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, Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Adalimumab for the Induction and Maintenance of Clinical Remission in Chinese Patients with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-reactive Protein

Coordinating Investigator: [redacted]

Study Sites: 15 sites in China

Publications: None

Studied Period (Years):	**Phase of Development:** 3
First Subject First Visit: 17 August 2015 Last Subject Last Visit: 15 December 2017 (last 70-day follow-up phone call)	

Objectives:

The primary objective of this study was to assess the efficacy and safety of adalimumab in inducing (at Week 4) and maintaining (at Week 26 in Week 8 responders) clinical remission, defined as Crohn's Disease Activity Index (CDAI) < 150, in Chinese subjects with moderately to severely active Crohn's disease (CD) and elevated high-sensitivity C-reactive protein (hs-CRP).

Additional objectives were to assess the effect of adalimumab treatment on other efficacy outcomes, including clinical response, steroid-free remission, and improvement in quality of life.

Methodology:

The study consisted of an 8-week double-blinded (DB) period followed by an open-label (OL) period of 18 weeks. Subjects were randomized in a 1:1 ratio to receive adalimumab or placebo at Baseline. Subjects randomized to adalimumab at Week 0 were to receive blinded adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and Week 6. Subjects randomized to placebo at Week 0 were to receive blinded placebo at Week 0 and Week 2, then receive blinded adalimumab 160 mg at Week 4 and 80 mg at Week 6. At Week 8, all subjects were to enroll in an 18-week OL period to receive adalimumab 40 mg every other week (eow).

At Week 4, all subjects on oral corticosteroids were to undergo a mandatory steroid dose taper. If the investigator felt that the steroid taper was not advisable, the subject was withdrawn from the study. If a subject had an inadequate response at or after Week 12, they could dose escalate to OL adalimumab 80 mg eow. An inadequate response was defined as CDAI ≥ 200 and an hs-CRP increase from Baseline of at least 1 mg/L and/or hs-CRP ≥ 5 mg/L. If the subject received OL 80 mg eow and continued to demonstrate inadequate response, he/she was to be withdrawn from the study.

Number of Subjects (Planned and Analyzed):

Planned: 200 subjects; Analyzed: 205 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible for study participation if they met all of the following inclusion criteria:

- Male or female of Chinese descent with full Chinese parentage 18 to 70 years (inclusive) of age at Baseline (Week 0).
- Confirmed diagnosis of CD for at least 3 months prior to Baseline (Week 0) (biopsy results must be available).
- hs-CRP ≥ 3 mg/L during the entire screening period.
- CDAI ≥ 220 and ≤ 450 at Baseline (Week 0) despite concurrent or prior treatment with an adequate course, in the opinion of the investigator, of at least 1 of the oral corticosteroids or immunosuppressants (IMM) or both as defined in the protocol.
- Negative tuberculosis (TB) Screening assessment. If the subject has evidence of a latent TB infection during the Screening assessment, the subject must initiate and complete a minimum of 3 weeks (or per local guidelines, whichever is longer) of an ongoing TB prophylaxis prior to Baseline.

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

Adalimumab 40 mg/0.8 mL, prefilled SC syringes; Bulk Product Lot Numbers: 14-006602, 16-001720

Duration of Treatment:

Up to 26 weeks: 8-week DB treatment period; 18-week OL period

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

Placebo for adalimumab, prefilled syringe; Bulk Product Lot Numbers: 14-002885, 16-000470

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects who achieved clinical remission (CDAI < 150) at Week 4.

The key Week 26 efficacy endpoint was the proportion of subjects who achieved clinical remission at Week 26 (CDAI < 150) in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8.

