

2.0 Synopsis

AbbVie Inc.	Individual Study Table Referring to Part of Dossier:	(For National Authority Use Only)
Name of Study Drug: Adalimumab	Volume:	
Name of Active Ingredient: Adalimumab	Page:	
Title of Study: A Multicenter, Open-Label Study of the Human Anti TNF Monoclonal Antibody Adalimumab to Evaluate the Long Term Safety and Tolerability of Repeated Administration of Adalimumab in Subjects with Ulcerative Colitis		
Coordinating Investigator: Remo Panaccione, MD, FRCPC		
Study Sites: 131 sites in Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Netherlands, New Zealand, Poland, Slovakia, Spain, Sweden, Switzerland, and the United States.		
Publications: 4		
Studied Period (Years): First Subject First Visit: 28 November 2007 Last Subject Last Visit: 26 November 2016	Phase of Development: 3	
Objectives: The primary objective of this study was to evaluate the long-term maintenance of response, safety, and tolerability of repeated administration of adalimumab in subjects with UC who participated in and successfully completed Study M06-826 or Study M06-827. The secondary objective was to assess pharmacokinetics (PK) of adalimumab following subcutaneous administration.		
Methodology: This was an open-label (OL) study in subjects who successfully completed Study M06-826 or Study M06-827. Subjects who entered this study from a blinded cohort were assigned to OL adalimumab, 40 mg every other week (eow). Any subjects entering from a blinded cohort with inadequate response upon entering the study who did not show response during the study, or who showed a response and then had a disease flare, may have had their adalimumab dose increased to 40 mg every week (ew), but no earlier than at the Week 12 visit. Similarly, subjects who entered from a blinded cohort and had clinical response or clinical remission who subsequently experienced a disease flare may have had their adalimumab dose increased to 40 mg ew, but no earlier than at the Week 12 visit. Subjects who entered this study from an open-label cohort continued their previous dosing regimen of eow or ew dosing. Subjects with inadequate response while receiving adalimumab 40 mg eow may have had their dose frequency increased to 40 mg ew at the Week 2 visit or thereafter. Any subject who continued to have inadequate response while receiving adalimumab 40 mg ew may have been withdrawn from the study.		

<p>Methodology (Continued):</p> <p>Beginning from Week 96, subjects who were in clinical response per partial Mayo score (a decrease in partial Mayo score ≥ 2 points and $\geq 30\%$ from Day 1/Baseline [Study M06-826 or Study M06-827] plus a decrease in the rectal bleeding subscore [RBS] ≥ 1 or an absolute RBS of 0 or 1) for at least 2 consecutive visits at least 14 days apart may have had the dose of adalimumab decreased from 40 mg ew to 40 mg eow, at the discretion of the investigator. Subjects who experienced a disease flare or inadequate response, as defined above, may have re-escalated their dose of adalimumab to 40 mg ew. Efficacy and safety measurements were performed throughout the study.</p>
<p>Number of Subjects (Planned and Analyzed):</p> <p>Planned: More than 800 subjects participated in Study M06-826 and Study M06-827 and were potentially eligible for this study.</p> <p>Analyzed: 592 subjects (safety); 585 (efficacy intent-to-treat analysis set 1)</p>
<p>Diagnosis and Main Criteria for Inclusion: Subject completed either Study M06-826 or Study M06-827 and was considered by the investigator to be a suitable candidate for participation. Subjects who had not responded to ew dosing in the preceding study were not eligible.</p>
<p>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</p> <p>Adalimumab 40 mg/0.8 mL via subcutaneous injection</p> <p>Bulk Product Lot Numbers: 06-006938, 07-012406, 07-014216, 08-015939, 08-019941, 09-025414, 10-001960, 10-005763, 11-003870, 11-005882, 13-000648, 15-000609, 14-002617</p>
<p>Duration of Treatment:</p> <p>Subjects could participate in the study for up to 388 weeks. This study was to conclude approximately 12 weeks after the following criteria had been satisfied:</p> <ul style="list-style-type: none">• Study drug received country and local (if applicable) regulatory approval for UC.• All applicable local reimbursement procedures were completed.
<p>Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:</p> <p>Not applicable.</p>
<p>Criteria for Evaluation</p> <p>Efficacy: Efficacy was evaluated by partial Mayo scores at each study visit (absolute scores and change from Baseline), Mayo scores at Weeks 48, 96, 144, 192, 240, 292, 340, and 388 or early termination (ET) (absolute scores and change from Baseline), Mayo subscores (endoscopy, rectal bleeding, stool frequency, Physician's Global Assessment [PGA]) at Weeks 48, 96, 144, 192, 240, 292, 340, and 388 or ET, and colectomy rates. Quality of life (QoL) was evaluated, using the Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form-36 Health Survey (SF-36), and Work Productivity and Activity Impairment Questionnaire, and health care resources utilization (physician visit, emergency room visits, hospital admissions, days in hospital).</p> <p>Pharmacokinetic: Blood samples for the measurement of adalimumab concentrations and anti-adalimumab antibodies were collected at Weeks 108 through 388 and at the ET visit.</p> <p>Safety: Adverse events, physical examination, vital signs, and laboratory data were assessed throughout the study.</p>

