



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 | Subject, Investigator |

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

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|---|--|
| 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: <ul style="list-style-type: none">• New active, inflammatory chorioretinal or retinal vascular lesions relative to Baseline• Inability to achieve $\leq 0.5+$ 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 (\pm 0.32) | 0.04 (\pm 0.143) | 0.13 (\pm 0.328) | 0.05 (\pm 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

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 (\pm 11.968) | -1.3 (\pm 10.98) | -5.34 (\pm 11.899) | -1.68 (\pm 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 occurrences (all) | 1 / 120 (0.83%) 1 | 6 / 119 (5.04%) 6 | |
| Nausea subjects affected / exposed occurrences (all) | 7 / 120 (5.83%) 8 | 6 / 119 (5.04%) 7 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 4 / 120 (3.33%) 5 | 7 / 119 (5.88%) 9 | |
| Skin and subcutaneous tissue disorders Hyperhidrosis subjects affected / exposed occurrences (all) | 3 / 120 (2.50%) 3 | 7 / 119 (5.88%) 8 | |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 120 (0.00%) 0 | 6 / 119 (5.04%) 7 | |
| Insomnia subjects affected / exposed occurrences (all) | 8 / 120 (6.67%) 8 | 9 / 119 (7.56%) 12 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 12 / 120 (10.00%) 14 | 10 / 119 (8.40%) 13 | |
| Back Pain subjects affected / exposed occurrences (all) | 3 / 120 (2.50%) 3 | 9 / 119 (7.56%) 10 | |
| Muscle Spasms subjects affected / exposed occurrences (all) | 4 / 120 (3.33%) 4 | 7 / 119 (5.88%) 8 | |
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) | 4 / 120 (3.33%) 5 | 7 / 119 (5.88%) 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none">• 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none">• 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none">• 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. |

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| 11 February 2011 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • Inclusion Criteria and Study Procedures: <ul style="list-style-type: none"> - 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: <ul style="list-style-type: none"> - 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • 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. |

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| 15 March 2012 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • 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. Syphilis 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • 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 | <p>Substantial changes included:</p> <ul style="list-style-type: none"> • 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