# 2.0 Synopsis

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| **AbbVie Inc.** | **Individual Study Table Referring to Part of Dossier:**<br>**Volume:**<br><br>**Page:** | **(For National Authority Use Only)** |
| **Name of Study Drug:**<br>Adalimumab | | |
| **Name of Active Ingredient:**<br>Adalimumab | | |
| **Title of Study:** 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 | | |
| **Coordinating Investigator:** Prof. Antoine Brezin, Centre Cochin Ambulatoire d'Ophtalmologie, Paris, France | | |
| **Study Sites:** Subjects were randomized and enrolled at 62 study sites located in Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Mexico, the Netherlands, Poland, Portugal, Spain, Switzerland, the United Kingdom, and the United States (US) (main study), and at 10 sites in Japan (Japan sub-study). | | |
| **Publications:** None | | |
| **Studied Period (Years):**<br>First Subject First Visit: 10 August 2010<br>Last Subject Last Visit: 14 May 2015 (Day 70 follow-up phone call) | **Phase of Development:** 3 | |
| **Objectives:**<br>The objective of this study was to evaluate the efficacy and safety of adalimumab 80 mg loading dose followed by a 40 mg dose given every other week (eow) subcutaneously (SC) starting at Week 1 compared with placebo in subjects requiring systemic corticosteroids (oral prednisone 10 to 35 mg/day) for inactive non-infectious intermediate uveitis, posterior uveitis, or panuveitis. | | |
| **Methodology:**<br>This was a Phase 3, randomized, double-masked, placebo-controlled, multicenter study of adalimumab. Subjects were randomized into 1 of 2 arms in a 1:1 ratio double-masked fashion using baseline immunosuppressant (IMM) usage as the stratification factor. Subjects from Japan were randomized in a separate stratum. Due to the small sample size, no stratification by baseline IMM usage was used for subjects from Japan. One arm was to receive adalimumab 80 mg SC loading dose at baseline followed by 40 mg doses eow starting at Week 1. The other arm was to receive matching placebo. Subjects needed to be on oral prednisone 10 to 35 mg/day at baseline (or oral corticosteroid equivalent). | | |

**Methodology (Continued):**

Beginning at Week 2, all subjects were to follow a protocol-defined mandatory prednisone taper schedule, such that all subjects who continued in the study were to have discontinued prednisone no later than Week 19. Subjects who entered the study on topical corticosteroids were to undergo a standardized taper schedule beginning at Week 1 until all subjects had completely discontinued oral prednisone by Week 9.

The study included a screening period, treatment period, and follow-up period. The maximum double-masked treatment period was to end after 80 weeks (treatment period) or when approximately 96 (84 to 107) treatment failures had occurred (in ex-Japan subjects only). Study visits were to occur at Baseline, Weeks 2 and 4, and every 4 weeks thereafter with the exception that a Week 27 visit was to occur instead of a Week 28 visit. Starting at Week 2 and every visit thereafter, all subjects were to be assessed for treatment failure.

Subjects determined as treatment failures were to be discontinued from the study. Subjects who were treatment failures at or after Week 2 were given the opportunity to enroll in the open-label rollover study, Study M11-327, if entry criteria were met and their site was participating in the rollover study. Likewise, at the end of this study, Study M10-880, all remaining subjects who did not have a treatment failure event had the opportunity to enroll in Study M11-327, if entry criteria were met and their site was participating in the rollover study.

Subjects who discontinued prior to the end of the study were to have an early termination visit. Subjects were to have a 70-day follow-up phone call or clinical visit to obtain follow-up information on any new or ongoing adverse events (AEs). The 70-day follow-up phone call or clinic visit was not required for subjects who continued into the roll-over study, Study M11-327.

Japan sub-study: The study was to end at sites in Japan when either approximately 96 (84 to 107) events of treatment failure had occurred in the main study or when 17 events of treatment failure had occurred in the Japan sub-study, whichever occurred later.

**Number of Subjects (Planned and Analyzed):**

**Planned:**

220 subjects were planned to be enrolled (main study); an additional 30 subjects were planned to be enrolled for the Japan sub-study.

