



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 Study of the Human Anti-TNF Monoclonal Antibody Adalimumab in Pediatric Subjects with Moderate to Severe Ulcerative Colitis				
Coordinating Investigator: [REDACTED] MD				
Study Sites: 19 sites in Austria, Belgium, Canada, Spain, United Kingdom, Israel, Poland, Slovakia, and the US; 5 sites in Japan				
Publications: None				
Studied Period (Years): First Subject First Visit: 13 October 2014 Last Subject Last Visit: 07 February 2020	Phase of Development: 3			
Objective: The objective of the study is to demonstrate the efficacy and safety, and to assess the pharmacokinetics of adalimumab administered subcutaneously in pediatric subjects with moderate to-severe ulcerative colitis (UC).				
Methodology: Study M11-290 is a Phase 3, multicenter, randomized, double blind (DB) trial designed to evaluate the efficacy and safety of adalimumab in pediatric subjects with moderate to severe UC who have failed therapy with corticosteroids and/or immunosuppressant (IMM). The study consists of a Main Study (conducted in subjects enrolled outside of Japan) and a Japan Substudy (conducted in subjects enrolled at sites in Japan only, analyzing integrated data of the Main Study and Japan Substudy as well as data from Japanese subjects alone). Prior to Protocol Amendment 4 (Main)/Protocol Amendment 4.01 (Japan Substudy), enrolled subjects were randomized 3:2 at Baseline to 1 of 2 DB adalimumab induction doses, induction high dose (I-HD) or induction standard dose (I-SD). At Week 8, subjects demonstrating a clinical response per Partial Mayo Score (PMS) were randomized to the following groups: adalimumab maintenance standard dose (M-SD), adalimumab maintenance high dose (M-HD), or placebo. Subjects were to continue their blinded treatment during the maintenance period until Week 52.				



Methodology (Continued):

After Protocol Amendment 4 (Main)/Protocol Amendment 4.01 (Japan Substudy), enrolled subjects received adalimumab induction high dose open-label (I-HD-OL). At Week 8, subjects demonstrating a clinical response per PMS were randomized and stratified by Week 8 remission status per PMS in a 1:1 ratio to 1 of 2 adalimumab maintenance treatment groups, M-SD or M-HD. Subjects were to continue their blinded treatment during the maintenance period until Week 52.

Prior to Amendment 4, internal placebo was chosen as the control group during maintenance period per regulatory requirement. After Amendment 4, per agreement with the regulatory agencies, randomization to the internal placebo group was ceased, and external placebo was used as comparator for co-primary and ranked secondary efficacy endpoints instead.

Number of Subjects (Planned and Analyzed):

101 planned, 101 analyzed: 93 subjects in global sites outside Japan; 8 subjects in Japan.

Diagnosis and Main Criteria for Inclusion:

Pediatric subjects with moderate to severe UC (Mayo score of 6 to 12 points and endoscopy sub score of 2 to 3) from 4 to less than 18 years old, who have failed therapy with corticosteroids and/or IMM and meet all of the inclusion criteria and none of the exclusion criteria were eligible for enrollment.

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

Test Product: Adalimumab

Doses: Prior to Protocol Amendment 4 (Main)/Protocol Amendment 4.01 (Japan Substudy), subjects randomized to I-HD group receive adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. Subjects randomized to I-SD group received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and matching placebo at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. At Week 8, subjects randomized to M-SD group receive 0.6 mg/kg (maximum dose of 40 mg) every other week, and subjects randomized to M-HD group received 0.6 mg/kg (maximum dose of 40 mg) every week. After Protocol Amendment 4 (Main)/Protocol Amendment 4.01 (Japan Substudy), enrolled subjects (I-HD-OL group) received adalimumab 2.4 mg/kg (maximum dose of 160 mg) at Baseline and at Week 1, 1.2 mg/kg (maximum dose of 80 mg) at Week 2, followed by 0.6 mg/kg (maximum dose of 40 mg) at Week 4 and Week 6. At Week 8, subjects received either M-SD or M-HD.