Statistical Methods

Efficacy: All statistical analyses were performed descriptively. Descriptive statistics were provided for demographic, efficacy, and QoL parameters. Continuous variables were summarized by the number of observations, mean, standard deviation, median, minimum, and maximum; whereas discrete variables were summarized by counts and percentages.

Pharmacokinetic: Summary statistics for adalimumab serum concentration at each time of scheduled sampling were calculated. In addition, pharmacokinetic model-based analyses were performed with the focus on clearance and volume of distribution.

Safety: Treatment-emergent AEs were defined as events that began or worsened either on or after the first dose of the study drug in Study M10-223 and before switch to commercial product or within 70 days after the last dose of the study drug, if subjects terminated the study.

Summary/Conclusions

Efficacy Results:

At Baseline of Study M10-223, the median Mayo score was 3.0 (mean = 3.5), and the median partial Mayo score was 2.0 (mean = 2.5), suggesting mild or no disease activity in at least 50% of subjects. Approximately half of all subjects (52.4%) were in remission per partial Mayo score. Subjects continued to respond well to adalimumab treatment, as observed by the increase over time in the percentage of subjects in remission per partial Mayo score. Mean and median Mayo scores and partial Mayo scores were low at Baseline and decreased through Week 292 of this study, indicating low disease activity. Change values for mean and median Mayo scores and partial Mayo scores were at or near 0.0. The mean endoscopy scores of 1.0 (indicating mucosal healing) at Baseline of this study also was maintained through Week 292 with median changes of 0.0.

Low mean and median Mayo subscores for endoscopy, stool frequency, rectal bleeding, and PGA decreased slightly from Baseline to Week 292, indicating mild to no disease activity in most of the subjects.

Eighteen subjects in the ITT-1 analysis set underwent colectomy during this study for a 5-year colectomy rate of 3.88%.

Improved quality of life and sustained work productivity were observed through Week 292, and low rates of emergency room visits and hospital admissions were reported.

Pharmacokinetic Results: PK data will be analyzed and presented in a separate report.

Safety Results: Overall, 83.8% of subjects had at least 1 treatment-emergent AE (225.6 events/100 PYs), and 39.2% had an AE assessed as possibly or probably related to study drug (33.8 events/100 PYs). Serious AEs were reported for 26.7% of subjects (13.4 events/100 PYs), and severe AEs were experienced by 23.3% of subjects (11.8 events/100 PYs). Two subjects had treatment-emergent fatal AEs (cardio-respiratory arrest and right ventricular failure), and 2 subjects died > 70 days post study (pulmonary embolism and cardiopulmonary arrest). Infections were reported by 58.1% of subjects (53.8 events/100 PYs), including 7.8% (3.0 events/100 PYs) with serious infections. Five cases of TB were reported (one active and four latent) during the study.

Summary/Conclusions (Continued)

Safety Results (Continued):

The evaluation of adverse events along with laboratory parameters, vital signs, and pregnancies in subjects with moderate to severe UC who were treated with adalimumab in the long-term extension Study M10-223 confirmed the favorable safety findings from the pivotal studies and were consistent with the established safety profile of adalimumab across multiple indications. Exposure-adjusted incidence rates of AEs and SAEs were in the range of or lower than the overall safety experience with adalimumab in clinical trials. No safety concerns were identified with respect to long-term treatment with adalimumab of subjects with moderate to severe UC.

Conclusions: The results from this OL study provide evidence that adalimumab is effective in the maintenance of symptomatic control and endoscopic healing. Adalimumab was well tolerated in subjects with UC and treatment with adalimumab was associated with low hospitalization and colectomy rates and quality of life improvements. Additionally, the data confirm the established favorable safety profile of adalimumab.