Other key secondary efficacy endpoints included:

- The proportion of subjects who achieved CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 4;
- The proportion of subjects who achieved CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who achieved decrease in CDAI ≥ 70 points from Baseline plus at least 30% reduction in hs-CRP from Baseline at Week 8;
- The proportion of subjects who discontinued corticosteroid use and achieve clinical remission (CDAI < 150) at Week 26 in subjects who were taking steroids at Baseline and who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8;

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Proportion of subjects who discontinued corticosteroid use and achieve CDAI < 150 plus a reduction in hs-CRP of at least 50% from Baseline at Week 26 in subjects who were taking steroids at Baseline and who achieved decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 8;
- Proportion of subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 4;
- Proportion of subjects who achieved decrease in CDAI ≥ 70 points from Baseline plus a reduction in hs-CRP of at least 30% from Baseline at Week 4;
- Proportion of subjects who achieved CDAI < 150 and hs-CRP < 3 mg/L at Week 4;
- Proportion of subjects who achieved CDAI < 150, hs-CRP < 3 mg/L at Week 26 in subjects who achieved clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8;
- Proportion of subjects who achieved Inflammatory Bowel Disease Questionnaire (IBDQ) remission (IBDQ ≥ 170 points) at Week 4;
- Proportion of subjects who achieved IBDQ remission at Week 26 in subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline) at Week 8;
- Change from Baseline in fecal calprotectin level at Week 4.

Safety:

Treatment-emergent adverse events (TEAEs), physical examinations, vital signs, and laboratory data were assessed throughout the study. In addition, TB evaluation by QuantiFERON-TB test and chest x-rays (CXRs)/computed tomography (CT) scans were performed throughout the study.

Statistical Methods

The Statistical Analysis Plan (SAP) for this study was completed prior to final database lock (version 1.0, dated 26 October 2017). There were no changes to the planned analyses after finalization of the SAP.

Efficacy:

The comparisons between treatment groups on the primary efficacy variable during the DB placebo-control period (Week 0 – 4) was performed using the Cochran-Mantel-Haenszel (CMH) test and stratified by CDAI ≤ 300 and > 300 at Baseline (Week 0) and corticosteroid use at Baseline. A CMH based two-sided 95% confidence interval for the difference between the treatment groups was calculated. The ITT set was used for the analysis. Missing CDAI was imputed using the non-responder imputation (NRI) approach.

For the key secondary efficacy endpoint at Week 26, the one sample Exact test was performed by comparing it to the clinically meaningful constant rate, and the two-sided 95% CI was provided. For other key efficacy endpoints, continuous variables were analyzed using Analysis of Covariance (ANCOVA) model including factor for treatment group, stratification factors and Baseline values. For categorical endpoints with comparison between the treatment groups, the difference in proportions of subjects between treatment groups was analyzed using the CMH test adjusted for stratification variables. Additionally, the CMH based two-sided 95% confidence interval for the difference in proportions was provided. For categorical endpoints with comparison to the clinically meaningful constant rate, the one sample Exact test was performed and the two-sided 95% CI was provided.

Statistical Methods (Continued)

Efficacy (Continued):

Subjects who dose escalated were imputed using NRI for visits after dose escalation. The last observation carried forward (LOCF) method was also used as the sensitivity analyses.

Safety:

All safety analyses were performed using the Safety set, which included all subjects who enrolled into this study and received at least 1 dose of study drug. AEs were coded using the MedDRA version 20.0. Frequency, severity, and causal relationship of TEAEs were tabulated by system organ class and preferred term. AEs by maximum relationship to study drug, and AEs by maximum severity were summarized by number and percentage. TEAEs were summarized separately for the double-blind placebo-controlled dosing period (Week 0 to Week 4) and during the administration of adalimumab (the first dose of adalimumab to 70 days after the last dose of adalimumab).

Summary/Conclusions

Efficacy Results:

The primary efficacy endpoint was achieved, with a statistically significantly higher proportion of subjects in the adalimumab group achieving clinical remission at Week 4 than subjects in the placebo group. While adalimumab had a positive effect on clinical remission in subgroups with moderate disease (Baseline CDAI ≤ 300) and severe disease (Baseline CDAI > 300), subjects with moderate disease were more likely to achieve clinical remission at Week 4 with adalimumab treatment than subjects with severe disease. Similarly, while adalimumab treatment had a positive effect on clinical remission in both subgroups categorized by Baseline hs-CRP, a higher proportion of subjects with a Baseline hs-CRP < 30 mg/L achieved clinical remission with adalimumab treatment at Week 4 than subjects with a Baseline hs-CRP ≥ 30 mg/L. Subgroup analyses demonstrated that use of corticosteroids and IMMs at Baseline was not associated with differences in remission rates at Week 4.

