

At or after Week 8, the subjects who had an inadequate response (defined below) during the double-blind period could switch to the rescue arm, where the subjects from the placebo group received adalimumab 160 mg initially, followed by adalimumab 80 mg 2 weeks later; subjects from the adalimumab group received adalimumab 40 mg initially and 2 weeks later under double-blinded conditions. All subjects in the rescue arm received adalimumab 40 mg eow at 4 weeks or later, with the possibility of escalating to 80 mg eow in case of inadequate response or disease flare at or after 8 weeks. Clinical assessment of disease activity by endoscopy was done during Screening, at Weeks 8, 32, and 52, and every 48 weeks thereafter. Follow-up examination was performed at 28 days after early termination by visit and at 70 days after the last dose of study drug by visit or telephone. Additionally, after Week 52, subjects could self-inject study drug as appropriate.

Definition of inadequate response:

- Subject with a Baseline Partial Mayo score of 3–7 who presented with a Mayo Partial Score greater than or equal to their Baseline score on 2 consecutive visits at least 14 days apart.
- Subject with a Baseline Partial Mayo score of 8 or 9 who presented with a Mayo Partial Score ≥ 7 on 2 consecutive visits at least 14 days apart.

Definition of disease flare:

- Subject who presented with a Mayo Partial Score difference of ≥ 3 compared to the Mayo Partial Score at Week 52 or at the last evaluation prior to the disease flare on 2 consecutive visits at least 14 days apart.

Number of Subjects (Planned and Analyzed):

Planned: 255 subjects; Randomized: 274 subjects; Treated with study drug: 273 subjects; Treated with adalimumab: 266 subjects

Diagnosis and Main Criteria for Inclusion:

Japanese adult subjects with active UC with a Mayo Score of 6–12 points at Baseline and an endoscopy subscore of 2–3 during the Screening Period, despite concurrent treatment with at least one oral corticosteroid or immunosuppressant. Diagnosis of UC was based on “The diagnostic criteria of ulcerative colitis” (1998, Study Group of the Health, Labour and Welfare Ministry) for longer than 90 days before Baseline.

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

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

Placebo pre-filled syringes

Dose: placebo 0.8 mL

Route: subcutaneous injection

Lot number: [REDACTED]

Criteria for Evaluation

Efficacy:

The primary variables of this study were the proportion of subjects with a clinical remission at Week 8 and the proportion of subjects with a clinical remission at Week 52.

The secondary efficacy variables were the following at Week 8, Week 32, and Week 52:

- Proportion of subjects who achieve clinical remission.
- Proportion of subjects with response per Mayo score.
- Proportion of subjects with mucosal healing.
- Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1).
- Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1).
- Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1).
- Proportion of IBDQ responders.

Safety:

Treatment-emergent adverse events, vital signs, clinical laboratory assessments, and physical examinations were used for safety evaluation. All nonserious adverse events occurring from the time of study drug administration until 70 days following discontinuation of study drug administration had elapsed were collected

The investigator used the following definitions to rate the severity of each adverse event:

- Mild: The adverse event was transient and easily tolerated by the subject.
- Moderate: The adverse event caused the subject discomfort and interrupted the subject's usual activities.
- Severe: The adverse event caused considerable interference with the subject's usual activities and may have been incapacitating or life-threatening.

The investigator used the following definitions to assess the relationship of the adverse event to the use of study drug:

- Probably Related: An adverse event had a strong temporal relationship to study drug or recurred on re-challenge and another etiology was unlikely or significantly less likely.
- Possibly Related: An adverse event had a strong temporal relationship to the study drug and an alternative etiology was equally or less likely compared to the potential relationship to study drug.
- Probably Not Related: An adverse event had little or no temporal relationship to the study drug and/or a more likely alternative etiology exists.
- Not Related: An adverse event was due to an underlying or concurrent illness or effect of another drug and was not related to the study drug (e.g., had no temporal relationship to study drug or had a much more likely alternative etiology).

