2.0 Synopsis

<table>
<tr><td>AbbVie Inc.</td><td rowspan="3">Individual Study Table Referring to Part of Dossier:
Volume:

Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Study Drug:
Adalimumab</td></tr>
<tr><td>Name of Active Ingredient:
Adalimumab</td></tr>
<tr><td colspan="3">Title of Study: 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</td></tr>
<tr><td colspan="3">Coordinating Investigator: Glenn J. Jaffe, MD, Duke Eye Center, Durham, NC, USA</td></tr>
<tr><td colspan="3">Study Sites: Subjects were randomized and enrolled at 67 study sites located in Argentina, Australia, Austria, Belgium, Canada, the Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Mexico, Poland, Spain, Switzerland, the United Kingdom, and the United States (US) (main study) and 7 sites in Japan (Japan sub-study)</td></tr>
<tr><td colspan="3">Publications: 1 abstract</td></tr>
<tr><td colspan="2">Studied Period (Years):
First Subject First Visit: 10 August 2010
Last Subject Last Visit: 29 August 2014</td><td>Phase of Development: 3</td></tr>
<tr><td colspan="3">Objectives:
The objective of this study was to evaluate the efficacy and safety of adalimumab 80 mg loading dose at Baseline followed by a 40 mg dose given every other week (eow) subcutaneously (SC) starting at Week 1 compared with placebo in subjects requiring high-dose systemic corticosteroids for active non-infectious intermediate uveitis, posterior uveitis, or panuveitis.</td></tr>
<tr><td colspan="3">Methodology:
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 recruited in the Japan sub-study were randomized in a separate stratum. Due to the small sample size, no stratification by baseline IMM usage was used for subjects enrolled in the Japan sub-study. 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. Both arms were to receive a standardized prednisone burst of 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.</td></tr>
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Methodology (Continued):

The study included a screening period, a treatment period, and a follow-up period. The maximum double-masked treatment period was to end after 80 weeks (treatment period) or when the 138th treatment failure event occurred (in ex-Japan subjects only). Study visits were to be at baseline, Weeks 1, 4, 6, and 8, and every 4 weeks thereafter with the following exception: a study visit was to occur at Week 27 and there was not to be a study visit at Week 28. Starting at Week 6 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 Week 6 and at subsequent visits thereafter 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 M10-877, all remaining subjects who did not have a treatment failure event had the opportunity to enroll in Study M11-327.

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 the 138th event of treatment failure had occurred in the main study or when the 19th event of treatment failure had occurred in the Japan sub-study.

Number of Subjects (Planned and Analyzed):

Planned:

Two hundred and thirty four (234) subjects were planned to be enrolled (main study); an additional 32 subjects were planned to be enrolled for the Japan sub-study.

Analyzed:

Main Study Data: A total of 223 subjects were randomized and enrolled (main study data, which excludes Japan). Six subjects at 2 sites were excluded from the intent-to-treat (ITT) analyses due to incomplete efficacy source data and general GCP compliance issues at the sites; therefore, the ITT set for the main study data is comprised of 217 subjects.

Japan Sub-Study Data: A total of 16 subjects were randomized and enrolled 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 239 subjects were randomized and enrolled at 74 study sites. Six subjects at 2 sites were excluded from the efficacy analyses; therefore, the ITT set for the integrated analysis is comprised of 233 subjects.

