2.0   Synopsis

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

Title of Study: An Open-Label Multicenter Study to Evaluate the Impact of Adalimumab on Quality of Life, Health Care Utilization and Costs of Ulcerative Colitis Subjects in the Usual Clinical Practice Setting

Investigator: Prof. Simon Travis DPhil FRCP, Professor of Clinical Gastroenterology, Translational Gastroenterology Unit, John Radcliffe Hospital, Headington, Oxford, United Kingdom

Study Sites: 92 sites located in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Greece, Ireland, Israel, Italy, Poland, Portugal, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, and the United Kingdom

Publications: None

Studied Period (Years): First Subject First Visit: 22 May 2012 Last Subject Last Visit: 02 April 2015	**Phase of Development:** 3b

Objectives:

The primary objectives were to study the effect of adalimumab on quality of life (QOL) (as measured by Short Inflammatory Bowel Disease Questionnaire [SIBDQ]), the utilization of health care resources, and the costs of care for subjects with ulcerative colitis (UC) who were treated with adalimumab in the usual clinical practice setting. The secondary objectives were to further assess the effect of adalimumab disease activity and to collect additional safety data in subjects with UC.

Methodology:

This was a Phase 3b, multicenter, multi-country, open-label study.

Subjects who met all of the inclusion criteria and none of the exclusion criteria were to be enrolled into the study. All subjects received an open-label induction dose of 160 mg adalimumab at Week 0 (Baseline), 80 mg of adalimumab at Week 2, followed by maintenance dose of 40 mg of adalimumab every other week (eow) at Week 4 through Week 26.

Non-responders to adalimumab were discontinued from treatment at Week 8. Non-response was defined as a Physician's Global Assessment (PGA) score 2 and did not achieve a decrease of 2 points on the Simple Clinical Colitis Activity Index (SCCAI) compared with Baseline (Week 0). Subjects who discontinued from study drug were invited to continue in the study (without receiving adalimumab) to provide assessments through the Week 26 Visit. Subjects who had not responded to adalimumab at Week 8 and elected not to continue in the study had the Premature Discontinuation Visit procedures performed at Week 8 instead of the Week 8 Visit procedures. Subjects who continued in the study after the study drug was discontinued at the Week 8 Visit had post-Week 8 visits completed, with the exception of dispensing study drug.

Methodology (Continued):

After Week 8, dose escalation to 40 mg weekly was allowed for flare or non-response. The subject came in for an Unscheduled Visit assessment at or after Week 9 and received additional study drug for the weekly dosing schedule. If the subject failed to regain a response (subject had a PGA score 2 and did not achieve SCCAI response [did not achieve a decrease of 2 points compared with Baseline {Week 0}]) after escalation to weekly adalimumab, the subject was discontinued from the study drug and was invited to continue in the study to provide assessments through the Week 26 Visit.

Subjects were allowed to dose de-escalate to 40 mg eow at any time per the Investigator's discretion.

If a subject discontinued study drug prior to the Week 26 Visit, the subject could (1) continue to participate in the study to provide assessments, without receiving study drug (the subject received standard of care treatment per the Investigator's discretion) or (2) withdraw from study participation completely and have the Premature Discontinuation Visit procedures performed.

Effectiveness and safety assessments were performed throughout the study.

Number of Subjects (Planned and Analyzed):

Planned: Approximately 455 subjects

Analyzed: 463 subjects (safety); 461 subjects (intent-to-treat)

Diagnosis and Main Criteria for Inclusion:

Subjects were male or female between the ages of 18 and 75 years old at the time of the Screening Visit who had a diagnosis of active UC (PGA score of 2 or 3 and SIBDQ 45), confirmed by a colonoscopy with biopsy or flexible sigmoidoscopy with biopsy, for greater than 90 days prior to Week 0 (Baseline) and failed conventional treatment. Subjects had at least one episode of rectal bleeding within 7 days of Screening (i.e., at least blood streaks in stool was reported) and within 7 days of Week 0 (Baseline).