If an adverse event met any of the following criteria, it was to be reported to the sponsor as a serious adverse event: death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, persistent or significant disability/incapacity, important medical event requiring medical or surgical intervention to prevent serious outcome, spontaneous abortion, elective abortion

Pharmacokinetic:

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

Statistical Methods

Analyzable populations:

The subjects who received at least one dose of study drug of double-blinded portion and had at least one efficacy evaluation were included in the "full efficacy analysis set (FAS)." In order to evaluate the impact of major protocol violations on the results of the trial, additional analyses was performed on the "per-protocol set (PPS)" after all subjects with major protocol deviations were excluded from the FDA population. The primary efficacy analysis was performed using the PPS in addition to the FAS. "The rescue arm population" consisted of all subjects who switched to rescue treatment before Week 52. "The open-label population" consisted of all subjects who completed 52 weeks of the double-blind portion and received open-label treatment at or after Week 52. The safety analysis population consisted of all subjects who received at least one dose of the study medication. Among the safety analysis population, the subjects who were in the double-blind portion were referred to as the "double-blind safety analysis population," the subjects who switched to rescue treatment before Week 52 were referred to as the "rescue arm safety population," and the subjects who completed 52 weeks of the double-blind portion and received open-label treatment at or after Week 52 were referred to as the "open-label safety population."

In this final report, the following analysis sets were used:

- All Adalimumab (AA) Analysis Set (N = 266) was defined as all subjects who received at least one dose of adalimumab during the study (adalimumab treatment groups in the double-blind portion, and anyone in placebo group who received adalimumab rescue treatment or open-label treatment).
- Minimum Final Visit Completer (N = 141) was defined as all subjects, including both completers and early terminators, who had adalimumab exposure greater than the minimum final visit. These subjects were analyzed only for the efficacy.
- Dose-Escalation (DE) Analysis Set (N = 112) was defined as all adalimumab subjects whose dose of adalimumab was escalated from 40 mg eow to 80 mg eow for inadequate response or flare. These subjects were analyzed for efficacy and for safety (adverse events only) using the data before and after the dose escalation date separately.
- Self-Injection (SI) Analysis Set (N = 74) defined as all adalimumab subjects who administered the study medication to themselves or by his/her family after Week 52 of the study. These subjects were analyzed for the safety (AEs only) using the data prior- and post- first date of self-injection, separately.

Demographics and baseline characteristics:

Demographic and baseline characteristics among the 3 treatment groups were summarized for the FAS and the PPS. Prior medication was defined as medication with a start date before the first study drug dose or an unknown start date. Concomitant medication was defined as medication begun between the first study drug treatment and last study drug treatment, or with unknown dates of administration. In this final report, demographic and baseline characteristics was summarized for AA Analysis Set. A concomitant medication was defined as any medication begun on or after the first adalimumab dose to the last adalimumab dose.

Efficacy:

The primary analysis was demonstrated using descriptive statistics and a chi-square test for the proportion of subjects with a clinical remission at Week 8 and the proportion of subjects with a clinical remission at Week 52 in the adalimumab 160 mg/80 mg and adalimumab 80 mg/40 mg groups versus the placebo group. Results for subjects who had a missing Mayo score for any reason, such as early termination, were considered “not remission” in the analysis.

The secondary efficacy analysis was demonstrated using chi-square test in the 3 treatment groups at Week 8, Week 32, and Week 52 for the following:

- Proportion of subjects who achieved clinical remission.
- Proportion of subjects with response per Mayo score.
- Proportion of subjects with mucosal healing.
- Proportion of subjects with Rectal Bleeding subscore indicative of mild disease (≤ 1).
- Proportion of subjects with Physician's Global Assessment subscore indicative of mild disease (≤ 1).
- Proportion of subjects with Stool Frequency subscore indicative of mild disease (≤ 1).
- Proportion of IBDQ responders.