Mode of Administration: Subcutaneous

Lot Number:

Adalimumab (Main study): 16-001044, 78300XD80, 86384XD80, 13-002485, 14-004808, 14-005113, 14-006494, 15-000258, 15-004007

Adalimumab (Japan Substudy): 13-005306, 13-001150, 14-007022, 16-001044, 17-005911, 18-003308

Placebo (Main study): 14-004060, NORG07, 12-004934

Placebo (Japan Substudy): 12-004934, 14-004060, 18-004846

Duration of Treatment: 52 weeks

Criteria for Evaluation**Efficacy:**

The co-primary efficacy endpoints are:

1. The proportion of subjects who achieve clinical remission at Week 8 as measured by PMS (defined as a PMS ≤ 2 and no individual subscore > 1);
2. The proportion of subjects who responded at Week 8 per PMS and achieve clinical remission at Week 52 as measured by Mayo score (defined as a Mayo Score ≤ 2 and no individual subscore > 1).

The ranked secondary efficacy endpoints are:

1. Proportion of subjects in Mayo clinical response at Week 52 in Week 8 responders per PMS;
2. Proportion of subjects who achieve mucosal healing at Week 52 as measured by Mayo endoscopy subscore (defined as ≤ 1) in Week 8 responders per PMS;
3. Proportion of subjects who achieve Mayo clinical remission at Week 52 in Week 8 remitters per PMS;
4. Proportion of subjects receiving corticosteroid at Baseline who have discontinued corticosteroid prior to Week 52 and are in Mayo clinical remission at Week 52 in Week 8 responders per PMS.

Pharmacokinetic:

To be provided in a separate report.

Safety:

The following safety evaluations were performed during the study: monitoring of adverse events (AEs), changes in vital signs, physical examinations, and laboratory tests.

Statistical Methods**Efficacy:**

The efficacy analysis was performed in the intent-to-treat-E (ITT-E) population for the Week 8 efficacy endpoints and in the modified ITT (mITT) population for the Week 52 efficacy endpoints. The ITT-E population is a subpopulation of the ITT population (includes all subjects who received at least one dose of the study medication during induction period), where subjects who received open-label high induction dose are excluded. The mITT population consists of all Week 8 PMS Responders who were randomized at Week 8 and received at least one dose of the study medication during maintenance period. The non-responder imputation (NRI) was used to impute missing values for binary efficacy endpoints. Subjects who did not complete the induction period or who received rescue therapy during the maintenance period were considered as failures from that time point forward. Both last observation carried forward (LOCF) and observed case analyses were performed for continuous efficacy endpoints.

Statistical Methods (Continued)**Efficacy (Continued):**

In order to derive robust external placebo assumptions for the co-primary and ranked secondary endpoints, a thorough literature search of placebo-controlled clinical studies in subjects with moderate to severe UC who had failed conventional therapy was performed. Studies M06-826 and M06-827 in adults and Studies GEMINI 1 and OCTAVE Sustain in adults were chosen based on a number of criteria. For all co-primary and ranked secondary endpoints where available, separate estimates for anti-tumor necrosis factor (TNF) naïve placebo patients and anti-TNF experienced placebo patients were derived by endpoint. The estimates for anti-TNF naïve placebo patients and anti-TNF experienced placebo patients were then combined as a weighted mean according to the assumed proportion of anti-TNF naïve and experienced subjects. To be conservative, the upper limit of the 95% confidence interval for the weighted mean was used as the external placebo assumption.

Japan Substudy Only

Efficacy analyses were performed for subjects enrolled at sites outside of Japan (Main Study), for subjects enrolled at sites in Japan (Japan Substudy), and for subjects enrolled at all sites (Integrated population).

Pharmacokinetic:

To be provided in a separate report.