Diagnosis and Main Criteria for Inclusion:

- Male or female subjects were ≥ 18 years of age.
- Diagnosed with non-infectious intermediate uveitis, posterior uveitis, or panuveitis (subjects diagnosed with isolated anterior uveitis were excluded from this study).
- Subject must have had active disease at the Baseline visit as defined by the presence of at least 1 of the following parameters in at least 1 eye despite at least 2 weeks of maintenance therapy with oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent):
  - Active, inflammatory, chorioretinal, and/or inflammatory retinal vascular lesion
  - ≥ 2+ anterior chamber (AC) cells (Standardization of Uveitis Nomenclature [SUN] criteria)
  - ≥ 2+ vitreous haze (VH) (National Eye Institute [NEI]/SUN criteria)
- Subject was on oral prednisone at a dose of ≥ 10 mg/day to ≤ 60 mg/day (or oral corticosteroid equivalent) for at least 2 weeks prior to screening and remained on the same dose from Screening to Baseline visit.
- 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 PPD (< 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 in 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 mg, 5 mg, and 20 mg tablets

Bulk Product Lot Numbers: 10-000501, 10-001721, 11-002230, 11-003682, 12-000742, 12-004923, 12-006574, 12-007690, 13-000322, 13-002127, 13-001951, 13-002581, 10-000224, 10-000499, 11-002238, 11-003737, 11-005764, 12-000744, 12-003508, 12-003691, 12-006223, 12-006848, 10-000225, 10-000500, 11-002485, 11-003669, 11-003739, 11-005757, 12-003509, 12-003695, 12-006225, 12-007717, 11-005759, 11-005761, 12-001801

Duration of Treatment:

Main Study: The maximum double-masked treatment period for this study was to end after 80 weeks (treatment period) or when the 138th treatment failure event occurred (in ex-Japan subjects).

Japan Sub-Study: Dosing was to continue until the subject was determined as a treatment failure or the study ended. The study was to end at sites in Japan when either the 138th event of treatment failure had occurred in the main study or when the 19th event of treatment failure had occurred in the Japanese sub-study. A total of 16 subjects with active non-infectious intermediate uveitis, posterior uveitis, or panuveitis were randomized and enrolled at 7 study sites located in Japan (Japan study data). By the time the main study had reached its target number of treatment failures and was completed, 16 of 32 planned Japan subjects had been enrolled in the Japan sub-study; therefore, the sub-study completed with fewer than the planned number of subjects.

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

Criteria for Evaluation

Efficacy:

The primary efficacy endpoint was the time to treatment failure (i.e., inability to achieve or maintain disease control), which was analyzed using a composite of 4 components of the primary endpoint: 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 best state achieved to Final/Early Termination visit
- No. 2 change in VH grade from best state achieved to Final/Early Termination visit
- No. 3 change in logarithm of the Minimum Angle of Resolution (logMAR) best corrected visual acuity (BCVA) from best state to final visit
- No. 4 time to optical coherence tomography (OCT) evidence of macular edema in at least 1 eye on or after Week 6
- No. 5 percent change in central retinal thickness from best state achieved to Final/Early Termination visit
- No. 6 change in Visual Functioning Questionnaire (VFQ)-25 total score from best state to final visit
- No. 7 change in VFQ-25 distance vision from best state achieved to the Final/Early Termination visit
- No. 8 change in VFQ-25 near vision from best state achieved to Final/Early Termination visit
- No. 9 change in VFQ-25 ocular pain from best state achieved 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 central retinal thickness
- 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)
  - SF-36® Health Status Survey (SF-36)
  - Health Resource Utilization Questionnaire (HRU)

Criteria for Evaluation (Continued)

Pharmacokinetic (PK):

Summarizing serum adalimumab concentrations at each time point of scheduled sampling (samples for PK were to be collected at baseline and Weeks 1, 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 (V/F) of adalimumab were to be performed. The results of analyses are provided separately from this report.

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 Japanese Subjects Recruited in Japan):

Primary efficacy analyses are provided for the ITT set. The ITT set includes all randomized subjects recruited outside Japan, and it excludes 6 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 the time to treatment failure. The analysis of time to treatment failure in the ITT set represents the primary efficacy analysis. For the primary endpoint Kaplan-Meier estimates were calculated and Kaplan-Meier curves were plotted for each treatment group. Treatment failure rates with 95% confidence interval (CI) were calculated at 3, 6, 9, 12, and 18 months for each treatment group. Treatment failures were counted as events. Dropouts due to reasons other than treatment failure were considered as censored observations at the time of dropping out. A proportional hazards model with treatment as factor was used to evaluate the time to treatment failure. The hazard ratio (HR) with 95% CI and *P* value from the log-rank test were presented.