**Analyzed:**

**Main Study Data:** A total of 229 subjects were enrolled and randomized (main study data, which excluded Japan). Three subjects at 2 sites were excluded from the intent-to-treat (ITT) analyses due to incomplete efficacy source data and general Good Clinical Practice (GCP) compliance issues at the sites; therefore, the ITT set for the main study data is comprised of 226 subjects.

**Japan Sub-Study Data:** A total of 32 subjects were enrolled and randomized at study sites located in Japan.

**Integrated Study Data:** The integrated study data is comprised of the main study data and the Japan sub-study data. A total of 261 subjects were enrolled and randomized at 72 study sites. Three subjects at 2 sites were excluded from the efficacy analyses; therefore, the ITT set for the integrated analysis is comprised of 258 subjects.

**Diagnosis and Main Criteria for Inclusion:**

- Male or female subjects ≥ 18 years of age.
- Diagnosed with non-infectious intermediate uveitis, posterior uveitis, or panuveitis (subjects diagnosed with isolated anterior uveitis were excluded from the study).
- Subject must have had inactive disease for ≥ 28 days prior to the Baseline visit, was taking ≥ 10 mg of oral prednisone to maintain this inactive state, and fulfilled 3 of the following criteria based on the investigator's clinical judgment at the Screening and Baseline visits for both eyes:
  - Without active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion
  - ≤ 0.5+ anterior chamber (AC) cells (Standardization of Uveitis Nomenclature [SUN] criteria)
  - ≤ 0.5+ vitreous haze (VH; National Eye Institute [NEI]/SUN criteria)
- Subject was on oral prednisone at a dose of 10 to 35 mg/day (or oral corticosteroid equivalent) at baseline and the dose had not been increased in the past 28 days or decreased in the past 14 days.
- Subject did not have previous, active, or latent tuberculosis (TB). Only 1 TB test was required to allow the subject in the study. Subjects with either negative purified protein derivative (< 5 mm of induration) or negative QuantiFERON®-TB Gold test (or interferon-gamma release assay [IGRA] equivalent) were eligible. Subjects with a repeat indeterminate QuantiFERON®-TB Gold test (or IGRA equivalent) result were not eligible.
- Japan sub-study: Additionally, subjects from Japan were excluded if they met either of the following criteria: subject had positive hepatitis C result at screening; or subject had a positive or indeterminate β-D-glucan test.

**Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:**

**Adalimumab** 40 mg/0.8 mL, pre-filled SC syringes

Bulk Product Lot Numbers: 09-025414, 11-003870, 11-005882, 13-000648, 10-001959

**Prednisone** 1 and 5 mg tablets

Bulk Product Lot Numbers: 10-000501, 10-001721, 11-002230, 11-003682, 12-000742, 12-004923, 12-004925, 12-006222, 12-006574, 12-006575, 12-007690, 13-000646, 13-002127, 13-001276, 13-001709, 13-002567, 13-002582, 14-000795, 14-000800, 10-000224, 10-000499, 11-002238, 11-003737, 11-005764, 12-000744, 12-003508, 12-003691, 12-006223, 12-006848, 12-007245, 13-003949, 14-001184, 11-005759, 13-003949

**Duration of Treatment:**

**Main Study:** The maximum double-masked treatment period was to end after 80 weeks (treatment period) or when approximately 96 (84 to 107) treatment failures had occurred (in ex-Japan subjects only).

**Japan Sub-Study:** The study was to end at sites in Japan when either approximately 96 (84 to 107) events of treatment failure had occurred in the main study or when 17 events of treatment failure had occurred in the Japan sub-study, whichever occurred later.

**Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:**

Placebo for adalimumab 0.8 mL solution, pre-filled SC syringes

Bulk Product Lot Numbers: 08-017132, 11-004399, 12-007038

**Criteria for Evaluation**

**Efficacy:**

The primary efficacy endpoint was the time to treatment failure (i.e., inability to maintain disease control), which was analyzed using a composite of 4 components: new active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesions; AC cell grade; VH grade; and visual acuity.

There were 9 ranked secondary variables.

