for a maximum of 80 weeks or until treatment failure. Subjects continued to receive prednisone orally, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

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, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

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, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

Primary: Time to Treatment Failure on or After Week 2

End point title	Time to Treatment Failure on or After Week 2

End point description:

Treatment failure was defined by the occurrence of a uveitis flare (the inability to maintain disease control). To be considered treatment failure, ≥ 1 of these criteria had to be present in at least 1 eye at Week 2 or all other visits:
• New active, inflammatory chorioretinal, and/or inflammatory retinal vascular lesions relative to Baseline
• 2-step increase relative to Baseline in anterior chamber cell grade or vitreous haze grade
• Worsening of best corrected visual acuity by ≥ 15 letters relative to baseline.
Time to treatment failure was analyzed using the Kaplan-Meier method. Dropouts for reasons other than treatment failure at any time during the study were censored at the drop out date.
The primary analysis was performed in the intent-to-treat (ITT) population which included all randomized subjects recruited outside Japan; 3 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	111	115	127	131
Units: months				
median (inter-quartile range (Q1-Q3))	8.3 (3 to 99999)	99999 (4.7 to 99999)	5.6 (2.6 to 99999)	99999 (3.9 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: Adalimumab v Main Study: Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	0.84

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	258
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.74

Notes:

[2] - Difference

Secondary: Change in Anterior Chamber (AC) Cell Grade in Each Eye From Baseline to the Final/Early Termination Visit

End point title	Change in Anterior Chamber (AC) Cell Grade in Each Eye From Baseline 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.

End point type	Secondary

End point timeframe:

Baseline 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	110[3]	115[4]	126[5]	131[6]
Units: units on a scale				
arithmetic mean (standard deviation)				
Left eye	0.57 (± 1.001)	0.41 (± 0.969)	0.61 (± 1.005)	0.46 (± 0.996)
Right eye	0.53 (± 0.963)	0.4 (± 0.927)	0.6 (± 0.992)	0.44 (± 0.95)

Notes:

[3] - Participants with values at both time points

[4] - Participants with values at both time points

[5] - Participants with values at both time points

[6] - 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: Adalimumab v Main Study: Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.218 [8]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.08

Notes:

[7] - Difference

[8] - From ANOVA of change from baseline 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	257
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.164 [10]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.15
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.06

Notes:

[9] - Difference

[10] - From ANOVA of change from baseline 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 Baseline to the Final/Early Termination Visit

End point title	Change in Vitreous Haze (VH) Grade in Each Eye From Baseline 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.

End point type	Secondary
End point timeframe:	
Baseline 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	110[11]	115[12]	126[13]	131[14]
Units: units on a scale				
arithmetic mean (standard deviation)				
Left eye	0.33 (± 0.733)	0.16 (± 0.601)	0.35 (± 0.749)	0.18 (± 0.614)
Right eye	0.27 (± 0.605)	0.18 (± 0.604)	0.36 (± 0.729)	0.18 (± 0.602)

Notes:
[11] - Participants with values at both time points
[12] - Participants with values at both time points
[13] - Participants with values at both time points
[14] - 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: Adalimumab v Main Study: Placebo
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.07 [16]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.01

Notes:

[15] - Difference

[16] - From ANOVA of change from baseline 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	257
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.016 [18]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	-0.03

Notes:

[17] - Difference

[18] - From ANOVA of change from baseline 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 Baseline 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 Baseline 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.	
End point type	Secondary
End point timeframe:	
Baseline 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	110[19]	115[20]	126[21]	131[22]
Units: logMAR				
arithmetic mean (standard deviation)				
Left eye	0.06 (± 0.239)	0.01 (± 0.251)	0.07 (± 0.23)	0.02 (± 0.241)

Right eye	0.02 (± 0.198)	-0.01 (± 0.165)	0.04 (± 0.216)	0 (± 0.169)

Notes:

[19] - Participants with values at both time points

[20] - Participants with values at both time points

[21] - Participants with values at both time points

[22] - 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	225
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.096 [24]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.01

Notes:

[23] - Difference

[24] - From ANOVA of change from baseline 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	257
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	= 0.044 [26]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.09
upper limit	0

Notes:

[25] - Difference

[26] - From ANOVA of change from baseline to final/early termination visit with treatment and race

(Japanese versus non-Japanese) as factors adjusted for clustered observations.