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

Statistical Methods (Continued)

Efficacy (Continued):

Main Study Data (Excludes Japanese Subjects Recruited in Japan) (Continued):

- Change from best state achieved prior to Week 6 to Final/Early Termination Visit in AC cell grade, VH grade, logMAR BCVA, and percent change from best state achieved prior to Week 6 to Final/Early Termination Visit in central retinal thickness were compared between treatment groups using analysis of variance (ANOVA) adjusted for clustered observations (i.e., observations from each of the subject's eyes) with treatment as factor. For percent change in central retinal thickness the analysis was additionally adjusted for type of OCT machine. Change in VFQ-25 was compared between treatment groups using ANOVA with treatment as factor. Subjects dropping out through Week 6 were excluded from the analysis of AC cells, VH grade, logMAR BCVA, central retinal thickness, and VFQ-25. Missing values were imputed by LOCF. The time to OCT evidence of macular edema in at least 1 eye on or after Week 6 were compared between the treatment groups in a proportional hazards model with treatment as factor. OCT evidence of macular edema on or after Week 6 was counted as an event. Dropouts due to reasons other than OCT evidence of macular edema were 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.

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 analyzed as observed only.

Post hoc analyses were conducted using a definition of macular edema based on central retinal thickness and excluding subjects with macular holes or reghmatogenous detachment. Macular edema was defined as center point thickness ≥ 260 microns for Stratus OCT machine, ≥ 320 microns for Cirrus OCT machine, ≥ 340 microns for Spectralis OCT machine and excluding subjects with macular hole and/or retinal detachment.

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.

Statistical Methods (Continued)

Pharmacokinetic:

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 AEs 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:

The majority of the 217 subjects (ITT) were female and white, with mean age of 42.7 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, or panuveitis and the majority of subjects (90.8%) 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 bodily pain component ($P = 0.041$) and EQ VAS ($P = 0.047$), 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 between treatment groups. The majority of subjects (> 60%) did not have evidence of macular edema in either eye at baseline.

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 was statistically significantly reduced by 50% for subjects in the adalimumab group (HR: 0.5, 95% CI: 0.36, 0.70; $P < 0.001$ from log rank test). 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 (median = 5.6 months) compared to subjects in the placebo group (median = 3 months) (ITT). 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, the largest difference for treatment failure reason between treatment groups was VH grade (14.5% and 36.4% for adalimumab and placebo groups, respectively). Time to treatment failure based on the components of the primary endpoint including active inflammatory lesions, AC cell grade, VH grade, and logMAR BCVA (each analyzed separately, with logMAR BCVA analyzed post hoc) demonstrated that over the course of the study, the risk of treatment failure for subjects in the adalimumab group was statistically significantly reduced by 62% ($P = 0.001$), 49% ($P = 0.010$), 68% ($P < 0.001$), and 44% ($P = 0.040$), respectively, compared to subjects in the placebo group.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Main Study Data (Continued):

Nine ranked secondary variables were tested in hierarchical order for statistical significance between the adalimumab and placebo groups. Statistically significant and clinically relevant differences in favor of adalimumab versus placebo were met for the following 3 ranked secondary efficacy variables for mean change from best state prior to Week 6 to the final visit (ITT):

- No. 1 change in AC cell grade from best state achieved to Final/Early Termination visit ($P = 0.011$)
- No. 2 change in VH grade from best state achieved to Final/Early Termination visit ($P < 0.001$)
- No. 3 change in logMAR BCVA from best state achieved to Final/Early Termination visit ($P = 0.003$)

The following 4 ranked secondary efficacy variables further down in the hierarchy used for multiple testing reached nominal significance:

- No. 5 percent change in central retinal thickness from best state achieved to Final/Early Termination visit ($P = 0.020$)
- No. 6 change in VFQ-25 total score from best state achieved to Final/Early Termination visit ($P = 0.010$)
- No. 8 change in VFQ-25 near vision from best state achieved to Final/Early Termination visit ($P = 0.036$)
- No. 9 change in VFQ-25 ocular pain from best state achieved to Final/Early Termination visit ($P < 0.001$)

Statistically significant differences were not observed for ranked secondary endpoints No. 4 and No. 7 (time to OCT evidence of macular edema [cystic formation visualized on OCT] in at least 1 eye on or after Week 6 and change in VFQ-25 distance vision from best state achieved prior to Week 6 to the Final/Early Termination visit, respectively); however, results were numerically in favor of adalimumab and are clinically relevant (ITT). When analyzing ranked secondary endpoints No. 4 and No. 5 (post hoc) using the definition of macular edema based on central retinal thickness (macular edema was defined as center point thickness ≥ 260 microns for Stratus OCT machine, ≥ 320 microns for Cirrus OCT machine, ≥ 340 microns for Spectralis OCT machine) rather than cystic formation, and only in subjects without macular hole and/or retinal detachment, statistically significant differences between treatment groups in favor of adalimumab were shown ($P = 0.023$ and $P = 0.014$ for time to OCT evidence of macular edema at or after Week 6 and for percent change in central retinal thickness from best state achieved to final visit, respectively).

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 50% compared to subjects in the placebo group (HR: 0.5, 95% CI: 0.36, 0.70; $P < 0.001$) Kaplan-Meier curves summarizing treatment failures over time showed separation at the first measurable time point (Week 6) and remained separated throughout the duration of the study. Subjects in the adalimumab group had a longer median time to treatment failure of 5.6 months compared to subjects in the placebo group who had a median time to treatment failure of 3 months.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Main Study Data (Continued):

- **Efficacy on Multiple Disease Manifestations (inflammation, visual acuity, and central retinal changes):** Analysis of the time to treatment failure based on individual triggers related to inflammation, specifically active inflammatory lesions, AC cell grade, and VH grade, demonstrated that adalimumab reduced the risk of treatment failure by 62% ($P = 0.001$), 49% ($P = 0.010$), and 68% ($P < 0.001$), respectively, compared to placebo. Statistically significant differences were seen in favor of adalimumab versus placebo in AC cell grade and VH grade, for both mean change from best state achieved to Final/Early Termination visit (–0.29 grades difference between groups [$P = 0.011$] and –0.027 grades difference between groups [$P < 0.001$] for AC cell grade and VH, respectively), and mean area under the curve (AUC; for which AUC is defined as the area under the curve of AC cell grade or VH grade over time with AC cell grade or VH grade plotted on the y-axis and the time to treatment failure on the x-axis) (mean differences between groups of 34.28 [$P = 0.008$] and 35.42 [$P = 0.004$] for AC cell grade and VH grade, respectively). Statistically significant differences in favor of adalimumab versus placebo were seen for logMAR BCVA for both mean change from best state achieved to Final/Early Termination visit (–0.07 logMAR units difference between groups [$P = 0.003$]) and mean AUC (mean difference between groups; 26.17; $P = 0.008$). Adalimumab appeared to prolong the time to OCT evidence of macular edema (cystic formation visualized on OCT) in at least 1 eye on or after Week 6 (HR: 0.7, CIs: 0.39, 1.26; $P < 0.231$ from log rank test). When conducting the analysis (post hoc) with macular edema defined by clinically significant retinal thickening rather than cystic formation, and excluding subjects with macular hole and/or retinal detachment, the risk of macular edema for subjects in the adalimumab group was reduced by 67% compared to subjects in the placebo group (HR: 0.33, CIs: 0.12, 0.90; $P = 0.023$). Statistically significant differences in favor of adalimumab versus placebo were achieved for mean percent change from best state achieved to final visit in central retinal thickness (–11.4% difference between groups; $P = 0.020$). When conducting this analysis with subjects with macular hole and/or retinal detachment excluded (post hoc), the difference between groups became even more pronounced (–12.0% difference; $P = 0.014$).
- **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.
- **Effect on Vision-Related Functioning:** Furthermore, smaller mean reductions from best state achieved for VFQ-25 prior to Week 6 to Final/Early Termination visit were observed in the adalimumab group compared to the placebo group, with the exception of color vision. Mean reductions that were statistically significantly different between groups in favor of adalimumab included total score, general vision, near vision, ocular pain, and mental health. Distance vision, however, was not statistically significantly different between groups. Mean AUC of VFQ-25 total score was statistically significantly higher for the adalimumab group compared to the placebo group (mean difference 726.94, 95% CI: 162.99 – 1290.90, $P = 0.012$).