Safety:

The safety population, defined as all subjects who received at least one dose of the study drug, was used for safety analysis. Treatment-emergent AEs were summarized by treatment group using descriptive statistics. Serious AEs, AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation, were tabulated by system organ class and preferred term. Also, summaries by severity and relationship to study drug were done.

Summary/Conclusions**Efficacy Results:****Main Study**

Efficacy endpoints including clinical remission and response per PMS at Week 8, clinical remission and response per Mayo score as well as mucosal healing at Week 52 among responders to induction therapy, and clinical remission per Mayo score at Week 52 in Week 8 remitters were achieved by clinically meaningful proportions of subjects both on the adalimumab high and standard dose regimens. Efficacy analysis using PUCAI and Mayo score/PMS without the physician's global assessment score confirmed the results of the co-primary and secondary endpoints. For the co-primary efficacy variables, a statistically significantly greater proportion of subjects in the combined adalimumab I-HD and I-SD group as well as the I-HD group individually achieved clinical remission as measured by PMS at Week 8 compared with the external placebo control, and a statistically significantly greater proportion of subjects in the combined adalimumab M-HD and M-SD group as well as M-HD group individually who were Week 8 responders per PMS achieved clinical remission as measured by Mayo score at Week 52 compared with the external placebo control.

Summary/Conclusions (Continued)**Efficacy Results (Continued):**

For the 4 ranked secondary efficacy variables (proportion of subjects with clinical response per Full Mayo Score (FMS) at Week 52 in Week 8 responders per PMS, proportion of subjects with mucosal healing at Week 52 in Week 8 responders per PMS, proportion of subjects with clinical remission per FMS at Week 52 in Week 8 remitters per PMS, and proportion of subjects with corticosteroid-free clinical remission per FMS at Week 52 in Week 8 responders per PMS), all but the last one was achieved. Of note, corticosteroid-free clinical remission per FMS at Week 52 in subjects who achieved response following induction therapy was achieved by approximately 30% of adalimumab-treated subjects. In general, subjects in the I-HD and M-HD groups had better clinical outcomes than those in the I-SD and M-SD groups. In addition, efficacy results in anti-TNF naïve subjects were consistently better than subjects with prior anti-TNF use. Overall, these improved clinical outcomes translated to relatively low UC-related hospitalization and very low colectomy rates in the adalimumab-treated subjects.

Japan Substudy

In the Integrated populations, the co-primary efficacy variables, a statistically significantly greater proportion of subjects in the combined adalimumab I-HD and I-SD group as well as the I-HD group individually (Integrated ITT-E population) achieved clinical remission as measured by PMS at Week 8 compared with the external placebo control, and a statistically significantly greater proportion of subjects in the combined adalimumab M-HD and M-SD group as well as M-HD group individually who were Week 8 responders per PMS (Integrated mITT-E population) achieved clinical remission as measured by Mayo score at Week 52 compared with the external placebo. For subjects in Japan, the co-primary endpoint result rates compared with the external placebo rates were numerically higher for both the combined adalimumab I-HD and I-SD group as well the I-HD group individually at Week 8 (Japan ITT-E population) and for the M-HD group individually at Week 52 (Japan mITT-E population).

Statistical significance was achieved by the combined adalimumab M-HD and M-SD group as well as the M-HD group individually (Integrated mITT-E population) for all but the last one of the 4 ranked secondary efficacy endpoints (proportion of subjects with clinical response per FMS at Week 52 in Week 8 responders per PMS, proportion of subjects with mucosal healing at Week 52 in Week 8 responders per PMS, proportion of subjects with clinical remission per FMS at Week 52 in Week 8 remitters per PMS, and proportion of subjects with corticosteroid-free clinical remission per FMS at Week 52 in Week 8 responders per PMS).

Of note, numerically greater proportions of subjects in the combined adalimumab M-SD and M-HD group (31.3%) and the M-HD (35.3%) and M SD (26.7%) groups individually who were receiving corticosteroids at Baseline and were Week 8 responders per PMS were able to discontinue corticosteroids prior to Week 52 and achieved Mayo clinical remission at Week 52 compared with the external placebo control (Integrated mITT-E population). One subject in Japan (M-HD) was included in that group. Meaningful improvements in quality of life for subjects and activity of the caregivers were reported.