Secondary: Time to Optimal Coherence Tomography (OCT) Evidence of Macular Edema in At Least 1 Eye On or After Week 2

End point title	Time to Optimal Coherence Tomography (OCT) Evidence of Macular Edema in At Least 1 Eye On or After Week 2

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 2 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	95[27]	90[28]	106[29]	102[30]
Units: months				
median (inter-quartile range (Q1-Q3))	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)

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	185
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	= 0.491
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	1.69

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	208
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	= 0.185
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	1.28

Notes:

[32] - Difference

Secondary: Percent Change in Central Retinal Thickness in Each Eye From Baseline to the Final/Early Termination Visit

End point title	Percent Change in Central Retinal Thickness in Each Eye From Baseline 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.

End point type	Secondary

End point timeframe:

Baseline 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	108[33]	114[34]	124[35]	130[36]
Units: percent change				
arithmetic mean (standard deviation)				

Left eye (N = 107, 114, 122, 130)	6.4 (± 20.67)	4.5 (± 29.82)	6.3 (± 19.75)	5.2 (± 29.91)
Right eye (N = 108, 113, 124, 129)	7.7 (± 28.88)	5.4 (± 34.83)	9.9 (± 30.79)	3.9 (± 33.34)

Notes:

[33] - Participants with values at both time points

[34] - Participants with values at both time points

[35] - Participants with values at both time points

[36] - 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: Adalimumab v Main Study: Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	= 0.451 [38]

(Japanese versus non-Japanese) and OCT machine as factors adjusted for clustered observations.

Secondary: Change in Visual Functioning Questionnaire 25 (VFQ-25) Total Score From Baseline to the Final/Early Termination Visit

End point title	Change in Visual Functioning Questionnaire 25 (VFQ-25) Total Score From Baseline 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.

End point type	Secondary

End point timeframe:

Baseline 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	109[41]	115[42]	125[43]	131[44]
Units: units on a scale				
arithmetic mean (standard deviation)	1.24 (± 10.698)	3.36 (± 11.73)	1 (± 10.225)	2.79 (± 12.018)

Notes:

[41] - Participants with values at both time points

[42] - Participants with values at both time points

[43] - Participants with values at both time points

[44] - 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	224
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	= 0.16 [46]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	2.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.84
upper limit	5.08

Notes:

[45] - Difference

[46] - From ANOVA of change from baseline 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	256
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	= 0.205 [48]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	1.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.97
upper limit	4.52

Notes:

[47] - Difference

[48] - From ANOVA of change from baseline to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Secondary: Change in VFQ-25 Subscore Distance Vision From Baseline to the Final/Early Termination Visit

End point title	Change in VFQ-25 Subscore Distance Vision From Baseline 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:

Baseline 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	109[49]	115[50]	125[51]	131[52]
Units: units on a scale				
arithmetic mean (standard deviation)	0.76 (± 16.248)	2.64 (± 17.165)	0.6 (± 15.978)	2.96 (± 17.121)

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	224
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	= 0.401 [54]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	1.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.53
upper limit	6.29

Notes:

[53] - Difference

[54] - From ANOVA of change from baseline 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	256
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	= 0.256 [56]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	2.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.73
upper limit	6.45

Notes:

[55] - Difference

[56] - From ANOVA of change from baseline to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Secondary: Change in VFQ-25 Subscore Near Vision From Baseline to the Final/Early Termination Visit

End point title	Change in VFQ-25 Subscore Near Vision From Baseline 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 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	109[57]	115[58]	125[59]	131[60]
Units: units on a scale				
arithmetic mean (standard deviation)	3.98 (± 17.397)	3.88 (± 18.302)	3.73 (± 17.17)	2.89 (± 20.503)

Notes:

[57] - Participants with values at both time points

[58] - Participants with values at both time points

[59] - Participants with values at both time points

[60] - 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	224
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	= 0.967 [62]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.81
upper limit	4.61

Notes:

[61] - Difference

[62] - From ANOVA of change from baseline 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	256
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	= 0.714 [64]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.53
upper limit	3.79

Notes:

[63] - Difference

[64] - From ANOVA of change from baseline to final/early termination visit with treatment and race (Japanese versus non-Japanese) as factors.