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Main Study Data (Continued):

- **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; however, change from best state achieved prior to Week 6 to Final/Early Termination visit showed a statistically significantly larger reduction in work time missed in the adalimumab group compared to the placebo group (mean difference between groups –10.61, 95% CI: –18.75, –2.47, $P = 0.011$). At Final/Early Termination visit, values for EQ-5D predicted value and EQ VAS were higher in the adalimumab group compared to the placebo group. A statistically significant difference between groups in favor of adalimumab was observed for EQ-5D predicted value when looking at change from best state achieved prior to Week 6 to Final/Early Termination visit, indicating better health-related quality of life over time for the adalimumab group. Similar reductions from best state achieved prior to Week 6 were observed in the adalimumab and placebo groups for HADS, with no statistically significant differences between the groups.

Japan Sub-Study Data:

- The majority of 16 subjects were female (11/16), all were Japanese, and mean age was 50.88 years of age. No clinically meaningful differences between treatment groups for demographics, medical history, uveitis history, or baseline characteristics were observed. All subjects were diagnosed with non-infectious intermediate uveitis, posterior uveitis, or panuveitis and the majority of subjects (87.5%) reported the diagnosis as affecting both eyes.
- Analysis of the primary efficacy endpoint, time to treatment failure (analyzed using a composite of 4 components of the primary endpoint: inflammatory chorioretinal and/or inflammatory retinal vascular lesions; AC cell grade; VH grade; and visual acuity), did not show a difference between the adalimumab and placebo groups (HR: 1.20, 95% CI: 0.41, 3.54).
- Because the sub-study ended when the main study was completed, a total of only 16 subjects were randomized and enrolled. The small sample size of this study limits the comparison of efficacy data between the 2 treatment groups and the interpretation of the findings should be made with caution.

Integrated Study Data (Main Study Data + Japan Sub-Study Data):

For the 233 subjects (ITT), demographics and medical history including uveitis history were similar to the findings reported for the main study data. Similarly, using the integrated data, baseline characteristics matched the main study data with the one exception: Baseline characteristics that included a statistical comparison between treatment groups, no statistically significant differences in baseline disease activity were observed.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Integrated Study Data (Main Study Data + Japan Sub-Study Data) (Continued):

When the main and Japanese data from Study M10-877 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. In all cases, the results of the various efficacy analyses were directionally similar. As was shown with the main study data, statistically significant differences in favor of adalimumab versus placebo were met for the primary end point (the risk of treatment failure for subjects in the adalimumab group was reduced by 44% compared to subjects in the placebo group (HR: 0.56, 95% CI: 0.40, 0.76; $P < 0.001$ from log rank test) and for the first 3 ranked secondary efficacy endpoints (changes in best state achieved to final visit AC cell grade, vitreous haze grade, and logMAR BCVA; *P* values: 0.019, < 0.001, and 0.008, respectively). Though the efficacy results for the integrated data were directionally similar to main study data, there were a few instances for which the results of the integrated data efficacy analyses did not reach statistically significant differences between treatment groups as had been shown with the main study data and these instances are listed below.