- No. 1 change in AC cell grade from baseline to Final/Early Termination visit
- No. 2 change in VH grade from baseline to Final/Early Termination visit
- No. 3 change in logarithm of the minimum angle of resolution (logMAR) best corrected visual acuity (BCVA) from baseline to Final/Early Termination visit
- No. 4 time to optical coherence tomography (OCT) evidence of macular edema based on central retinal thickness (CRT) at or after Week 2
- No. 5 percent change in CRT from baseline to Final/Early Termination visit
- No. 6 change in Visual Functioning Questionnaire (VFQ)-25 total score from baseline to Final/Early Termination visit
- No. 7 change in VFQ-25 subscore distance vision from baseline to Final/Early Termination visit
- No. 8 change in VFQ-25 subscore near vision from baseline to Final/Early Termination visit
- No. 9 change in VFQ-25 subscore ocular pain from baseline to Final/Early Termination visit

Other efficacy variables:

- Inflammation
  - Measures of Inflammation – AC cell grade and VH grade
  - Control of Inflammation – steroid-free quiescence and lack of inflammation
- Visual acuity – logMAR BCVA
- Macular edema – time to macular edema and change in CRT
- Patient-reported Outcomes (PROs)
  - VFQ-25
  - EuroQol-5D Questionnaire™ (EQ-5D)
  - Hospital Anxiety and Depression Scale (HADS)
  - Work Productivity and Activity Impairment, Questionnaire: Specific Health Problem Questionnaire (WPAI-SHP)
  - Health Resource Utilization Questionnaire (HRU)

**Pharmacokinetics:**

In addition to summarizing serum adalimumab concentrations at each time point of scheduled sampling (samples for PK were to be collected at baseline and Weeks 2, 8, 12, 27, 36, 52, unscheduled visit [if applicable] and at the Final/Early Termination visit if the subject terminated prior to Week 52), population PK model based analyses with the focus on estimating apparent clearance and apparent volume of distribution of adalimumab were to be performed. The results of analyses are provided separately from this report.

The number and percentage of subjects who developed anti-adalimumab antibodies was to be determined.

**Safety:**

AEs, physical examination, vital signs, and laboratory data were assessed throughout the study.

**Statistical Methods**

Demographics and baseline values were compared between treatment groups and a 2-sided *P* value was provided.

**Efficacy:**

Main Study Data (excludes subjects recruited in the Japan sub-study):

Primary efficacy analyses are provided for the ITT set. The ITT set includes all randomized subjects recruited outside Japan, and it excludes 3 subjects from 2 sites for which efficacy source data was incomplete and/or there were general GCP compliance issues at the sites.

The statistical test for the primary endpoint and the ranked secondary endpoints were performed at a 2-sided significance level of 0.05. All other statistical tests were also 2-sided at a significance level of 0.05.

The primary efficacy endpoint was to be the time to treatment failure on or after Week 2 and was to be compared between the adalimumab group and the placebo group using a log-rank test at a 2-sided significance level of 5%. Treatment failures were to be counted as events. Dropouts due to reasons other than treatment failure at any time during the study were to be considered as censored observations at the time of dropping out. In a sensitivity analysis, time to treatment failure was to be compared between the treatment groups in a proportional hazards model with treatment and baseline IMM usage as factors. Further sensitivity analyses for the primary endpoint were to be specified in the statistical analysis plan prior to database lock.

The 2-sided testing of ranked secondary endpoints was to be initiated only in case of statistically significant differences between the treatment groups for the primary endpoint. The statistical test for the ranked secondary variables was to be carried out in the hierarchical order shown and was to be performed at the significance level of 5%. This means that statistically significant results for the higher ranked secondary variable were mandatory to initiate the testing of the next variable with a lower rank and that the multiple significance level of 5% two-sided was controlled. The ranked secondary efficacy variables were analyzed as follows:

- Change in AC cell grade, change in VH grade, change in logMAR BCVA, and change in CRT were to be compared between treatment groups using analysis of variance (ANOVA) adjusted for clustered observations (i.e., observations from each of the subject's eyes). For percent change in CRT, the analysis was additionally to be adjusted for type of OCT machine. Change in VFQ-25 was to be compared between treatment groups using ANOVA. Missing values were to be imputed by last observation carried forward (LOCF). The time to OCT evidence of macular edema based on CRT was to be compared between the treatment groups with a log rank test. OCT evidence of macular edema 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.

