2.0 Synopsis

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

Title of Study:
A Multi-Center Study of Adalimumab in Japanese Subjects with Intestinal Behçet's Disease

Investigator: [redacted]

Study Sites: 65 sites in Japan

Publications: None

Studied Period (Years): First Subject First Visit: 13 October, 2010 Last Subject Last Visit: 28 June, 2013	**Phase of Development:** 3

Objective:
To investigate efficacy, long-term safety and pharmacokinetics of adalimumab sc for Japanese subjects with intestinal Behçet's disease who were refractory to conventional therapies.

Methodology:
This study was a phase 3, multi-center, open-label, uncontrolled study to evaluate efficacy, safety and pharmacokinetics of adalimumab in Japanese patients with intestinal Behçet's disease who were refractory to conventional therapies. This study was conducted at multi-centers in Japan with 20 (planned) intestinal BD patients in total. This study was planned to be conducted during Sep. 2010 to approval in Japan.

Subjects who met all of the inclusion criteria and none of the exclusion criteria were given subcutaneous injections of adalimumab 160/80 mg at Week 0/2 and 40 mg eow starting at Week 4 to Week 50. After Week 52, subjects could continue the treatment with 40 mg eow. At or after Week 8, the subjects who had inadequate response or disease flare could have the dose escalation to adalimumab 80 mg eow. If a subject who was receiving adalimumab 80 mg eow dosing post Week 8 continued to have inadequate response or disease flare, the subject was to be withdrawn from the study. Disease activity was evaluated by combination of global assessment of gastrointestinal symptoms and endoscopic improvement during Screening, Week 8 to Week 12, at Week 24 and Week 52 [redacted] Self-injection of study drug was permitted after Week 8.

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Definition of inadequate response:

- Subject who presents with global assessment of gastrointestinal symptoms ≥3 on 2 consecutive visits at least 14 days apart.
- If endoscopy was performed, subjects whose ileocecal typical ulcer did not reduce or expanded compared to screening.

Definition of disease flare:

- Subject presents with global assessment of gastrointestinal symptoms ≥2 on 2 consecutive visits at least 14 days apart after the subject presents with global assessment of gastrointestinal symptoms ≤1.
- If endoscopy was performed, subjects whose ileocecal typical ulcer expanded to > 1/2 after the ulcer had once reduced to ≤1/4 compared to screening.

Number of Subjects (Planned and Analyzed):
Planned: 20 subjects; Analytical population: 20 subjects.

Diagnosis and Main Criteria for Inclusion:
Japanese patients ≥15 years of age with diagnosis of intestinal Behçet's disease [redacted] ith typical ulcer [redacted] ≥1 cm at ileocecal region at the screening endoscopy, and with a global assessment of gastrointestinal symptoms of ≥3 at baseline. If patients have previously been administered infliximab [redacted] 2) patients who experienced initial response and then loss of response (per investigator's opinion) to infliximab, or 3) patients who were intolerant to infliximab.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:
Adalimumab pre-filled syringes containing 40 mg adalimumab/0.8 mL
Dose: adalimumab 40 mg
Route: subcutaneous injection
Lot number: [redacted]

Duration of Treatment: Until the approval of intestinal Behçet's disease in Japan

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

Criteria for Evaluation

Efficacy:

The primary endpoint of this study was the proportion of the subjects of both whose global assessment of gastrointestinal symptoms and endoscopic improvement became ≤1 (marked improvement rate) at Week 24.

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Major secondary endpoints at Week 24 and Week 52 are below:

- Proportion of the subjects who achieved marked improvement (both whose global assessment of gastrointestinal symptoms and endoscopic improvement become ≤1) (Week 24 is the primary endpoint)
- Proportion of the subjects who achieved complete remission (both whose global assessment of gastrointestinal symptoms and endoscopic improvement become 0)
- Proportion of the subjects whose global assessment of gastrointestinal symptoms is 0
- Proportion of the subjects whose global assessment of gastrointestinal symptoms is ≤1
- Proportion of the subjects whose endscopic improvement is 0
- Proportion of the subjects whose endscopic improvement is ≤1
- Proportions of the subjects whose abdominal pain is ≤1, diarrhea is ≤1 or other gastrointestinal symptom [abdominal discomfort, abdominal fullness] score is ≤1
- Proportion of the subjects whose global assessment of gastrointestinal symptoms improved for at least 1 point
- Proportion of the subjects whose endscopic improvement is ≤2
- [redacted]
- Change from Baseline in IBDQ score
- Change from Baseline in SF-36 score
- Proportions of the subjects whose Behçet's disease symptoms other than gastroenterologic symptoms (oral, skin, eye and vulvar [genital] symptoms) were 0 (disappeared).
- Change from Baseline in CRP

Safety:

Treatment-emergent AE, vital signs, clinical laboratory, and physical examination were used for safety evaluation.

