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 Human Anti-TNF Monoclonal Antibody Adalimumab to Investigate Efficacy, Safety and Pharmacokinetics after Dose Escalation in Japanese Subjects with Crohn's Disease		
Investigator: Satoshi Motoya, MD, PhD		
Study Sites: 12 sites in Japan		
Publications: 1		
Studied Period (Years): First Subject First Visit: 18 September 2013 Last Subject Last Visit: 01 October 2015	**Phase of Development:** 3	
Objective: The primary objective of this study is to evaluate the efficacy, safety, and pharmacokinetics after dose escalation of adalimumab in patients with Crohn's disease who lost response to maintenance adalimumab 40 mg eow.		
Methodology: The study was a 52-week open-label single arm study in which subjects were given adalimumab 80 mg by subcutaneous (SC) injection at Baseline (Week 0) and then every other week (eow) from Week 2 through Week 50. No dose reduction to 40 mg eow was allowed during the study. A follow-up phone call was made approximately 70 days after the last dose of study drug administration unless subjects left the study to initiate treatment with commercially available Humira®.		
Number of Subjects (Planned and Analyzed): 28 subjects planned 28 subjects analyzed		

Diagnosis and Main Criteria for Inclusion:

Adult subjects (≥ 15 years of age) with Crohn's disease (CD) were eligible for inclusion in this study if they had received treatment with commercially available Humira® – initially as an induction dose of adalimumab 160 mg at Week 0 and then 80 mg at Week 2, achieved a CR-70 at Week 4, and then lost response during maintenance treatment with Humira® 40 mg eow. The definition of a lost response was an increase in CDAI ≥ 50, as compared to the timepoint with the lowest CDAI score after initiation of Humira® treatment, and an absolute CDAI score of ≥ 200. Subjects had to satisfy the definition of lost response at both Screening and at Week 0. In addition, subjects were to have a CRP value ≥ 1 mg/dL at Screening. If subjects were female, they could not be of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, and/or hysterectomy) or if they were of childbearing potential, they had to be practicing an approved method of birth control throughout the study and for 150 days after the last dose of adalimumab, as the impact of adalimumab on pregnancy is not known. Subjects were to be in good health based on the results of their medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead electrocardiogram performed at Screening. Subject were to have a negative tuberculosis screening assessment and if there was evidence of a latent tuberculosis (TB) infection; the subject was required to initiate and complete a minimum of 21 days of TB prophylaxis or have documented completion of a full course of TB prophylaxis prior to Baseline (Week 0).

Subjects were excluded if they had other active gastrointestinal conditions (e.g., colitis, *C. difficile*) that could interfere with assessment of the subject's CD. To avoid bias in the evaluation of efficacy and safety by intestinal condition, subjects were excluded from the study if they had an obstructive stricture, a surgical bowel resection 6 months prior to Week 0 or were planning a resection while enrolled in the study, had an ostomy or ileoanal pouch (subjects with a previous ileo-rectal anastomosis were not excluded), or have short bowel syndrome. To avoid bias in the evaluation of efficacy and safety by concomitant use of other medications, subjects could not have been treated with any investigational drug of chemical or biologic nature within a minimum of 28 days or 5 half-lives (whichever was longer) of the drug prior to Week 0; was on oral corticosteroids, oral 5-aminosalicylates (5-ASA), or Crohn's-related antibiotics (e.g., fluoroquinolones, such as ciprofloxacin or nitroimidazole derivatives, such as metronidazole) that was not a stable dose for at least 14 days prior to Week 0 or had discontinued use within 14 days of Week 0, or had received an injection of corticosteroids (other than topical use) within 28 days of Week 0; was on immunomodulators (azathioprine, 6-MP, or MTX) that had been initiated within 90 days of Week 0 or was not on a stable dose for at least 28 days prior to Week 0 or had discontinued use within 28 days of Week 0; had received cyclosporine, tacrolimus (other than topical use), or mycophenolate mofetil within 28 days prior to Week 0; had received any biological agents (other than Humira®) or cytapheresis, such as leukocytapheresis (LCAP) or granulocytapheresis (GCAP) within 56 days of Week 0; or was on enteral nutrition and had not been on a stable amount for at least 28 days prior to Week 0 or had discontinued use within 28 days of Week 0.