- Ranked secondary endpoints:
  - Statistically significant differences were not observed for ranked secondary endpoints No. 4, No. 5, No. 7, and No. 8 (time to OCT evidence of macular edema, percent change in central retinal thickness, change in VFQ-25 distance vision from best state achieved prior to Week 6 to the final visit, and change in VFQ-25 near vision from best state achieved prior to Week 6 to the final visit); however, results were numerically in favor of adalimumab and are clinically relevant (ITT).
  - For ranked secondary endpoint No. 5: Mean percent change from best state achieved prior to Week 6 to the final visit in central retinal thickness was not statistically significantly different between adalimumab and placebo ($P = 0.428$) in the protocol defined analysis or post hoc analysis (subjects with macular hole and/or retinal detachment excluded; $P = 0.409$). However, in both analyses, mean percent change from best state achieved prior to Week 6 to the final visit in central retinal thickness demonstrated numerical differences in favor of adalimumab suggesting less increase in central retinal thickening in subjects who received adalimumab.
- Vision-Related Functioning:
  - Similar to the main study data, smaller mean reductions from best state achieved for VFQ-25 prior to Week 6 to final visit were observed in the adalimumab group compared to the placebo group, with the exception of color vision and peripheral vision. However, the subscores for which statistical significant differences between groups in favor of adalimumab differed from the main study data. Mean reductions that were statistically significantly different between groups in favor of adalimumab included total score, general health, general vision, ocular pain, and mental health. Distance vision and near vision, however, were not statistically significantly different between groups.

Pharmacokinetic Results:

The results of analyses are provided separately from this report.

Summary/Conclusions (Continued)

Safety Results:

Main Study Data:

No statistically significant differences were observed between treatment groups for frequency of treatment-emergent adverse events (TEAEs), TEAEs considered by the investigator to be at least possibly related to study drug (placebo/adalimumab), or TEAE stratified by severity.

There was 1 death (adalimumab group, renal failure chronic, not adalimumab related). A statistically significantly higher percentage of subjects in the adalimumab group experienced at least 1 serious adverse event (SAE) compared to the placebo group (15 [13.5%] and 5 [4.5%], respectively; $P = 0.020$). The incidence rates of SAEs were 28.83 events per 100 patient-years (E/100 PYs) and 13.56 E/100PYs for adalimumab and placebo groups, respectively. All PTs were unique; none were reported by more than 1 subject. No statistically significant differences were observed between treatment groups in SAEs that were considered by the investigator as possibly or probably related to study drug (placebo/adalimumab) or TEAEs leading to study drug (placebo/adalimumab) discontinuation. No statistically significant differences were observed between treatment groups in SAEs that were considered by the investigator as possibly or probably related to study drug (placebo/adalimumab), TEAEs leading to study drug (placebo/adalimumab) discontinuation, or uveitis-related TEAEs (per the investigator and after additional medical review).

For those TEAEs of special interest that were reported, fewer than 3 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 statistically significantly higher proportion of subjects in the adalimumab group compared with the placebo group (44.1% and 28.6%, respectively; $P = 0.018$). The incidence rates of treatment-emergent infection were 156.98 E/100 PYs and 124.29 E/100PYs for adalimumab and placebo groups, respectively. The most frequently reported infection by both treatment groups was nasopharyngitis. Statistically significant differences were observed between the placebo group and the adalimumab group for nasopharyngitis and urinary tract infection with more subjects reporting these events in the adalimumab group (P values ≤ 0.010). Two subjects (1.8%) in the placebo group and 5 subjects (4.5%) in the adalimumab group reported ≥ 1 serious treatment-emergent infection with no statistically significant difference observed between groups and no unique PT was reported more than once. The rate of serious infection was similar in both groups (8.01 and 6.78 E/100 PYs for adalimumab and placebo groups, respectively).
- Two adalimumab subjects (1.8%) reported treatment-emergent TB-related events. One subject was hospitalized due to active TB. The SAE was considered by the investigator to be possibly related to study drug. One subject reported a non-serious event of mycobacterium TB complex test positive. This event of inactive TB was considered by the investigator to be probably related to study drug.
- Two adalimumab subjects reported a malignancy (1.8%). One subject (0.9%) was hospitalized due to a carcinoid tumor of the gastrointestinal tract; this SAE was considered by the investigator to be not related to study drug. One subject (0.9%) reported an SAE of glioblastoma multiforme and this event was considered by the investigator to be probably related to study drug.