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

Adalimumab 40 mg/0.8 mL via subcutaneous injection

Bulk Product Lot Numbers: 10-005763, 11-005882, 13-000648

Duration of Treatment: The duration of the study was 39 weeks, which included a Screening period of up to 21 days, a 26-week treatment period, and a 70-day follow-up phone call. The Screening period was extended as necessary for subjects who required initiation of prophylactic anti-tuberculosis therapy, or repeat screening procedure(s) or laboratory test(s), or due to external, non-subject-related circumstances (e.g., delay of availability of screening test results), after consultation with and approval of the AbbVie Medical Monitor.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

Criteria for Evaluation

Efficacy:

The ranked primary effectiveness endpoints were as follows:

1. Change in SIBDQ at Week 26 from Baseline;
2. Change (6 months after treatment start versus 6 months prior to treatment start) in costs of UC-related medical care excluding adalimumab costs.

The secondary effectiveness endpoints were as follows:

*   Change (6 months after treatment start versus 6 months prior to treatment start) in total all-cause direct health care costs;
*   Change (6 months after treatment start versus 6 months prior to treatment start) in direct UC-related health care costs and indirect UC-related health care costs;
*   Change (6 months after treatment start versus 6 months prior to treatment start) in UC related and all cause hospitalization;
*   Change in subject satisfaction (TSQM) at Week 26 from Week 0 (Baseline);
*   Change (6 months after treatment start versus 6 months prior to treatment start) in UC related outpatient utilization, including emergency department visits, unscheduled consultation, exam procedures;
*   Percent (%) of subjects with absence of blood in stool at Week 26;
*   Change in SIBDQ from Week 0 (Baseline) over time;
*   Change in PGA from Week 0 (Baseline) over time;
*   Change in SCCAI from Week 0 (Baseline) over time;
*   Change in EQ-5D-5L from Week 0 (Baseline) over time;
*   Change in WPAI from Week 0 (Baseline) over time.

Direct UC-related health care costs were defined as costs associated with health care resource utilization, which included the expenses for inpatient, outpatient, and pharmaceutical services within the health care delivery system. Direct costs were calculated based on the health care resource utilization.

Indirect UC-related health care costs were defined as the expenses incurred from the cessation or reduction of work productivity as a result of the morbidity and mortality associated with UC, which included work loss, worker replacement, and reduced work productivity from illness and disease. Indirect costs were calculated based on WPAI.

Safety:

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

Statistical Methods

Efficacy:

Hypothesis testing for the ranked primary endpoints was performed in the hierarchical order using the two-sided paired t-test for mean change equal zero. The change in SIBDQ at Week 26 was tested first. If the null hypothesis of no change from baseline was rejected at $= 0.05$, then the change in costs of UC-related medical care (excluding adalimumab costs) was tested at significance level $= 0.05$.

Continuous secondary effectiveness endpoints were analyzed using paired t-test.

Categorical secondary effectiveness endpoints were analyzed using McNemar's test.

Continuous data were described by mean, standard deviation, minimum, median, and maximum; categorical data were described by frequency and percentage.

Costs were assigned based on the health care resource utilization using standardized average monthly costs from the United Kingdom. Indirect average monthly costs were calculated using WPAI based on the average wages from the United Kingdom.

Safety:

Treatment-emergent AEs reported were summarized by frequency and percentage as well as per 100 patient-years (PYs). The events were coded using the Medical Dictionary for Drug Regulatory Affairs version 17.1 and summarized by system organ class and preferred term.

Clinical laboratory data were summarized with mean change from baseline, with cross tabulation from baseline to final values, and with the proportion of subjects who change to potentially clinical significant values during study from baseline values that were not potentially clinical significant. Vital signs were analyzed with mean change from baseline.

Summary/Conclusions

Efficacy Results:

SIBDQ total score was statistically significantly improved from a mean of 30.9 at Baseline to a mean of 48.3 at Week 26 ($P < 0.001$).

Compared with 6 months prior to treatment start, there was a statistically significant decrease in UC-related medical care costs 6 months after treatment start, excluding adalimumab cost (mean decrease of £1,383.80; $P < 0.001$). There were statistically significant decreases in both all-cause direct health care costs (mean decrease of £1,297.80; $P < 0.001$) and UC-related direct and indirect costs (mean decrease of £4,308.30; $P < 0.001$) 6 months post-treatment compared with 6 months prior to treatment.

The mean PGA was 2.2 at Baseline consistent with a moderate to severe disease severity. Statistically significant and clinically meaningful improvements in PGA and SCCAI from baseline were seen as early as Week 2 and were maintained through Week 26. Reduction of SCCAI from baseline over time was detected regardless of disease severity or prior anti-TNF status but was greater in subjects who adhered to adalimumab during the study.

