2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		

Title of Study: A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis

Coordinating Investigator: [redacted]

Study Sites: Subjects were enrolled at 85 study sites located in Argentina, Australia, Austria, Belgium, Brazil, Canada, the Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Japan, Mexico, Poland, Portugal, Spain, Switzerland, the United Kingdom, and the United States

Publications: 1 manuscript and 5 abstracts (based on results through Week 78)

Studied Period (Years): First Subject First Visit: 10 December 2010 Last Subject Last Visit: 21 May 2018 (last 70 day follow-up call)	**Phase of Development:** 3

Objective: The objective of this study was to evaluate the long-term safety and efficacy of adalimumab 40 mg dose given every other week (eow) subcutaneously (SC) in adult subjects with non-infectious intermediate uveitis, posterior uveitis, or panuveitis who participated in Studies M10-877 or M10-880.

Methodology:

This was a Phase 3 open-label (OL) multicenter study of adalimumab in adult subjects who had either discontinued from the placebo-controlled randomized lead-in studies (Study M10-877 or Study M10-880) for having met "treatment failure" criteria or had completed the lead-in studies without treatment failure.

The purpose of this study was to collect longer-term data under close to real world practice conditions, to supplement the data from the controlled studies where adherence to the stringent study protocols, for instance regarding the concomitant use of immunosuppressants (IMMs), or mandatory taper of corticosteroids, was required. The study was originally planned for 78 weeks, but was extended for ethical reasons to allow subjects with a good response to adalimumab to stay in the study until regulatory and/or reimbursement in their specific country was available. As country regulatory and/or reimbursement approval of adalimumab in this indication occurred, subject numbers declined at study visits beyond Week 78, making results at later visit less robust than those of the interim analysis conducted at Week 78 due to the smaller subject numbers.

Methodology (Continued):

Subjects who rolled over from the lead-in studies were evaluated for entry into this study at the final or last visit in the lead-in study. Therefore, the Study M11-327 Baseline (Week 0) visit was meant to be performed on the same day as the Final/Early Termination visit in the lead-in studies. However, Week 0 of Study M11-327 could have occurred up to 28 days after the Final/Early Termination visit of the lead-in study. The study included a Screening assessment at Week 0, a treatment period, and a 70-day follow-up period. Scheduled study visits occurred at Weeks 0, 2, 4, 8, 12, 18, and every 12 weeks thereafter. Starting at Baseline, all subjects received OL adalimumab 40 mg dose eow by SC administration regardless of treatment assignment in either of the lead-in studies. Subjects who discontinued prior to the end of the study were to have an early termination visit.

Subjects who entered the study due to treatment failure in Study M10-877 or Study M10-880 and failed to achieve adequate control of their disease flare within the first 8 weeks may have been discontinued from the study. Any subject who experienced a uveitis flare as determined by the investigator ≥ 4 weeks during the study was to be discontinued from the study, unless it was determined by the investigator that the flare was triggered by a reduction or discontinuation in concomitant corticosteroid or systemic IMM therapy where further adjustment to the concomitant therapy may have been warranted. In this case, if a subject continued to have an active uveitis flare for ≥ 4 weeks after adjusting concomitant therapy, he/she was to be discontinued from the study.

Number of Subjects (Planned and Analyzed):

Planned:

Approximately 400 subjects were planned to be enrolled.

Analyzed:

A total of 424 subjects were enrolled and received at least 1 dose of study drug (Safety set). The intent-to-treat (ITT) set was composed of 364 subjects: 7 were excluded due to incomplete efficacy source data or general Good Clinical Practice compliance issues at the lead-in study site; 53 subjects were excluded because:

- the subject developed proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy during the study (an exclusion criterion);
- the subject underwent a cataract surgery during the study;
- the subject had previous vitrectomy or was vitrectomized during the study.

Diagnosis and Main Criteria for Inclusion:

- Subject must have successfully enrolled in either Study M10-877 or Study M10-880 and either met the endpoint of "Treatment Failure" or completed the study without treatment failure
- Subject must not have prematurely discontinued from Study M10-877 or Study M10-880 for any reason other than from a treatment failure event
- Subject must not have had:
  - corneal or lens opacity that precluded visualization of the fundus or that likely required cataract surgery during the duration of the trial
  - intraocular pressure of ≥ 25 mmHg and was being treated with ≥ 2 glaucoma medications or had evidence of glaucomatous optic nerve injury

Diagnosis and Main Criteria for Inclusion (Continued):

- proliferative or severe non-proliferative diabetic retinopathy or clinically significant macular edema due to diabetic retinopathy
- neovascular/wet age-related macular degeneration
- abnormality of vitreo-retinal interface (i.e., vitreomacular traction, epiretinal membranes, etc.) with the potential for macular structural damage independent of the inflammatory process
- a systemic inflammatory disease that required therapy with a prohibited IMM agent at the time of study entry.