Summary/Conclusions (Continued)

Safety Results (Continued):

Main Study Data (Continued):

- A total of 14 subjects (4 placebo [3.6%] and 10 adalimumab [9.0%]) reported an allergic reaction. Only allergic reactions reported for the SOC of skin and subcutaneous tissue disorders were reported by a statistically significantly higher proportion of subjects in the adalimumab group compared with the placebo group (7.2% and 0.9%; $P = 0.019$). Four events of allergic reaction in 4 adalimumab subjects were assessed as at least possibly related by the investigator compared to 1 event in 1 subject from the placebo group. One adalimumab subject reported SAEs of anaphylactic reaction and urticaria; these events were considered by the investigator to be probably not related to study drug. No single event was reported by > 2 subjects in either treatment group.
- Injection site reactions were reported in 14 subjects (7 placebo [6.3%] and 7 adalimumab [6.3%]); there were no statistically significant differences between treatment groups. The majority of injection site reaction events were considered by the investigator to be probably related to study drug (placebo/adalimumab); none of the events were serious, severe, or led to premature discontinuation of study drug (placebo/adalimumab).
- Other TEAEs of special interest included 1 case each of oral candidiasis, lupus-like syndrome, cutaneous sarcoidosis, demyelination, neutropenia, and microcytic anemia reported in subjects treated with adalimumab. Additionally, the TEAE included 1 case each of non-cutaneous vasculitis and acute hepatitis in subjects treated with placebo.
- There were no reports of other TEAEs of special interest including Legionella infections, diverticulitis, opportunistic infection (excluding oral candidiasis and TB), parasitic infection, reactivation of Hepatitis B, progressive multifocal leukoencephalopathy, lymphoma, hepatosplenic T-cell lymphoma, nonmelanoma skin cancer, 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, worsening and new onset psoriasis, 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 significant and not clinically meaningful. Shifts in hematology, clinical chemistry, and urinalysis values from normal at baseline to low or high maximum values were generally infrequent. 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.

Summary/Conclusions (Continued)

Safety Results (Continued):

Japan Sub-Study Data:

- Because the sub-study ended when the main study was completed, a total of only 16 subjects were randomized and enrolled. The small sample size of this study limits the comparison of safety data between the 2 treatment groups and the interpretation of the findings should be made with caution.
- No deaths were reported during the Japan sub-study. One subject (adalimumab) reported an SAE (calculus ureteric) and the SAE was considered by the investigator as probably not related to study drug (adalimumab). No subjects experienced TEAEs leading to the discontinuation of study drug (placebo/adalimumab). Infections were the only TEAEs of special interest reported by subjects in the Japan sub-study, with nasopharyngitis being the most commonly reported infection.
- In this study with a small sample size, adalimumab was generally safe and well tolerated; except for the events associated with underlying medical conditions, the AE profile is 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.

Conclusions:

In this study, adalimumab was found to be effective in achieving and maintaining disease control both by reducing inflammation and decreasing vision loss in non-infectious intermediate uveitis, posterior uveitis, and panuveitis subjects requiring high-dose systemic corticosteroid. In this 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 the approved indications of adalimumab. No new safety signals were observed. The sample size of the Japan sub-study was too small to allow for definitive conclusions; integration of data from the main study with those of the Japan sub-study does not alter the overall efficacy and safety conclusions.