Complete specific details of the final statistical analysis variables were described and fully documented in the statistical analysis plan (SAP).

In this final report, efficacy was analyzed for the evaluation from the first adalimumab dose until approval of the UC indication in Japan.

In the evaluation of efficacy, the methods below were used to account for the missing data.

- Non-Responder Imputation (NRI): procedure used to handle non-response. Subjects with missing evaluations (because of lack of measurement or discontinuation of treatment) were handled as non-responders.
- Last Observation Carry Forward (LOCF): procedure to use the value observed immediately before to impute the missing value.
- Observed Cases (OC): Using the observed data.

Safety:

Treatment-emergent adverse events on or after the first adalimumab dose were summarized for the safety analysis population. A treatment-emergent adverse event was defined as an event with onset or worsening after the first adalimumab dose and within 70 days after the last study drug injection. The number and percentages of subjects experiencing treatment-emergent adverse events were tabulated by Medical Dictionary for Drug Regulatory Affairs (MedDRA) system organ class and MedDRA preferred term. MedDRA version 15.1 was used. 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 were also provided. Mean change in laboratory variables and vital sign variables at each visit were summarized for safety analysis population. The last evaluation prior to the first dose of adalimumab was used as Baseline for all safety analyses.

Pharmacokinetic:

Adalimumab concentration was summarized by treatment group at each time point using descriptive statistics including number of subjects, number of non-missing observations (n_{miss}), mean, median, standard deviation, coefficient of variation, minimum, maximum, and geometric mean. Virtual CL/F and V/F in Crohn's disease subjects were demonstrated by population PK analysis. Serum AAA concentrations were listed by treatment group at each collection time.

Summary/Conclusions

Efficacy Results:

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Conclusions reached as to efficacy during adalimumab treatment until the approval are shown below.

- In All Adalimumab Analysis Set (266 subjects), proportions of subjects with remission or clinical response per Mayo Score, mucosal healing, rectal bleeding subscore ≤ 1 , physician's global assessment subscore ≤ 1 , stool frequency subscore ≤ 1 , response in IBDQ score, response per Mayo partial score, complete or partial response in UC-DAI score, or remission in IBDQ score were maintained in high-level for approximately 4 years with adalimumab treatment.
- Change from Baseline in Mayo score, Mayo partial score, component of Mayo score, IBDQ score, SF-36 physical or mental summary score maintained the improvement for approximately 4 years with adalimumab treatment.
- The proportion of subjects being steroid-free for ≥ 90 days and achieving remission per Mayo score at the visit in subjects who were taking steroids at Baseline was maintained at a high level for approximately 4 years with adalimumab treatment.
- In the Dose Escalation Analysis Set, the proportion of subjects with clinical response per Mayo partial score was increased after the dose escalation. More than half of the subjects showed clinical response per Mayo partial score after dose escalation, and this was maintained for approximately 4 years after dose escalation; thus, dose escalation of adalimumab showed efficacy.

Based on the results above, adalimumab treatment, including dose escalation to 80 mg eow, provided long-term (approx. 4 years) improvement of UC symptoms and QOL.

Pharmacokinetic Results:

[REDACTED]

Safety Results:

The detailed safety evaluation during the double-blind period is shown in the interim clinical study report up to Week 52 [R&D/11/285]. The following description is based on the safety data collected during the adalimumab treatment period until study completion following approval of the UC indication in Japan.