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

Adalimumab, 40 mg/0.8 mL, SC injection, bulk lot number 13-000648.

Duration of Treatment: 52 weeks

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

None

Criteria for Evaluation

Efficacy:

The primary endpoint of this study was the proportion of subjects who achieved CR-50 (CDAI decrease ≥ 50 from Week 0) at Week 8.

The major secondary efficacy variables were as follows:

- Proportion of subjects who achieved clinical remission (CDAI < 150) at each visit.
- Proportion of the subjects who achieved CR-50 at each visit (Week 8 was primary endpoint).
- Proportion of subjects who achieved CR-70 (CDAI decrease ≥ 70 from Week 0) at each visit.
- Proportion of subjects who achieved CR-100 (CDAI decrease ≥ 100 from Week 0) at each visit.
- Change in CRP from Week 0 at each visit.

Pharmacokinetic/Immunogenicity:

Adalimumab serum concentrations were determined at Baseline (Week 0) and Weeks 2, 4, 8, 12, 24, 36, and 52 and at the Early Termination Visit if the subject discontinued prior to Week 52.

Presence of anti-adalimumab antibodies (AAA) was determined at Baseline (Week 0) and Weeks 8, 24, 36, and 52 and at the Early Termination Visit if the subject discontinued prior to Week 52.

Infliximab concentration and the presence of human anti-chimeric antibodies (HACA) were also determined in subjects who had a history of prior exposure to infliximab.

Safety:

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

Statistical Methods

Efficacy:

The primary analysis was demonstrated using point estimation and 95% CI of the proportion of subjects who achieved CR-50 (CDAI decrease ≥ 50 from Week 0) at Week 8. The subjects who had missing values for any reason, such as early termination, were included in the analysis using nonresponder imputation (NRI). The criterion for efficacy of adalimumab was 30% of the lower limit of the 95% CI of CR-50 at Week 8.

In the secondary analyses, discrete variables were summarized by counts and percentages and continuous variables were summarized by descriptive statistics at each visit. Subjects who had missing data for any reason, such as early termination (including subjects who discontinued from the study at Week 8 per protocol-defined nonresponse) were included in the analysis using NRI for discrete variables or last observation carried forward (LOCF) for continuous variables.

Pharmacokinetic/Immunogenicity:

Adalimumab serum concentrations were summarized at each time point of the scheduled sampling using descriptive statistics, including number of subjects, mean, median, standard deviation, coefficient of variation, minimum, and maximum.

The percentage of subjects who were AAA-positive was calculated.

Statistical Methods (Continued)

Safety:

The number and percentages of subjects who experienced treatment-emergent AEs (TEAEs) were tabulated by system organ class and preferred term using the Medical Dictionary for Regulatory Activities version 17.1 for both the interim and final analyses. In addition, a summary of TEAEs by severity and relationship to adalimumab were presented. A summary of treatment-emergent serious adverse events (SAEs), deaths, and TEAEs leading to discontinuation were also provided.

Interim statistical analyses were performed after all subjects completed their Week 24 evaluation. Final statistical analyses were performed after all subjects completed their participation in the study and either had their 70-day follow-up visit/phone call or initiated treatment with commercially available Humira®.

Summary/Conclusions

Efficacy Results:

The efficacy results of this OL study demonstrated that dose-escalation of adalimumab to 80 mg eow was effective in improving Crohn's disease activity in Japanese subjects with Crohn's disease who lost response to adalimumab 40 mg eow and these improvements were subsequently maintained up to 52 weeks.