Secondary: Change in VFQ-25 Subscore Ocular Pain From Baseline to the Final/Early Termination Visit

End point title	Change in VFQ-25 Subscore Ocular Pain From Baseline 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 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	109[65]	115[66]	125[67]	131[68]
Units: units on a scale				
arithmetic mean (standard deviation)	2.87 (± 17.233)	3.42 (± 21.32)	2.6 (± 17.339)	2.15 (± 21.689)

Notes:

[65] - Participants with values at both time points

[66] - Participants with values at both time points

[67] - Participants with values at both time points

[68] - 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	224
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	= 0.83 [70]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	0.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.56
upper limit	5.68

Notes:

[69] - Difference

[70] - From ANOVA of change from baseline 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	256
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	= 0.842 [72]
Method	ANOVA
Parameter estimate	Mean Difference
Point estimate	-0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.32
upper limit	4.34

Notes:

[71] - Difference

[72] - From ANOVA of change from baseline to final/early termination visit with treatment and race (Japanese vs. 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 147 days in the placebo arm and 245 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:

Participants 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. Participants continued to receive prednisone orally, 10 to 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

Reporting group title	Adalimumab

Reporting group description:

Participants 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. Participants continued to receive prednisone orally, 10 - 35 mg/day at study entry followed by a protocol-defined mandatory taper until Week 19.

Serious adverse events	Placebo	Adalimumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 130 (7.69%)	8 / 131 (6.11%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung Adenocarcinoma Stage Iv			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fibula Fracture			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus Fracture			

subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic Dissection			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis			
subjects affected / exposed	2 / 130 (1.54%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive Crisis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac Tamponade			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Dysarthria			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Status Migrainosus			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			

subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness Transient			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroidal Neovascularisation			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Detachment			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subretinal Fluid			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis Aseptic			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (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 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia Legionella			
subjects affected / exposed	0 / 130 (0.00%)	1 / 131 (0.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 131 (0.00%)	
occurrences causally related to treatment / all	1 / 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	Placebo	Adalimumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 130 (60.00%)	88 / 131 (67.18%)	
Investigations			
Alanine Aminotransferase Increased			
subjects affected / exposed	1 / 130 (0.77%)	9 / 131 (6.87%)	
occurrences (all)	1	14	
Aspartate Aminotransferase Increased			
subjects affected / exposed	1 / 130 (0.77%)	8 / 131 (6.11%)	
occurrences (all)	1	11	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 130 (3.85%)	7 / 131 (5.34%)	
occurrences (all)	5	7	
Nervous system disorders			
Headache			
subjects affected / exposed	17 / 130 (13.08%)	17 / 131 (12.98%)	
occurrences (all)	22	22	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 130 (6.92%)	14 / 131 (10.69%)	
occurrences (all)	11	17	
Injection Site Pain			
subjects affected / exposed	9 / 130 (6.92%)	8 / 131 (6.11%)	
occurrences (all)	9	16	
Pyrexia			
subjects affected / exposed	8 / 130 (6.15%)	6 / 131 (4.58%)	
occurrences (all)	8	7	
Eye disorders			
Cystoid Macular Oedema			
subjects affected / exposed	7 / 130 (5.38%)	7 / 131 (5.34%)	
occurrences (all)	11	8	
Dry Eye			
subjects affected / exposed	8 / 130 (6.15%)	5 / 131 (3.82%)	
occurrences (all)	8	5	
Eye Pain			

subjects affected / exposed	6 / 130 (4.62%)	9 / 131 (6.87%)	
occurrences (all)	6	10	
Uveitis			
subjects affected / exposed	9 / 130 (6.92%)	6 / 131 (4.58%)	
occurrences (all)	9	6	
Visual Acuity Reduced			
subjects affected / exposed	10 / 130 (7.69%)	6 / 131 (4.58%)	
occurrences (all)	11	9	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 130 (6.92%)	4 / 131 (3.05%)	
occurrences (all)	10	4	
Nausea			
subjects affected / exposed	9 / 130 (6.92%)	4 / 131 (3.05%)	
occurrences (all)	10	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 130 (4.62%)	11 / 131 (8.40%)	
occurrences (all)	6	11	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 130 (2.31%)	9 / 131 (6.87%)	
occurrences (all)	3	9	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	12 / 130 (9.23%)	28 / 131 (21.37%)	
occurrences (all)	18	30	
Back Pain			
subjects affected / exposed	7 / 130 (5.38%)	10 / 131 (7.63%)	
occurrences (all)	8	11	
Pain In Extremity			
subjects affected / exposed	3 / 130 (2.31%)	10 / 131 (7.63%)	
occurrences (all)	5	12	
Infections and infestations			
Influenza			