Other efficacy endpoints were analyzed using ANOVA with treatment as factor if quantitative in nature. Either observed values or LOCF was used. For time to event data Kaplan-Meier estimates were calculated and Kaplan-Meier curves were plotted for each treatment group. The time to event data were compared between the treatment groups using a proportional hazards model with treatment as the only factor. For binary endpoints, proportions were compared between treatment groups using a chi-square test. Missing values were imputed as non-response.

**Statistical Methods (Continued)**

**Efficacy (Continued):**

Main Study Data (excludes subjects recruited in the Japan sub-study) (Continued):

For cumulative HRU data, the ratio of the total number of utilizations (i.e., over all subjects) and the total time under observation (i.e., over all subjects) were calculated across all subjects in each treatment group. HRU was summarized as observed only.

Japan Sub-Study Data:

The analyses performed for this data set followed the same methods as described for the main study data with the exception that due to the small study population no inferential statistics were performed.

Integrated Study Data (main study data + Japan sub-study data):

The analyses performed for this data set followed the same methods as described for the main study data.

**Pharmacokinetics:**

The specifics of analyses are provided separately from this report.

**Safety:**

Main Study Data (excludes subjects recruited in the Japan sub-study):

Safety analyses were conducted in the safety set. The safety set includes all subjects recruited outside Japan who received at least 1 dose of study drug (placebo or adalimumab). Data were analyzed according to treatment received. The number and percentage of subjects with treatment-emergent adverse events (TEAEs) are displayed with counts and percentages. The changes in laboratory data and vital signs are summarized using descriptive statistics.

Japan Sub-Study Data:

The analyses performed for this data set followed the same methods as described for the main study data with the exception that due to the small study population no inferential statistics were performed.

Integrated Study Data (main study data + Japan sub-study data):

The analyses performed for this data set followed the same methods as described for the main study data.

**Summary/Conclusions**

**Efficacy Results:**

Main Study Data:

A majority of the 226 subjects (ITT) were female and white, and the mean age was 42.5 years. No statistically significant demographic differences were observed between the placebo and adalimumab groups. All subjects were diagnosed with non-infectious intermediate uveitis, posterior uveitis, panuveitis, or intermediate/posterior uveitis, and the majority of subjects (95.6%) reported the diagnosis as affecting both eyes. For baseline characteristics that included a statistical comparison between treatment groups, no statistically significant differences in baseline disease activity were observed, with the exception of SF-36 role – emotional functioning component ($P = 0.023$) and VFQ-25 color vision ($P = 0.027$), both of which showed a higher baseline mean for the adalimumab group compared with the placebo group. For baseline characteristics that did not include a statistical comparison, the treatment groups were numerically similar. The majority of subjects (≥ 89.5%) did not have evidence of macular edema based on CRT in either eye at baseline.

**Summary/Conclusions**

**Efficacy Results:**

Main Study Data (Continued):

The primary efficacy endpoint was the time to treatment failure with comparison between the adalimumab and placebo arms. Over the course of the study, the risk of treatment failure for subjects in the adalimumab group was reduced by 43% compared to subjects in the placebo group (hazard ratio [HR]: 0.57, 95% confidence interval [CI]: 0.39, 0.84; *P* = 0.004 from log rank test). The median time to treatment failure was 8.3 months for placebo subjects and not estimable (> 18 months) for adalimumab subjects because fewer than half of the subjects had experienced treatment failure at the conclusion of the study. The number of reasons met for treatment failure was higher for the placebo group compared with the adalimumab group. Of the 4 pre-specified reasons for treatment failure, visual acuity showed the largest difference between the placebo and adalimumab groups (20.7% and 8.7%, respectively).