- During the adalimumab treatment period, 98.1% in the All Adalimumab Analysis Set reported treatment-emergent adverse events. The proportion of subjects with an adverse event at least possibly related to study drug was 53.4%, with an adverse event at least probably not drug related to study drug was 78.6%, with a severe adverse event was 7.1%, with a serious adverse event was 33.8%, and with an adverse event leading to discontinuation was 24.4%. The proportion of subjects with infection was 80.1%, and some subjects who experienced infection experienced an event that was serious (7.9%). Adverse events of special interest reported in $\geq 5\%$ of subjects were UC worsening/flare (21.8%), injection site reactions (11.7%), and hematologic disorders including pancytopenia (5.6%). Two deaths and adverse events leading to death (tuberculosis and death) were reported in double-blind 160/80 mg group. The causalities for these events were not related.
- The frequency of adverse events by event per 100 patient-years (PY) was 431.5 events during adalimumab treatment period, which was decreased from double-blind treatment period (547.9 events); the same tendency was observed for serious adverse events, severe adverse events, adverse events leading to discontinuation, and serious infections.
- Treatment-emergent adverse events reported for $\geq 10\%$ of subjects by MedDRA preferred term were nasopharyngitis (60.9%), UC (worsening) (21.8%), headache (15.8%), back pain (11.7%), and dental caries, upper respiratory tract inflammation, eczema, and rash (10.2% each). All adverse events reported in this study have been already reported in the previous clinical study for adalimumab in Japan.
- Severe adverse events were reported in 7.1% in the All Adalimumab Analysis Set. Severe adverse events reported by $\geq 1\%$ of subjects were UC and rectal cancer (1.1%).
- Adverse events were reported in 53.4% in the All Adalimumab Analysis Set. Adverse events at least possibly related to study drug reported $\geq 3\%$ of subjects were injection site reaction (9.4%), nasopharyngitis (6.4%), and antinuclear antibody increased (3.4%).
- Two subjects (both in the double-blind 160/80 mg group) died due to an adverse event (tuberculosis and death). Both of the adverse events had an onset after the last dose and were judged as severe, and considered probably not related and not related to study drug.
- Serious adverse events were reported for 33.8% (22.3 events/100PY) in the All Adalimumab Analysis Set. Commonly reported serious adverse events were UC (14.3%) and pneumonia bacterial, gastrointestinal dysplasia, medical observation (hospitalization for initiation of infliximab treatment), colonic polyp, and rectal cancer (1.1% each). The only serious adverse event at least possibly related to study drug and reported in ≥ 2 subjects was UC.
- Adverse events leading to discontinuation were reported for 24.4% in the All Adalimumab Analysis Set. Commonly reported adverse events leading to discontinuation were UC (10.9%) and rectal cancer (1.1%). The only adverse event at least possibly related to study drug and leading to discontinuation reported in ≥ 2 subjects was UC.

- Infections were reported for 80.1% (137.5 events/100PY) in the All Adalimumab Analysis Set. Commonly reported infections were nasopharyngitis (60.9%), influenza (7.5%), gastroenteritis (6.8%), pharyngitis (5.6%), and enteritis infectious and oral herpes (5.3% each). Serious infections were reported in 7.9% (4.0 events/100PY). Serious infections at least possibly related to study drug were reported in 10 subjects (1 event each); all resolved after discontinuation of study drug.
- Injection site reactions were reported for 11.7% in the All Adalimumab Analysis Set. Commonly reported injection site reactions (≥ 2 subjects) were injection site reaction (9.4%), injection site pruritus (1.1%), and injection site erythema and injection site pain (0.8% each). All injection site reactions were mild and at least probably related to study drug and all were managed without study drug interruption or discontinuation.
- Hematologic disorders were reported for 5.6% in the All Adalimumab Analysis Set. Reported hematologic disorders were anemia (4.5%) and leukopenia (1.1%). All hematologic disorders were not related or probably not related to the study drug except for 1 event of leukopenia, which was considered as possibly related. All the events were managed without study drug interruption or discontinuation.
- Allergic reactions were reported for 4.5% in the All Adalimumab Analysis Set. Commonly reported allergic reactions (≥ 2 subjects) were urticaria (1.9%) and asthma (1.1%). All allergic reactions were not related or probably not related to the study drug except for 1 event of swelling face. All the events were managed without study drug interruption or discontinuation.
- UC worsening/flare adverse events were reported for 21.8% in the All Adalimumab Analysis Set. Serious UC worsening/flare adverse events were reported for 14.3% and UC worsening/flare adverse events leading to discontinuation were reported for 10.9%.
- Opportunistic infections were reported for 3.8% in the All Adalimumab Analysis Set. Commonly reported opportunistic infections (≥ 2 subjects) were cytomegalovirus infection (2.3%) and esophageal candidiasis (0.8%).
- Liver failure and other liver events were reported for 3.0% in the All Adalimumab Analysis Set. The only commonly reported liver failure and other liver events (≥ 2 subjects) was hepatic steatosis (3.0%). All liver failure and other liver events were not related or probably not related to study drug. All the events were managed without study drug interruption or discontinuation.
- Malignancy adverse events were reported for 2.6% in the All Adalimumab Analysis Set. The only commonly reported malignancy (≥ 2 subjects) was rectal cancer (1.1%). No lymphoma occurred.
- During the adalimumab treatment period, intestinal stricture-related adverse events were reported for 1.9% and events of vasculitis were reported for 1.1% in the All Adalimumab Analysis Set.