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, 10-001959, 11-003870, 11-005882, 13-005618, 13-000648, 14-002610, 14-002617, 14-006602, 15-000609, 15-005080, 15-005871

Duration of Treatment: The mean duration of treatment was 140.4 weeks (approximately 2.7 years). Including the lead-in studies, the mean treatment duration was 157.7 weeks (approximately 3 years). Maximum treatment duration for any subject was 362 weeks (approximately 7 years). Of the 424 subjects who entered Study M11-327 from the lead-in studies, approximately 75% and 50% were still enrolled at Week 78 and at Week 150, respectively, with a gradually decreasing sample size with longer treatment duration.

Criteria for Evaluation

Efficacy:

The following key endpoints were used to evaluate the long-term efficacy of adalimumab to treat subjects with non-infectious intermediate uveitis, posterior uveitis, or panuveitis. Endpoints were to be assessed at each study visit; both eyes were to be assessed. At entry, subjects were categorized as having inactive uveitis (defined as not having experienced treatment failure in the lead-in study) or active uveitis (defined as having experienced treatment failure in the lead-in study).

- Proportion of subjects with:
  - no new active, inflammatory, chorioretinal, or inflammatory retinal vascular lesions (i.e., subjects in quiescence) in both eyes
  - a Grade $\leq$ 0.5+ in anterior chamber (AC) cells in both eyes on Slit Lamp Exam according to Standardization of Uveitis Nomenclature (SUN) criteria
  - a Grade $\leq$ 0.5+ in vitreous haze (VH) in both eyes on indirect ophthalmoscopy according to National Eye Institute (NEI)/SUN criteria
  - Proportion of subjects without a worsening of best corrected visual acuity (BCVA) by $\geq$ 15 letters on the Early Treatment Diabetic Retinopathy Study eye chart in both eyes
- Percent change in central retinal thickness (1 mm subfield) in each eye
- Change in NEI Visual Functioning Questionnaire (VFQ-25; a patient-reported outcome) score
- Proportion of subjects achieving a $\geq$ 50% reduction in IMM load

Safety:

Adverse events (AEs), physical examination, vital signs, and laboratory data were assessed throughout the study.

Statistical Methods

Efficacy:

Demographics and baseline characteristics of the study subjects were summarized using descriptive statistics.

Efficacy analyses were provided for the ITT set. All efficacy analyses were descriptive. Results were given overall and stratified between subjects who entered into the study with active (defined as experiencing treatment failure in the lead-in study) versus inactive uveitis (defined as not experiencing treatment failure in the lead-in study). Continuous variables were summarized by the number of non-missing observations, mean, standard deviation, median, quartiles, and minimum and maximum. Categorical variables were summarized by counts and percentages.

Safety:

Safety analyses were conducted in the safety set, which included all subjects who received at least 1 dose of adalimumab. The number and percentage of subjects with treatment emergent AEs (TEAEs) were displayed with counts and percentages. The changes in laboratory data and vital signs were summarized using descriptive statistics.

Summary/Conclusions

Efficacy Results:

This study was initially planned to run for 78 weeks, but was extended for ethical reasons, to avoid leaving patients untreated who had responded well to adalimumab treatment until regulatory and/or reimbursement approval for the treatment of uveitis in adults was obtained for their respective countries. A subject was considered to be a completer once regulatory and/or reimbursement approval in their country was attained. Of subjects in the ITT set (364 subjects), a sizeable number of subjects (~75% were still enrolled at Week 78 and about 50% (181 subjects) were still enrolled at Week 150, with continual decline in subject numbers at longer treatment durations. Data were collected through Week 366 (maximum), but with a gradually decreasing sample size that became too small toward the end of the study to allow for meaningful conclusion.

The majority of subjects in the ITT set were female and white with a mean age of 42.3 years. The majority of subjects had panuveitis (51.4%), followed by posterior uveitis (27.7%), and intermediate uveitis (20.1%). The mean disease duration of uveitis was 62.3 months.

Overall, over 40% of subjects reported using concomitant uveitis-related corticosteroids at Baseline (58.8% and 7.3% of subjects with active and inactive uveitis at study entry, respectively), and over 30% of subjects reported using concomitant systemic IMMs at Baseline.