Analysis of time to treatment failure based on the components of the primary endpoint (active inflammatory lesions, AC cell grade, VH grade, and logMAR BCVA each analyzed separately) demonstrated that over the course of the study, the risk of treatment failure based on logMAR BCVA was statistically significantly reduced by 67% for subjects in the adalimumab group compared to the placebo group (*P* = 0.002). The rates of treatment failure based on active inflammatory lesions and AC cell grade were numerically lower in the adalimumab group compared with placebo; however, the between-group differences were not statistically significant. There was no numerical or statistically significant difference between treatment groups for treatment failure based on VH grade.

Nine ranked secondary variables were tested in hierarchical order for statistical significance between the adalimumab and placebo groups. Overall, no statistically significant differences were observed between the treatment groups for any of the ranked secondary efficacy variables; however, results were numerically in favor of adalimumab for all ranked secondary variables except No. 8 (change in VFQ-25 subscore near vision; ITT).

In summary, results from efficacy analyses of the main study data suggest the following:

- **Early and Sustained Efficacy:** The risk of treatment failure for subjects in the adalimumab group was reduced by 43% compared to subjects in the placebo group (HR: 0.57, 95% CI: 0.39, 0.84; *P* = 0.004). Kaplan–Meier curves summarizing treatment failures over time separated at the first measurable time point (Week 2) and remained separated throughout the duration of the study. The median time to treatment failure was 8.3 months for placebo subjects and not estimable (> 18 months) for adalimumab subjects because fewer than half of the subjects experienced treatment failure at the conclusion of the study.
- **Effect on Vision Loss:** An analysis of time to treatment failure based on the primary endpoint components showed that the risk of treatment failure based on logMAR BCVA was reduced by 67% for subjects in the adalimumab group compared with the placebo group (*P* = 0.002). In addition, mean AUC of logMAR BCVA was higher for the adalimumab group compared to the placebo group and the difference between the groups was statistically significant (*P* = 0.009).
- **Effect on Inflammation:** An analysis of time to treatment failure based on the primary endpoint components showed rates of treatment failure based on AC cell grade were numerically lower in the adalimumab group compared with placebo; however, the between-group difference was not statistically significant. There was no numerical or statistically significant difference between treatment groups for VH grade.

**Summary/Conclusions (Continued)**

**Efficacy Results (Continued):**

Main Study Data (Continued):

- **Effect on Lesions:** An analysis of time to treatment failure based on the primary endpoint components showed rates of treatment failure based on active inflammatory lesions were numerically lower in the adalimumab group compared with placebo; however, the between-group difference was not statistically significant. Results for time to OCT evidence of macular edema based on CRT at or after Week 2 showed that over the course of the study, the risk of macular edema for subjects in the adalimumab group was reduced by 25% compared to subjects in the placebo group; however, the difference between groups was not statistically significant (HR: 0.75, $P = 0.491$). The results for mean percent change from baseline to Final/Early Termination visit in CRT were numerically in favor of adalimumab but not statistically significant compared to placebo.
- **Steroid-Sparing Effect:** The proportions of subjects in quiescence (AC cell grade and VH grade ≤ 0.5 and no active inflammatory lesions), steroid-free quiescence, with lack of inflammation (AC cell and VH grade 0 as well as no active inflammatory lesions), and with steroid-free lack of inflammation were higher in the adalimumab group compared to the placebo group at most time points. However, statistically significant differences were observed inconsistently, and in some cases numbers were small.
- **Effect on Vision-related Functioning:** Smaller mean reductions (worsenings) or larger increases (improvements) in VFQ-25 scores from baseline to Final/Early Termination visit were observed in the adalimumab group compared to the placebo group, with the exception of color vision, peripheral vision, and near vision. Only mean changes in general vision and mental health were statistically significantly different between the groups in favor of adalimumab ($P = 0.003$ and $P = 0.022$, respectively). Mean AUC of VFQ-25 total score (observed values) was higher for the adalimumab group compared to the placebo group and the difference between the groups was statistically significant ($P = 0.011$), suggesting better overall vision-related functioning over time and/or longer time to treatment failure for the adalimumab group.
- **Effect on Health-related Quality of Life and Work Productivity:** Other PROs such as work time missed, and work and activity impairment did not show statistically significant differences between the treatment groups. There also were no statistically significant differences between groups in mean EQ-5D predicted values and mean EQ VAS. Similar reductions from baseline to Final/Early Termination visit were observed in the adalimumab and placebo groups for HADS with no statistically significant differences between the groups. More placebo than adalimumab subjects visited a physician (15 versus 10 subjects, respectively). No subjects in either group were admitted to the hospital and 1 subject in the placebo group used the emergency room.