Summary/Conclusions (Continued)**Efficacy Results (Continued):**

In general, subjects in the I-HD and M-HD groups of the integrated populations of the Induction and Maintenance periods had better clinical outcomes than those in the I-SD and M-SD groups. In addition, efficacy results in anti-TNF naïve subjects were consistently better than subjects with prior anti-TNF use. Overall, these improved clinical outcomes translated to relatively low UC-related hospitalization rates ($\leq 20\%$) for all adalimumab treatment groups (Integrated ITT population). Two subjects in the Integrated population, both outside Japan, underwent colectomy during the study. In the Japan ITT population, 1 subject had a UC-related hospitalization during each of the Induction and Maintenance periods. Overall, efficacy results for the Japan ITT-E and mITT-E populations were consistent with the results for the respective Integrated ITT populations.

Pharmacokinetic Results: To be provided in a separate report.

Safety Results:Main Study

Overall, 73 (78.5%) of the 93 subjects experienced at least 1 treatment-emergent adverse event (TEAE) with adalimumab exposure, including adalimumab as rescue therapy after a disease flare. No deaths nor malignancies were reported. Serious AEs and TEAEs leading to study drug discontinuation were low in frequency and consistent with the underlying disorder.

During Induction, similar proportions of subjects in the I-SD and I-HD groups experienced TEAEs. The proportions of subjects with serious AEs (SAEs), severe TEAEs, TEAEs leading to discontinuation were slightly higher in the I-SD group than the I-HD group; however, the numbers of subjects were very small and should be interpreted with caution. Similar proportions of subjects in the adalimumab M-SD and M-HD groups experienced TEAEs during Maintenance up to the first disease flare. The proportions of subjects with severe TEAEs and TEAEs leading to discontinuation were higher in the M-SD group than the M-HD group. Due to the low number of subjects, TEAEs leading to discontinuation need to be interpreted with caution. In addition, incidence rates of SAEs were higher in subjects who received the adalimumab standard dose regimens compared to subjects who were treated with the high dose regimens, and about half of all SAEs were UC-related.

During Induction, the proportion of subjects who experienced TEAEs assessed by the investigator as having at least a reasonable possibility of being related to study drug was low and similar between the I-SD and the I-HD groups. Similarly, during Maintenance, the proportion of subjects who experienced TEAEs assessed by the investigator as having at least a reasonable possibility of being related to study drug was low and similar between the M-SD and the M-HD groups. Most TEAEs reported during the study were mild to moderate in severity.

The proportion of subjects experiencing AESIs were generally low, except for infections. Most infections were mild, nonserious and easily manageable. The occurrences of AESIs were relatively balanced across treatment groups, except for hematologic disorders and injection site reactions; in both categories, the proportion of subjects reporting AESIs was higher in the M-SD group than the M-HD group.

Summary/Conclusions (Continued)**Safety Results (Continued):**

The mean changes in hematology, clinical chemistry, and urinalysis parameter values during the study were not considered clinically relevant. Shifts in hematology, chemistry, and urinalysis values from normal or high at Baseline to low at the final visit, low or normal at Baseline to high at the final visit, or from Baseline to worst post-Baseline Common Toxicity Criteria (CTC) grade were generally infrequent and not considered to be clinically significant. Potentially clinically significant CTC Grade ≥ 3 hematology values during the study were infrequent and not considered to be clinically significant. No subjects had CTC Grade ≥ 3 chemistry values during the study. Potentially clinically significant liver function values during the study were infrequent and not considered to be clinically significant. No subject met the criteria for Hy's law.

Mean changes from Baseline in vital signs were not considered to be clinically significant.

No pregnancies were reported during the study. No new safety risks have been identified after a review of all product complaints associated with the study drug during the study.