Adalimumab treatment was associated with an increase in the number of subjects who experienced uveitis control during the study. At Week 150, 85.0% of subjects overall were in quiescence and 65.0% were in steroid-free quiescence. The effect was most evident in subjects with active uveitis at study entry, in whom an increase in the rate of quiescence from 7.5% (18/240) at Week 0 to 79.7% (98/123) at Week 150 was observed. The proportion of subjects with inactive uveitis at study entry in quiescence was maintained throughout the study, with an increase from 83.9% (104/124) at Week 0 to 96.5% (55/57) at Week 150.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Adalimumab treatment was associated with improvement in visual acuity, as measured by the decrease in mean logarithm of the minimum angle of resolution (logMAR) BCVA of both eyes, from 0.20 ± 0.275 at Week 0 to 0.10 ± 0.255 at Week 150. The mean logMAR BCVA of both eyes decreased in subjects with active uveitis at study entry from Week 0 to Week 150, indicating improvement in visual acuity, and was generally maintained at baseline levels in subjects with inactive uveitis from Week 0 to Week 150, indicating that deterioration in visual acuity was generally absent in subjects with inactive uveitis. In addition, 92.7% and 100.0% of subjects with active and inactive uveitis at study entry, respectively did not have worsening in BCVA, defined as deterioration of ≥ 15 letters, at Week 150 compared to baseline.

Adalimumab treatment was associated with a reduction in inflammation as measured by AC cell grade and VH grade, a reduction in active inflammatory lesions, and a reduction in central retinal thickening as assessed by optical coherence tomography (OCT).

Adalimumab was associated with improvement in many aspects of vision-related functioning in subjects with active uveitis at study entry, as measured by increases in VFQ-25 total score and all subscores at Week 150 compared to Week 0, and generally maintained baseline vision-related functioning at Week 150 in subjects with inactive uveitis at study entry, with a slight worsening for some subscores.

Adalimumab had a corticosteroid sparing effect in all subjects. Uveitis-related mean daily systemic corticosteroid dose was reduced by 84.0%, from 9.4 mg/day at Week 0 to 1.5 mg/day at Week 150, and was generally maintained at subsequent timepoints. Adalimumab also had an IMM sparing effect.

Overall, when evaluated by uveitis status at study entry, the proportion of subjects with active uveitis who achieved disease control was increased at Week 150, and disease control was maintained through Week 150 in subjects with inactive uveitis. Although the number of subjects continually decreased at later timepoints, particularly beyond Week 78, because study sites were closed out when regulatory and/or reimbursement approval was achieved in participating countries, the efficacy results at visits beyond Week 150 (the timepoint at which approximately 50% of the enrolled subjects were still in the study) were generally aligned with the results observed at earlier timepoints.

In summary, the results of the study support the sustained efficacy of treatment with adalimumab in achieving and maintaining disease control through control of inflammation in subjects with active or inactive non-infectious intermediate uveitis, posterior uveitis, and panuveitis, including reducing a wide range of disease manifestations, while improving/maintaining visual acuity and minimizing concomitant systemic corticosteroid and IMM use.

Safety Results:

The majority of TEAEs were mild or moderate in severity; no particular pattern of TEAEs was observed. TEAEs leading to study drug discontinuation were reported in 77 subjects (18.2%).

Serious AEs (SAEs) were reported in 101 subjects (23.8%), with the most frequently (≤ 1.7%) reported being cataract, uveitis, and urinary tract infection. Four subjects died during the study (brain abscess, pancreatic carcinoma metastatic, death [accident], and B-cell lymphoma); with the exception of brain abscess (possibly related), the investigator considered these events as not related or probably not related to study drug.

Summary/Conclusions (Continued)

Safety Results:

The most frequently reported TEAEs of special interest were infections (275 subjects [64.9%]), injection site reactions (52 [12.3%]), and allergic reactions (28 subjects [6.6%]). There were no reports of Legionella infection, oral candidiasis, reactivation of Hepatitis B, progressive multifocal leukoencephalopathy, hepatosplenic T-cell lymphoma, melanoma, leukemia, cutaneous vasculitis, autoimmune hepatitis, Stevens-Johnson Syndrome, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, or Humira administration-related medication error TEAEs.

No patterns were identified in the analysis of clinical laboratory and vital signs parameters that suggest significant safety concerns for adalimumab. No subject met the criteria for a Hy's law case (3 × ULN values for ALT/SGPT or AST/SGOT concurrent with 2 × ULN value for total bilirubin and symptomatology), indicating no significant drug-induced liver injury following study drug treatment.

Conclusions:

The final results of Study M11-327 support the sustained efficacy of treatment with adalimumab in achieving and maintaining disease control (quiescence) through control of inflammation in subjects with active or inactive non-infectious intermediate uveitis, posterior uveitis, and panuveitis, while also improving/maintaining visual acuity and minimizing corticosteroid and IMM use. The long-term safety profile of adalimumab in adult subjects with non-infectious intermediate uveitis, posterior uveitis, and panuveitis was generally consistent with the safety profile established in the lead-in studies of adalimumab in uveitis (Studies M10-877 and M10-880). No new safety signals were identified.