Japan Sub-Study Data:

- The majority of subjects (19/32) were female, all were Japanese with the exception of one who was Japanese/Korean, and mean age was approximately 47 years. There were some differences in body weight, alcohol use, and tobacco use between the placebo and adalimumab treatment groups, but overall demographic characteristics were similar. All subjects were diagnosed with non-infectious posterior uveitis, or panuveitis and the majority of subjects (90.6%) reported the diagnosis as affecting both eyes.

**Summary/Conclusions (Continued)**

**Efficacy Results (Continued):**

Japan Sub-Study Data (Continued):

- Analysis of the primary efficacy endpoint, time to treatment failure, showed a difference between the adalimumab and placebo groups in favor of adalimumab (HR: 0.45, 95% CI: 0.20, 1.03). The median time to treatment failure was 2.9 months for adalimumab subjects and 2.1 months for placebo subjects.
- The small sample size of the Japan sub-study limits the comparison of efficacy data between the 2 treatment groups.

Integrated Study Data (main study data + Japan sub-study data):

For the 258 subjects (ITT), demographics, medical history including uveitis history, and most baseline characteristics were similar to the findings reported for the main study data, with minor exceptions relative to WPAI-SHP and VFQ-25 ocular pain.

When the main study and Japanese sub-study data were integrated, the findings for the primary endpoint, ranked secondary endpoints, and other efficacy endpoints followed the same trends as presented for the main study data. As was shown with the main study data, statistically significant differences in favor of adalimumab versus placebo were met for the primary endpoint. The risk of treatment failure for subjects in the adalimumab group was reduced by 48% compared to subjects in the placebo group (HR: 0.52, 95% CI: 0.37, 0.74; $P < 0.001$). As seen in the main study results, the effect of adalimumab started early and was sustained during the course of study compared to placebo. Subjects in the adalimumab group also took longer to experience treatment failure (> 18 months; not estimable because less than half of the subjects experienced treatment failure at the conclusion of the study) compared to subjects in the placebo group (median 5.6 months; ITT). Though the efficacy results for the integrated data were directionally similar to the main study data, a few noteworthy differences from the main study results are described below.

- Components of primary endpoint:
  - An analysis of the time to treatment failure based on components of the primary endpoint (active inflammatory lesions, AC cell grade, VH grade, and logMAR BCVA, each analyzed separately) demonstrated that over the course of the study, the risk of treatment failure for subjects in the adalimumab group was statistically significantly reduced by 55% ($P = 0.014$) based on active inflammatory lesions, by 54% ($P = 0.045$) based on VH grade, and by 67% ($P = 0.001$) based on logMAR BCVA, compared to the placebo group. This differs from the main study, in which a statistically significant treatment group difference was observed only for time to treatment failure based on logMAR BCVA.
- Ranked secondary endpoints:
  - Two ranked secondary efficacy variables (No. 2 and No. 3) reached nominal significance, favoring adalimumab: change in VH grade from baseline to Final/Early Termination visit ($P = 0.016$) and change in logMAR BCVA from baseline to Final/Early Termination visit ($P = 0.044$). This differs from the main study, in which no statistically significant differences were observed between the treatment groups for any of the ranked secondary efficacy variables.

**Summary/Conclusions (Continued)**

**Efficacy Results (Continued):**

**Pharmacokinetic Results:**

The results of analyses are provided separately from this report.

**Safety Results:**

Main Study Data:

No statistically significant differences were observed between treatment groups for the overall frequency of TEAEs, TEAEs considered by the investigator to be at least possibly related to study drug (adalimumab/placebo), severe TEAEs, serious TEAEs, or TEAEs leading to study drug discontinuation.