Response was achieved by 82.9% of subjects at Week 8 and was observed in 69.6% of subjects at Week 26. In subjects who required dose escalation, response was observed in 64.3% at Week 26.

SCCAI remission was observed in 49% of subjects at Week 8 and was maintained in a similar proportion of subjects at Week 26. Remission rates were higher in moderate, and adherent subjects, and in subjects who did not require dose escalation.

The percent of subjects without blood in stool statistically significantly increased from 0.9% at Week 0 to 55.1% at Week 8 and remained stable from Week 8 through Week 26.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Subject quality of life improved from Baseline and was maintained through Week 26 for all of the following: TSQM (effectiveness, side effects, convenience, and global satisfaction), SIBDQ total score and all sub-scores (bowel, social, systemic, and emotional), EQ-5D-5L (total score and VAS), and WPAI (work time missed, impairment while working, overall work impairment, and activity impairment).

Adalimumab induced and maintained reduction of UC symptoms and remission as well as improvement in quality of life in clinically meaningful proportions of subjects in this study.

Safety Results:

Mean duration of study drug exposure was 157.6 days in ITT Analysis Set; total patient-years exposure was 199.00 in Safety Analysis Set.

In the safety population, treatment-emergent AEs were reported by 74.3% of subjects (740.7 events/100 PYs). The most frequently reported AEs were ulcerative colitis (22.0%) and headaches (13.0%). Adverse events (primarily UC flare) led to discontinuation of study drug in 11.4% of subjects (31.2 events/100 PYs).

There was one treatment-emergent death: one subject died of accidental death (motorcycle accident), assessed by the Investigator as not related to study drug.

Serious AEs were reported for 14.0% of subjects (40.7 events/100 PYs). Ulcerative colitis was the most frequent SAE, reported by 41 subjects (8.9%).

Infections were reported by 29.6% of subjects (107 events/100 PYs). Most infections were nonserious, mild or moderate, and easily manageable. Nasopharyngitis (8.0%) was the most frequently reported infection. Serious infections were reported for 1.7% of subjects (5 events/100 PYs). One opportunistic infection excluding oral candidiasis and TB (esophageal candidiasis) was reported (0.2%, 0.5 events/100 PYs), which was nonserious.

Malignancies were reported for three subjects (0.6%, 1.5 events/100 PYs). All 3 subjects had risk factors for malignancy.

Allergic reactions were reported for 3.5% of subjects (8.5 events/100 PYs), most of which were mild or moderate in severity and most of which eventually resolved.

One subject (0.2%, 0.5 events/100 PYs) had treatment-emergent silent myocardial infarction; the event resolved.

One subject with a medical history of thromboembolic events had treatment-emergent cerebral hemorrhage and intracranial venous sinus thrombosis (0.2%, 1.0 events/100 PYs); both events eventually resolved.

Three subjects with a significant medical history had new onset or worsening psoriasis (0.6%, 1.5 events/100 PYs).

Hematologic disorders (including pancytopenia) were reported in 5.4% of subjects (13.6 events/100 PYs); four events of hematologic disorders were serious.

Injection site reactions were reported for 9.9% of subjects (34.7 events/100 PYs). No event of injection site reaction was serious.

Summary/Conclusions (Continued)

Safety Results (Continued):

No subjects reported treatment emergent legionella infection, diverticulitis, TB, reactivation of hepatitis B, progressive multifocal leukoencephalopathy, lymphoma, hepatosplenic T-cell lymphoma, NMSC, leukemia, lupus-like reactions or systemic lupus erythematosus, vasculitis, sarcoidosis, CHF, pulmonary embolism, interstitial lung disease, intestinal perforation, pancreatitis, Stevens-Johnson syndrome, erythema multiform, demyelinating disorder, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, liver failure or other liver events, or adalimumab administration related medication error.

Mean changes over time in hematology, chemistry, and urinalysis parameters were small and not clinically meaningful.

Study drug was well tolerated and no new safety signals were identified.

Conclusions:

The data provide evidence that adalimumab is effective in improving and maintaining symptomatic control and quality of life, and in decreasing costs of UC-related medical care in subjects with UC.