Pharmacokinetic:

Serum concentrations of adalimumab and anti-adalimumab antibody was assessed throughout the study.

Statistical Methods

Efficacy:

The primary analysis was demonstrated using point estimation of the proportion of subjects with marked improvement at Week 24. Evaluation at Week 24 was used even if the subjects were dose escalated to 80 mg eow before Week 24. The subjects who had missing data for any reason such as early-terminated

subject were included into analysis using non-responder imputation (NRI) [redacted] The criterion of the efficacy of adalimumab on this study was 25% as marked improvement rate at Week 24. [redacted] Discrete variables were summarized by counts and percentages, and continuous variables were summarized by descriptive statistics on the items below at Week 24 and Week 52. The subject who had missing data for any reason such as early-terminated subject was included into analysis using NRI for discrete variables or LOCF for continuous variables. [redacted]

Pharmacokinetic:

Description of pharmacokinetic analysis could be referred in the PK report [redacted]

Safety:

Adverse events with onset after the first study drug injection and within [redacted] days after the last study drug injection were summarized on the safety analysis population. The number and percentages of subjects experiencing treatment emergent adverse event was tabulated by Medical Dictionary for Drug Regulatory Affairs (MedDRA, version 15.1) system organ class and MedDRA preferred term. In addition, a summary of adverse events by severity and relationship to study drug was presented. Treatment-emergent adverse events that were judged by the investigator to be probably or possibly related and probably, possibly or probably not related to study drug were also tabulated. A summary of serious and severe adverse events, deaths, and adverse events leading to discontinuation was also provided.

Mean change in [redacted] at each visit was summarized for safety analysis population. [redacted]

Summary/Conclusions

Efficacy Results:

Primary and secondary efficacy endpoints during 24 weeks and 52 weeks treatment are described in detail in the Interim reports (R&D/12/301 and R&D/12/929). A conclusion of primary endpoint was shown below.

- Marked improvement rate at Week 24 in FAS using NRI method, the primary efficacy outcome, was 45.0% (9/20 subjects), which was higher than preliminarily defined threshold (25%). Marked improvement rate at Week 52 in FAS using NRI method was 60.0% (12/20 subjects), which was higher than Week 24.

Conclusions reached as to the long-term [redacted] efficacy in this study were shown below:

- [redacted]
- [redacted]

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- [redacted]
- [redacted]
- [redacted]

Overall, adalimumab treatment was efficacious to subject with Behçet's disease and it has maintained for [redacted]

Pharmacokinetic Results:

PK was evaluated up to Week 52 in this study, and the result is described PK report [redacted]

Safety Results:

The safety conclusions in this study are follows:

- In the Safety Analysis Set (20 subjects), treatment-emergent AE was reported in 100% (20 subjects, [redacted]). The most frequently reported AEs were [redacted] All these AEs were expected in the adalimumab clinical program or anticipated in patients with intestinal Behçet's disease.
- AEs considered possibly or probably related to the study drug were reported in 25.0% (5 subjects). [redacted]
- [redacted]
- No subject died.

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- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted] had Behçet's syndrome. [redacted] One subject [redacted] was discontinued due to this [redacted] event which was onset on Day [redacted] (after dose escalation to 80 mg eow). [redacted]
- [redacted]
- [redacted]

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- [redacted]
- No active tuberculosis was reported. [redacted]
- [redacted]
- [redacted]

Based on the safety results, long-term [redacted] treatment with adalimumab in subjects with Behçet's disease considered to be well tolerated. No new safety signal was detected, and the safety profile was similar to that in other Humira indications.

Conclusions:

Although this was a small and open-label study, Humira provided effective and well-tolerated treatment to patients with this rare disease whose symptoms persisted despite conventional therapies, both on the shorter term (24 weeks) and on the longer term [redacted] Humira was approved for use in the intestinal Behçet's disease indication in Japan based on clinical results at weeks 24 and 52. The present report is the final CSR on this clinical study, which was conducted until approval of the indication.

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