- During the adalimumab treatment period, tuberculosis (tuberculosis and mycobacterium tuberculosis complex test positive), non-cutaneous vasculitis (vasculitis and Takayasu's arteritis), pancreatitis (pancreatitis and acute pancreatitis), and worsening/new onset of psoriasis (psoriasis and pustular psoriasis) were reported in 2 subjects, respectively, and cutaneous vasculitis (vasculitic rash), cerebrovascular accident (cerebral haemorrhage), interstitial lung disease, and erythema multiforme was reported in 1 subject.
- The percentage of subjects with treatment-emergent adverse events in the Dose Escalation Analysis Set (N = 112) before dose escalation and after dose escalation was 75.9% (85 subjects, 424.1 events/100PY) and 85.7% (96 subjects, 437.7 events/100PY), indicating no obvious changes in frequency of adverse events after dose escalation. Adverse events that increased in the occurrence by both percentage and event per 100PY (excluding adverse events leading to discontinuation) were severe adverse events (before: 1.8%, 2.4 events/100PY, after: 4.5%, 3.6 events/100PY), serious adverse events (before: 8.9%, 14.6 events/100PY, after: 33.9%, 35.1 events/100PY), infection (before: 43.8%, 128.8 events/100PY, after: 65.2%, 140.4 events/100PY), serious infection (before: 3.6%, 4.9 events/100PY, after: 6.3%, 5.0 events/100PY), and opportunistic infection excluding tuberculosis and oral candidiasis (before: 1.8%, 2.4 events/100PY, after: 3.6%, 2.9 events/100PY), and UC worsening and flare (before: 9.8%, 15.8 events/100PY, after: 22.3%, 20.1 events/100PY). Most of the serious adverse events reported after dose escalation were related to UC. The frequencies of infection, serious infection, and opportunistic infection were almost unchanged. There was no concern regarding the safety of dose escalation to 80 mg eow and no particular increase in the occurrence of adverse events with dose escalation.

- The percentage of subjects with treatment-emergent adverse events in the Self-injection Analysis Set (N = 74) before and after self-injection was 87.8% (65 subjects, 433.1 events/100PY) and 90.5% (67 subjects, 292.8 events/100PY), indicating no obvious changes in frequency of adverse events after self-injection. One subject (Subject 012201) reported injection site reaction and interrupted self-injection.
- None of the laboratory values and vital signs showed clinically important changes from Baseline.

Based on the results summarized above, adalimumab treatment was well tolerated and demonstrated no concerns regarding the long-term (approx. 4 years) safety.

Conclusions:

This study was conducted in a double-blind fashion until Week 52, and then in an open-label fashion until after the approval of UC in Japan was obtained. While the initial primary analyses did not show a difference between adalimumab and placebo at Week 8 but did show a highly statistically significant difference at Week 52, the results of the open-label extension part of the study support that the efficacy seen at Week 52 was maintained, and in some patients for approximately 4 years.