There was 1 death (adalimumab group, aortic dissection and cardiac tamponade, not related). A similar percentage of subjects in the adalimumab and placebo groups had at least 1 serious adverse event (SAE; 7 [6.1%] and 9 [7.9%], respectively). The incidence rates of SAEs were 13.75 and 14.09 E/100PYs for the adalimumab and placebo groups, respectively. With the exception of deep vein thrombosis, which was reported by 2 subjects in the placebo group, all other SAEs occurred in 1 subject each.

Ten subjects (8.7%) in the adalimumab group and 7 subjects (6.1%) in the placebo group discontinued study drug (adalimumab/placebo) due to a TEAE. The incidence rates of TEAEs leading to discontinuation were 11.64 and 9.86 E/100PYs for adalimumab and placebo groups, respectively. With the exception of mycobacterium TB complex test positive (reported by 4 subjects) and pulmonary sarcoidosis (reported by 2 subjects), all other TEAEs leading to study drug discontinuation occurred in 1 subject each.

For those TEAEs of special interest that were reported, few subjects reported such events with the exception of infections (excluding oral candidiasis and TB), allergic reactions, and injection site reactions.

- Infections were reported by a higher proportion of subjects in the adalimumab group compared with the placebo group (54.8% and 43.9%, respectively); there was no statistically significant difference between the treatment groups. The incidence rates of treatment-emergent infection were numerically lower in the adalimumab group than in the placebo group (137.52 versus 149.36 E/100PYs). The most frequently reported infection by both treatment groups was nasopharyngitis. No statistically significant differences were observed between the treatment groups for any of the treatment-emergent infections.
  - Two subjects in each of the adalimumab and placebo groups reported ≥ 1 serious treatment-emergent infection with no statistically significant difference observed between groups, and no unique preferred term (PT) reported more than once. The incidence rate of serious infection was similar in both groups (3.17 and 2.82 E/100PYs for adalimumab and placebo groups, respectively).
  - One adalimumab subject (0.9%) reported a Legionella infection. The event was severe, resulted in hospitalization, and considered by the investigator as probably related to study drug.
  - One adalimumab subject (0.9%) reported oral candidiasis. The event was moderate in severity and considered by the investigator as probably not related to study drug.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

Main Study Data (Continued):

- Four subjects, 3 (2.6%) in the adalimumab group and 1 (0.9%) in the placebo group, reported an event of TB (PT of mycobacterium TB complex test positive). These TB events were considered to be latent, nonserious, and mild or moderate in severity. The investigator considered the events to be probably related to study drug in 2 subjects (1 adalimumab, 1 placebo) and not related to study drug in 2 adalimumab subjects. All 4 subjects discontinued study drug due to these events
- One adalimumab subject (0.9%) reported a malignancy. The subject had nonserious squamous cell carcinoma of skin of moderate severity and considered by the investigator as probably not related to study drug.
- Ten subjects, 4 (3.5%) in the adalimumab group and 6 (5.3%) in the placebo group, reported an allergic reaction. There were no statistically significant differences between treatment groups for any of the events. All subjects reported events that were nonserious and considered by the investigator as mild or moderate in severity and not related or probably not related to study drug. Events reported by > 1 subject were eye pruritus (4 subjects) and hypersensitivity (2 subjects).
- Two subjects, 1 each in the adalimumab and placebo groups, reported treatment-emergent non-cutaneous vasculitis (PT of Behcet's syndrome). These events were considered by the investigator as not related to study drug.
- Six subjects, 4 (3.5%) in the adalimumab group and 2 (1.8%) in the placebo group, reported treatment-emergent sarcoidosis; all of these subjects had a history of sarcoidosis at baseline. These events were considered by the investigator as not related or probably not related to study drug.
- One subject (0.9%), in the placebo group, reported an event of worsening of Ps. The event was considered by the investigator as not related to study drug.
- Three subjects, 2 (1.7%) in the adalimumab group and 1 (0.9%) in the placebo group, reported hematologic disorders. One adalimumab subject had serious neutropenia that was considered by the investigator as probably related to study drug and resulted in discontinuation of study drug. The other 2 subjects had nonserious leukopenia and thrombocytopenia (in adalimumab subject) and anemia (placebo subject) considered by the investigator as not related or probably not related to study drug.
- Two adalimumab subjects (1.8%) reported other liver events. One subject had nonserious hepatic steatosis considered by the investigator as possibly related to study drug, and the other subject had nonserious non-alcoholic steatohepatitis considered by the investigator as not related to study drug.
- Thirty-eight subjects, 23 (20%) in the adalimumab group and 15 (13.2%) in the placebo group, reported ≥ 1 TEAE of injection site reaction; there were no statistically significant differences between treatment groups. Events reported in > 2 subjects were injection site pain (17 subjects), injection site bruising and injection site rash (6 subjects each), and injection site erythema (4 subjects). Most of the injection site reaction events were considered by the investigator to be mild in severity and probably related to study drug; none of the events were serious, severe, or led to premature discontinuation of study drug.