The proportion of the subjects who achieved CR-50 at Week 8 (primary efficacy endpoint) was 75.0% and the lower limit of the 95% CI (55.1%) was higher than the criteria for efficacy (30%) defined in the protocol.

Following initiation of adalimumab dose-escalation, disease activity measures, as assessed by the proportions of subjects who achieved clinical remission, CR-50, CR-70, and CR-100 and the mean changes from Baseline in CRP and CDAI improved at Week 4 and Week 8. Mean disease activity measures were maintained or showed further improvement through Week 52.

Similar rates in the proportions of subjects who achieved CR-50 at Week 8 were observed among all subgroups, except for some subgroups with a small number of subjects (baseline corticosteroid use, CDAI at initiation of adalimumab induction treatment, and the duration between the date of first diagnosis of Crohn's disease and the date of initiation of adalimumab induction treatment). These results suggest that the efficacy of dose-escalation of adalimumab to 80 mg eow was not affected by the clinical background factors evaluated. In addition, no consistent pattern in the proportion of subjects who achieved CR-50 and CR-70 was observed between subjects who had prior infliximab experience and those who did not have prior infliximab experience. Dose-escalation of adalimumab to 80 mg eow led to higher proportions of infliximab-naïve subjects achieving clinical remission and CR-100 than infliximab-experienced subjects. These results should be interpreted with caution, as the number of subjects in these 2 subgroups were small and the groups were unequal in size.

Pharmacokinetic Results:

Pharmacokinetic results are presented in separate interim (R&D/15/0192) and final (R&D/15/1092) PK reports.

Summary/Conclusions (Continued)

Safety Results:

The safety results from Study M13-687 demonstrated that dose-escalation of adalimumab to 80 mg eow was generally safe and well tolerated in Japanese subjects with Crohn's disease who lost response to adalimumab 40 mg eow.

A total of 24 subjects (85.7%) reported at least 1 TEAE (447.6 E/100 PYs). The proportion of subjects who experienced any TEAE, severe or serious TEAEs, TEAEs leading to discontinuation, or serious infections did not increase with longer exposure to adalimumab. The most frequently reported TEAEs (≥ 10% of subjects) were nasopharyngitis (13 of 28 subjects [46.4%]), Crohn's disease (4 of 28 subjects [14.3%]), rash (4 of 28 subjects [14.3%]), and headache (3 of 28 subjects [10.7%]).

The majority of subjects (19 of 28 subjects [67.9%]) reported TEAEs that the investigator considered to have no reasonable possibility of being related to adalimumab. The majority of subjects reported TEAEs that the investigator considered to be mild to moderate in severity. Two subjects (7.1%) reported 3 TEAEs that were severe (Crohn's disease, ileus, and pneumonia bacterial).

No deaths were reported during this study. A total of 8 subjects (28.6%) experienced 11 treatment-emergent SAEs. The most frequently reported SAE was Crohn's disease (14.3%, 4 of 28 subjects) and all other SAEs were reported by 1 subject each (ileus, intestinal obstruction, small intestinal ulcer haemorrhage, subileus, anal abscess, pneumonia bacterial, and allergic transfusion reaction).

Nineteen subjects (67.9%) reported infectious AEs, including 2 subjects (7.1%) with serious infections (pneumonia bacterial and anal abscess).

Summary/Conclusions (Continued)

Safety Results (Continued):

No safety concerns were identified in the analysis of clinical laboratory and vital sign parameters during the study.

The safety data was consistent with the known safety profile established for adalimumab. No new safety signals for adalimumab were identified over the entire study.

Conclusions:

Dose-escalation of adalimumab to 80 mg eow was effective in improving Crohn's disease activity in Japanese subjects with Crohn's disease who lost response to maintenance adalimumab 40 mg eow. Adalimumab 80 mg eow was generally safe and well tolerated and no new safety signals were identified in this study. Overall, the results from Study M13-687 support a favorable benefit-risk profile for this patient population.