Adalimumab treatment of pediatric subjects with moderate to severe UC throughout the study was safe and well tolerated. The observations during this study were fully consistent with the established safety profile of adalimumab across indications and with the underlying disorder.

Japan Substudy

Overall, 81 of the 101 (80.2%) subjects in the Integrated Safety population experienced at least 1 TEAE with adalimumab exposure, including adalimumab as rescue therapy after a disease flare. No death, malignancy, active tuberculosis (TB), or demyelinating disorder were reported throughout the study. Serious AEs and TEAEs leading to study drug discontinuation were low in frequency and consistent with the underlying disorder.

During Induction, similar proportions of subjects in the I-SD and I-HD groups experienced TEAEs (Integrated Safety population). The proportions of subjects with SAEs, severe TEAEs, TEAEs leading to study drug discontinuation were slightly higher in the I-SD group than the I-HD group; however, the numbers of subjects are very small and should be interpreted with caution. Similar proportions of subjects in the adalimumab M-SD and M-HD groups experienced TEAEs during Maintenance up to the first disease flare. The proportions of subjects with severe TEAEs and TEAEs leading to study drug discontinuation were higher in the M-SD group than the M-HD group. Due to the low number of subjects, TEAEs leading to study drug discontinuation need to be interpreted with caution. In addition, incidence rates of SAEs were higher in subjects who received the adalimumab standard dose regimens compared to subjects who were treated with the high dose regimens, and the most frequently reported SAEs during Induction and Maintenance were UC related. For the Japan Safety population, no subject experienced an SAE and 1 subject (I-SD) had a TEAE leading to study drug discontinuation during Induction; 1 subject (M-SD) had an SAE during Maintenance. The proportion of subjects who experienced TEAEs assessed by the investigator as having at least a reasonable possibility of being related to study drug was low and similar between the I SD and the I-HD groups during Induction and the M-SD and M-HD groups during Maintenance (Integrated Safety population). Most TEAEs were mild to moderate in severity during both Induction and Maintenance, except for infections (Integrated Safety population).

Summary Conclusion (Continued)**Safety Results (Continued):**

Most infections were mild, nonserious, self-limiting or easily manageable, and resolved quickly. The occurrences of other AESIs were relatively balanced across treatment groups. For 1 subject (M-HD group), latent TB was reported during Maintenance up to the first disease flare. Injection site reactions and infections were the only AESIs reported by subjects in Japan.

The mean change from Baseline in hematology, clinical chemistry, and urinalysis parameter values during the study were considered clinically unremarkable. Shifts in hematology and chemistry parameters from normal or high at Baseline to low at the final post-baseline value and from normal or low at Baseline to high at the final post baseline value during both Induction and Maintenance were generally infrequent and not considered to be clinically meaningful. No subject met the criteria for Hy's law.

No clinically meaningful changes from Baseline in vital signs were observed. No pregnancies were reported during the study. No new safety risks were identified during the study after a review of all product complaints associated with the study drug was performed.

Overall, adalimumab treatment of pediatric subjects with moderate to severe UC throughout the study was safe and well tolerated. The safety results for the subjects in Japan were consistent with the results for the integrated population. Observations made during this study were fully consistent with the established safety profile of adalimumab across indications and with the underlying colitis disorder.

Conclusions:

In Phase 3 Study M11-290, the clinical efficacy of the adalimumab standard and high induction doses as well the maintenance of clinical response and remission with the adalimumab standard and high maintenance doses in pediatric subjects with moderate to severe UC were supported by both co-primary efficacy endpoints and all but 1 ranked of the secondary efficacy endpoints. Adalimumab was generally safe and well tolerated, and the safety profile was consistent with previous clinical trials for adalimumab with no new safety signals being observed. Efficacy and safety results for subjects in Japan were consistent with the integrated population (subjects enrolled at sites outside of Japan integrated with results for subjects enrolled at sites in Japan).