**Summary/Conclusions (Continued)**

**Safety Results:**

Main Study Data:

- There were no reports of other TEAEs of special interest including diverticulitis, opportunistic infection (excluding oral candidiasis and TB), parasitic infection, reactivation of hepatitis B, progressive multifocal leukoencephalopathy, lymphoma, hepatosplenic T-cell lymphoma, melanoma, leukemia, cutaneous vasculitis, autoimmune hepatitis, myocardial infarction, cerebrovascular accident, congestive heart failure, pulmonary embolism, interstitial lung disease, intestinal perforation, pancreatitis, Stevens-Johnson Syndrome, erythema multiforme, new onset psoriasis, demyelinating disorders, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, or adalimumab administration-related medication error TEAEs.

Overall, mean changes from baseline to final value in hematology, clinical chemistry, and urinalysis values were not clinically meaningful. Shifts in hematology, clinical chemistry, and urinalysis values from normal at baseline to low or high maximum values were generally infrequent and/or not unexpected for adalimumab. The changes of laboratory parameters in the majority of the subjects during the study were transient and resolved by the last study visit. No patterns were identified in the analysis of clinical laboratory and vital signs parameters that suggest significant safety concerns for adalimumab.

Japan Sub-Study Data:

- The small sample size of the Japan sub-study limits the comparison of safety data between the 2 treatment groups.
- No deaths were reported during the Japan sub-study. One subject in each treatment group had an SAE (a placebo subject had osteonecrosis and an adalimumab subject had lung adenocarcinoma stage IV). The SAE in the adalimumab subject was considered by the investigator as probably related to study drug (adalimumab) and was considered probably not related to study drug by the sponsor. One subject (adalimumab) reported a TEAE (drug eruption) leading to premature discontinuation of study drug, which was considered by the investigator as possibly related to study drug (adalimumab).
- The TEAEs of special interest occurring in the Japan sub-study were infections (2 placebo, 7 adalimumab subjects), malignancy (1 adalimumab subject), sarcoidosis (1 adalimumab subject), and injection site reaction (1 adalimumab subject).
- No patterns were identified in the analysis of clinical laboratory, vital signs, or other safety parameters that suggest significant safety concerns for adalimumab.
- In this sub-study, adalimumab was generally safe and well tolerated; except for the events associated with underlying medical conditions, the AE profile was consistent with the safety profile established across other approved indications. No new safety signals were identified.

Integrated Study Data (main study data + Japan sub-study data):

- Due to the small number of subjects enrolled and the lack of significant safety findings reported in the Japan sub-study, the overall safety results from the integrated data were similar to those described for the main study data as listed above.

**Summary/Conclusions (Continued)**

**Conclusions:**

In this study, adalimumab was found to be effective in maintaining disease control and was steroid sparing in subjects with inactive non-infectious intermediate uveitis, posterior uveitis, and panuveitis who were unable to discontinue chronic oral corticosteroids without a disease flare. In this study, adalimumab was generally safe and well tolerated. With the exception of events associated with underlying medical conditions, the AE profile was consistent with the safety profile established across the approved indications of adalimumab. No new safety signals were observed.