The key secondary efficacy endpoint was achieved: Subjects in the adalimumab group improved over 26 weeks of continued OL adalimumab 40 mg eow treatment; approximately two-thirds of subjects who had a clinical response at Week 8 achieved clinical remission at Week 26 ($P < 0.001$). These results well exceeded the predefined threshold of 30% for a clinically meaningful remission rate. Approximately half of the subjects maintained clinical response from Week 4 through Week 26. The percentage of subjects who achieved clinical response peaked at Week 8 (64.5%) and plateaued at around 50% through Week 26. Results for additional secondary efficacy endpoints further support the primary efficacy endpoint.

Dose escalation from 40 mg to 80 mg eow during the OL period because of inadequate response occurred in 20.5% of subjects and was associated with clinically meaningful rates of clinical response and clinical remission at Week 26 (51.2% and 26.8%, respectively).

Pharmacokinetic Results:

The pharmacokinetic (PK) results and conclusions are presented in a separate report.

Summary/Conclusions (Continued)

Safety Results:

Results demonstrate that adalimumab 160/80 mg followed by 40 mg eow and the option to dose-escalate to 80 mg adalimumab eow was generally safe and well tolerated in a Chinese population of patients with moderately to severely active CD and elevated hs-CRP. No deaths occurred during the study.

During the DB period Week 0 – 4, similar frequencies of TEAEs occurred in adalimumab and placebo groups. A small proportion of subjects experienced SAEs, discontinuations due to SAEs, and AESIs. Seven subjects (3.5%) who received adalimumab reported 8 serious infection TEAEs, and 2 of these TEAEs were considered by the investigator to have a reasonable possibility of being related to study drug (PTs of abdominal abscess, lung infection). No subjects reported active TB TEAEs during the study.

In subjects who received at least 1 dose of adalimumab in the study, 58.5% of subjects reported TEAEs that were considered by the investigator to have a reasonable possibility of being related to study drug. The most frequently reported TEAEs considered to have had a reasonable possibility of being related to adalimumab included WBC count decreased, leukopenia, and mycobacterium tuberculosis complex test positive. Serious TEAEs considered to have a reasonable possibility of being related to adalimumab were reported in 4.5% of subjects.

Mean changes in laboratory parameter values (hematology, clinical chemistry, and urinalysis) from Baseline to Week 8 (end of the DB period) and over time to the end of the study (Week 26), were not considered clinically meaningful. Shifts in hematology and clinical chemistry values from normal or high at Baseline to low at the final value or normal or low at Baseline to high at the final value were generally infrequent and not considered clinically meaningful, except for a shift from normal to low WBC count. Among subjects with reported TEAE of WBC count decreased, most subjects were treated with AZA concomitantly during the study. The majority of TEAEs of WBC count decreased were reported by the investigator as mild in severity and with a reasonable possibility of being related to the study drug.

Mean changes from Baseline values for vital sign parameters were not considered clinically meaningful.

There was 1 pregnancy in the adalimumab group, which was reported as an induced abortion.

No product complaints were identified for adalimumab in this study.

Conclusions:

In this study, adalimumab was efficacious in treating adult Chinese patients with moderately to severely active CD (CDAI $\geq$ 220 to $\leq$ 450) with elevated hs-CRP ($\geq$ 3 mg/L), who failed prior treatment with corticosteroids and/or IMM.

Adalimumab was effective in maintaining clinical remission in patients who responded to induction treatment. These findings were accompanied by improvements in quality of life (as measured by IBDQ) and reductions in objective markers of inflammation (hs-CRP and fecal calprotectin). Of note, corticosteroid doses could be tapered completely to achieve steroid-free remission.

Dose escalation to 80 mg eow for subjects with inadequate response to adalimumab 40 mg eow led to achievement of clinical response and remission of disease.

Summary/Conclusions (Continued)

Conclusions (Continued):

Safety results demonstrate that adalimumab 160/80 mg, followed by 40 mg eow and, with the option to escalate to 80 mg eow in the case of inadequate response, was generally safe and well tolerated in Chinese patients with moderately to severely active CD. The safety profile of adalimumab noted in this study was similar to what is known about the overall safety profile of the drug based upon decades of experience in global clinical studies and postmarketing surveillance in the treatment of CD and across the other indications of adalimumab.