subjects affected / exposed	7 / 130 (5.38%)	3 / 131 (2.29%)	
occurrences (all)	8	3	
Nasopharyngitis			
subjects affected / exposed	20 / 130 (15.38%)	23 / 131 (17.56%)	
occurrences (all)	28	32	
Sinusitis			
subjects affected / exposed	4 / 130 (3.08%)	8 / 131 (6.11%)	
occurrences (all)	11	12	
Upper Respiratory Tract Infection			
subjects affected / exposed	3 / 130 (2.31%)	10 / 131 (7.63%)	
occurrences (all)	4	10	
Urinary Tract Infection			
subjects affected / exposed	11 / 130 (8.46%)	13 / 131 (9.92%)	
occurrences (all)	15	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 March 2010	Substantial changes included: ● Revised efficacy variables to reflect updated scientific approach and statistical analyses ● Inclusion Criteria No. 3 and throughout protocol: changed "active" to active "inflammatory" chorioretinal and/or "inflammatory" retinal vascular lesion ● Increase the maximum allowable stable dose for an inactive uveitis patient to include up to 35 mg. ● Exclusion Criteria No. 9: changed BCVA worse than 20/400 to 20/200 and logMar from "> 1.34" to "> 1.0" ● Exclusion Criteria No. 10: added "All subjects with intermediate uveitis must have had a prior brain magnetic resonance imaging (MRI) at time of or after diagnosis of intermediate uveitis" ● Exclusion Criteria No. 14: changed dose of mycophenolate mofetil from ≤ 2 "mg" to ≤ 2 "gm" ● Concomitant Therapy: added text regarding concomitant and prohibited therapies to provide additional clarification regarding the use of topical or systemic corticosteroids ● Japan Sub-study: added active Hepatitis C and positive or indeterminate β-D-glucan as an exclusion criteria ● Japan Sub-study: Analysis of Efficacy: removed the following sentence: "An additional analysis the Time to Treatment Failure will be compared between the adalimumab group and the placebo group in the Japan ITT dataset using a log-rank test" as agreed upon with Japan's Pharmaceuticals and Medical Devices Agency (PMDA), the primary analysis will be performed on the integrated ITT dataset and a statistical test to compare the treatment groups in the Japan ITT dataset is not necessary.
23 April 2010	Substantial changes included: ● Best Corrected Visual Acuity Testing: Removed the requirement that the individual performing refraction and BCVA testing not be the Principal Investigator or the same person entering data on the eCRFs based on updated visual acuity requirements. ● Handling/Processing of Samples: added "Blood samples for Adalimumab and anti-adalimumab antibody (AAA) analysis will be collected by venipuncture into appropriately labeled evacuated serum collection tubes without gel separator at the required visits. Blood samples for Adalimumab analysis will also be obtained if a subject is discontinued from the study. Sufficient blood will be collected to provide approximately 1 mL serum. Allow the blood to clot for 30 minutes at room temperature before centrifugation." ● Collection of Samples for Analysis: Revised the number of pharmacokinetic (PK) and AAA samples that will be collected.

10 June 2010	Substantial changes included: ● Inclusion Criterion No. 5 – Revised sentence to read "Subject must have a history of experiencing a disease flare while tapering off their oral corticosteroid therapy within the past 18 months" to provide correct interpretation of the appropriate subject population to be included. ● Efficacy Variables – Removed "3 lines" throughout the protocol when assessing Best Corrected Visual Acuity to provide clarification that worsening of BCVA will be based on the number of letters. ● Added text 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. ● Exclusion Criterion No. 2: Added Human T Lymphotropic Virus Type 1 (HTLV-1) infection, Whipple's disease and HZV (herpes zoster virus). ● Prohibited Therapy: Added "anti-vascular endothelial growth factor (VEGF) therapy" and "periocular, intraocular or intravitreal injections."
11 February 2011	Substantial changes included: Inclusion Criterion: ● Added requirement for ≥10 mg oral prednisone for 90 days prior to Baseline ● Added option to use QuantiFERON®-TB Gold for TB screening ● Removed text requiring reading of purified protein derivative (PPD) test at study site and added text indicating TB screening tests are performed locally and annually ● Added instruction for TB prophylaxis ● Added instruction that subjects with documented completion of Center for Disease Control (CDC) recommended prophylaxis may conditionally be permitted to enroll ● Added increase of screening period up to 45 days if a subject is required to receive ≥ 28 days of TB prophylaxis Exclusion Criteria: ● Exclude subjects with 1 immunosuppressive therapy with dose that has not been stable for at least 28 days or who are on a dose outside of the allowed range listed ● Exclude subjects with macular edema due to diabetic retinopathy ● Changed description of demyelinating disease ● Expanded and clarified description of exclusionary infections ● Clarified that subjects with an active systemic viral infection or any active viral infection are excluded ● Added exclusion criterion that allows the prior use of intravitreal anti-VEGF therapy provided a 3 month washout period from Baseline is observed ● Added Ozurdex® (dexamethasone implant) and intravitreal methotrexate as prohibited therapy ● Exclude marijuana use including medical marijuana in the previous 12 months ● Exclude hepatitis B surface antigen positive subjects ● Removed requirement that Screening visit fundus photo is evaluated prior to the Baseline visit Removed central reader's precedence if assessment differs from investigator's assessment ● Added diagnosis of lupus like syndrome, multiple sclerosis or demyelinating disease and non-compliance with TB therapy as discontinuation criteria ● Added criteria that age-related eye disease study (AREDS) classification does not apply to subjects with pseudophakia
16 February 2011	Substantial changes included: ● Clarified that methotrexate, cyclosporine, mycophenolate mofetil or azathioprine cannot be discontinued within 28 days prior to the Baseline visit.

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. ● Provided details of the nature of syphilis confirmatory testing. ● 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: ● Changed period of inactive disease and minimum length of time the subject must be taking ≥ 10 mg of oral prednisone to 28 days prior to Baseline ● Removed allowance for subjects with positive TB tests except if a subject received Bacille Calmette-Guérin (BCG) vaccination or has history of an ulcerative reaction to a PPD skin test. If the PPD test is positive, the QuantiFERON®-TB Gold test must be performed. If the QuantiFERON®-TB Gold test is negative, the subject is eligible ● Added to criterion to require an MRI report completed within 90 days prior to Baseline to include a statement that reveals no hint of demyelinating disease such as multiple sclerosis for subjects who have intermediate uveitis or panuveitis that have signs of intermediate uveitis ● Clarified that immunosuppressive therapy including methotrexate, cyclosporine, mycophenolate mofetil or azathioprine should not be discontinued within 28 days prior to Baseline ● Modification to exclude subjects who received Retisert® within 3 years prior to Baseline or had complications related to the device. Added exclusion for those subjects who had Retisert® removed within 90 days prior to Baseline or complications related to device removal • 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, and if positive the subject would be excluded ● Exclude subjects with macular edema as the only sign of uveitis ● Exclude subjects with a history of scleritis • Exclude subjects who require TB Prophylaxis • Added “any TB-prophylaxis therapy” and “Retisert®" to list of prohibited medications ● Dilated Indirect Ophthalmoscopy: Added instruction to record the number of lesions, the location(s), size(s) and whether the lesions are active or inactive with a retinal drawing

15 March 2012	Substantial changes included: ● Clarified that at least one disease flare must occur within 18 months of Screening and that this flare has to occur during or up to a maximum of 28 days after tapering off the oral corticosteroid therapy. ● 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. Only 1 TB test is permitted to allow the subject in the study. Subjects with a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) result are not 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. ● Created Exclusion to allow prior use of cyclophosphamide provided a 30 day washout prior to Baseline is observed. Added chlorambucil and cyclophosphamide to prohibited concomitant medication list. ● Exclude subjects with cystoid macular edema unless the documented retinal changes are persistent, residual and stable as defined by the SUN criteria (persistent is > 3 months duration). ● Reduced intravitreal anti-VEGF therapy washout periods for Lucentis® (ranibizumab) or Avastin® (bevacizumab) to 45 days of Baseline or for anti-VEGF Trap (Aflibercept) for 60 days of Baseline. ● Changed to allow refractive laser surgery, retinal laser photocoagulation or neodymium-doped yttrium aluminium garnet (Nd:YAG) capsulotomy laser ≥ 30 days prior to Baseline visit.
21 December 2012	● Ranked secondary variables. ● 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: ● Removed interim analyses and reduced the total number of treatment failures to complete the study. ● Added Rituxan® (rituximab) as prohibited therapy. ● Added 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 eyedrop taper as prohibited medications.
19 February 2014	Substantial changes included: • Increase the number of Treatment Failures from currently planned 76 to approximately 96 to ensure approximately 80% statistical power.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported