Synopsis

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

Title of Study:
An Open-Label, Multicenter, Efficacy and Safety Study to Evaluate Two Treatment Algorithms in Subjects with Moderate to Severe Crohn's Disease (CD)

Coordinating Investigator: [redacted]

Study Sites: 59 sites in Canada, European Union, Israel, Japan, Russia, South Africa, Switzerland, Turkey, and Ukraine

Publications: 1 abstract

Studied Period (Years): First Subject First Visit: 11 February 2011 Last Subject Last Visit: 03 November 2016	**Phase of Development:** 3

Objective(s):
The primary objective was to demonstrate that tight control of disease activity using stringent criteria based on Crohn's disease Activity Index (CDAI) and biomarkers (i.e., high sensitivity C-reactive protein [hs-CRP], fecal calprotectin, and corticosteroid use) improves the rate of mucosal healing 48 weeks after randomization compared with management using less stringent criteria based only on CDAI and corticosteroid use.

Methodology:
This was a multicenter, randomized, open-label, active-controlled, 2-group, Phase 3, efficacy and safety study of prednisone, adalimumab, and azathioprine (AZA) using tight control versus clinically-driven management of CD to improve mucosal healing in subjects with moderately to severely active CD who were naïve to immunosuppressive and biologic therapy.

The study included a 1- to 3-week screening period, up to 8 weeks of prednisone treatment, a 48-week postrandomization treatment period, and a 70 day follow-up phone call or clinic visit, for a total duration of up to 69 weeks.

The study schedule was centered on the day of randomization; study visits/contact included the following (with ± 3 day window allowed for each visit):

– screening visit
– baseline (Week 0) visit
– Week 4 visit in subjects who initiated prednisone at Baseline and responded and tapered according to the protocol schedule (i.e., those not early randomized at or before Week 4).

Methodology (Continued):

– key visits: The first key visit was the randomization visit; subsequent key visits occurred every 12 weeks following the first key visit. Randomization normally took place 9 weeks after Baseline. However, subjects who fulfilled the early randomization criteria may have been randomized as early as the Baseline (Week 0) visit. Therapeutic option changes, if appropriate, occurred at key visits based on results from previous success criteria visits. The randomization visit was conducted on site. Subsequent key visits were performed as onsite visits when an escalation in therapeutic option was needed. Subjects who moved to Therapeutic Option 3 (TO3) Success or TO4 Success did not need to go to the site for that key visit. For subjects who did not need an escalation of therapeutic option, the onsite key visit may have been replaced with a phone call on the day of the key visit.

– success criteria visits: These occurred 1 week before the key visits (11 weeks after the previous key visit) to collect laboratory samples and data to calculate CDAI and to evaluate prednisone use. Subjects who were randomized prior to Week 9 (see below "Early Randomization") had a combined Success Criteria Visit 1 (SC1) and Key Visit 1 (K1) at randomization.

– + 2 week visits from a key visit: Subjects who initiated adalimumab every other week (eow) or AZA therapy for the first time had a + 2 week visit after starting adalimumab or AZA.

– + 6 week visits from a key visit: Subjects who initiated adalimumab eow or AZA therapy for the first time had a + 6 week visit after starting adalimumab or AZA.

Subjects underwent an endoscopy at Screening and at the final/early termination (ET) visit. Subjects who met entry criteria were enrolled and initiated an oral prednisone regimen at Baseline (Week 0). At the first key visit, subjects were randomized into 1 of 2 groups (Tight Control group or Clinically Driven group), with stratification according to screening smoking status, weight, and disease duration.

At and after randomization, treatment regimens in both randomized groups consisted of the same therapeutic options. Failure to fulfill success criteria as outlined for the 2 randomized groups led to changes in therapeutic options in a stepwise manner. All subjects started in TO1 (except subjects who were randomized before Week 9 or subjects who failed to meet success criteria at the first key visit [those subjects started in TO2]) and only proceeded to the next therapeutic option after failing to meet the success criteria in their group. Subjects who met all success criteria of their group at success criteria visits continued their current therapeutic option. Subjects receiving weekly adalimumab who met success criteria de-escalated to eow dosing (TO3 Success or TO4 Success).

The last dose of adalimumab was administered at either 1 week before or 2 weeks before the final visit depending on whether the subject was receiving weekly or eow dosing. Azathioprine and prednisone (as needed) could be continued through the end of the 48 week postrandomization treatment period.

Subjects had a 70-day follow-up following study drug discontinuation for an assessment of any new or ongoing adverse events (AEs), except subjects who continued on adalimumab therapy after ending study participation. Those subjects were not required to complete the 70-day follow-up, and any new AEs were reported through the mechanism used for all postmarketing adverse experiences. A 70-day contact was not required in instances where the last dose of study drug occurred 70 days or more prior to the last visit.

Subjects who met entry criteria were enrolled and at Baseline (Week 0) initiated an oral prednisone regimen.

Methodology (Continued):

Subjects were evaluated at success criteria visits, and therapeutic options were determined at the following key visits. Both randomized groups used the same therapeutic options.

Success Criteria Visits:

Treatment Arm	Visit Criteria
Tight Control Group	First key visit: CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at the previous success criteria visit, and absence of prednisone use at the first key visit.
	Second, third, and fourth key visits: CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at the previous success criteria visits, and absence of prednisone use during the week prior to the second, third, and fourth success criteria visits.
Clinically Driven Group	First key visit: CDAI decrease ≥ 70 compared to Baseline (CR-70) or CDAI < 200 at the first success criteria visit.
	Second, third, and fourth key visits: CDAI decrease ≥ 100 compared to Baseline (CR-100) or CDAI < 200, and absence of prednisone use during the week preceding the second, third, and fourth success criteria visits.

Therapeutic Options:

Therapeutic Option	Treatment
TO1	no adalimumab or AZA treatment
TO2	160 mg adalimumab (4 – 40 mg injections) administered subcutaneously (SC), followed by 80 mg adalimumab (2 – 40 mg injections) SC 2 weeks later, followed by 40 mg adalimumab SC eow
TO3	40 mg adalimumab SC weekly
TO3 Success	40 mg adalimumab SC eow (starting on the day of the key visit and then eow
TO4	40 mg adalimumab SC weekly and, in subjects with normal thiopurine methyltransferase (TPMT) enzyme activity, AZA oral 2.5 mg/kg/day rounded to the nearest dose (using 25 mg and 50 mg tablets). In subjects with intermediate TPMT enzyme activity, AZA was initiated at a dose of 1.25 mg/kg/day. In subjects who received AZA, the dose was adjusted according to abnormalities of white blood cell count, platelet count, liver function tests (i.e., alanine transaminase, aspartate transaminase, alkaline phosphatase), lipase, blood urea nitrogen, and serum creatinine.
TO4 Success	40 mg adalimumab SC eow + AZA. The adalimumab injection occurred on the day of the key visit and then eow.

Methodology (Continued):

Early Randomization: Subjects who were randomized early had active disease (CDAI > 220) and: 1) had been receiving corticosteroid therapy for 4 weeks, including 2 weeks of prednisone ≥ 40 mg or equivalent per day (or budesonide ≥ 9 mg per day) and the Investigator's assessed that it was in the best interest of the subject to taper prednisone; or 2) were intolerant to or had a medical contraindication for steroid therapy (e.g., diabetes mellitus, osteoporosis, glaucoma); or 3) the investigator's assessed that it was in the best interest of the subject to randomize early.

Subjects who randomized early had a combined Baseline, SC1 and K1 visit. Subjects who early randomized after Baseline and before Week 9 had a combined SC1 and K1 visit at randomization. All subjects who randomized early were assigned to TO2. In those subjects, a K+ 2 week visit and a K+ 6 week visit occurred. The next scheduled visit was 11 weeks after early randomization (second success criteria visit) followed by the second key visit 1 week later.

Rescue Group: If the Principal Investigator (PI) determined that a subject needed an escalation in therapeutic option before the next key visit, the subject may have been moved to the Rescue Group if CDAI was > 300 for 2 consecutive visits at least 7 days apart, with the first CDAI at or after 4 weeks from initiation of the current therapeutic option. The earliest entry into the Rescue Group was 5 weeks after the previous therapeutic option change. The subject then received the next therapeutic option and was considered a failure for the efficacy analyses.

Rescue Group entry was not allowed if the subject was within 6 weeks of his/her final visit. For subjects who did not meet the above Rescue Group CDAI criteria and for whom the PI determined that the Rescue Group was appropriate, the PI contacted the medical monitor. Elevation of hs-CRP ≥ 5 mg/L, fecal calprotectin ≥ 250 µg/g, or presence of ulceration on the endoscopy were taken into consideration.

All subjects in the Rescue Group followed the Tight Control success criteria (CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g, and absence of prednisone use) during the week preceding subsequent success criteria visits.

The visit schedule in the Rescue Group was as follows:

- key visit on the day of the switch to the Rescue Group.
- success criteria visit 11 weeks after the day of the switch, and then every 12 weeks until SC4.
- key visit 12 weeks after the day of the switch, and then every 12 weeks until K4.
- final/ET visit may have occurred sooner than 48 weeks after K1 (Randomization)

The key visit and success criteria visit numbering within the Rescue Group remained consistent with the numbering in the treatment arms. The last key visit in the Rescue Group was K4. In many cases, this meant that the subject had the final/ET visit sooner than 48 weeks after K1.

The investigator contacted the medical monitor if he/she determined that a subject who was moved to the Rescue Group needed a switch in therapeutic option prior to the next key visit. Elevation of hs-CRP ≥ 5 mg/L, fecal calprotectin ≥ 250 µg/g, and presence of ulceration on the endoscopy were to be taken into consideration.

Number of Subjects (Planned and Analyzed):

Planned: 240 subjects; Analyzed: 244 (122 in each Tight Control and Clinically Driven group)

Diagnosis and Main Criteria for Inclusion:

Inclusion:

- adult males and females ≥ 18 and ≤ 75 years of age at the Baseline
- a diagnosis of ileal colonic (including rectal) or ileocolonic CD confirmed using imaging technology not more than 6 years prior to Baseline
- moderate to severe CD defined as CDAI ≥ 220 and ≤ 450 at Baseline for subject not receiving prednisone or equivalent at Baseline/≥ 200 and ≤ 450 at Baseline for subject receiving prednisone ≤ 20 mg or equivalent for ≥ 7 days before Baseline/> 150 and ≤ 450 at Baseline for subject receiving prednisone > 20 mg or equivalent for ≥ 7 days before Baseline
- sum of deep ulcerations, superficial ulcerations, surface involved by disease, surface involved by ulceration Crohn's Disease Endoscopy Index of Severity (CDEIS) subscores in at least 1 ileal or non-ileal segment > 6, with the presence of ulcers, AND total CDEIS > 6 on Screening endoscopy
- hs-CRP ≥ 5 mg/mL (≥ 47.6 mmol/L) and/or fecal calprotectin ≥ 250 µg/g at Screening.

Exclusion:

- Previous or current biologic use or use of immunomodulators (e.g., methotrexate, azathioprine, 6-mercaptopurine, Janus kinase inhibitor, alpha-integrin inhibitors) for CD or participation in a CD study with immunomodulator(s). Current use of immunomodulators for non-CD at Baseline.
- Greater than 2 previous courses (total duration ≥ 4 weeks for burst and taper; prednisone or equivalent ≥ 40 mg [budesonide ≥ 9 mg] for at least 2 weeks) or corticosteroids (systemic corticosteroid or budesonide) for CD.
- Deficient TPMT enzyme activity (≤ 20 mU/L) OR intermediate TPMT enzyme activity (> 20 and ≤ 67 mU/L) and subject did not consent to undergo a weekly laboratory surveillance for 4 weeks or longer according to local guidelines if escalated to Therapeutic Option 4 (adalimumab and AZA).
- Any Montreal Classification B3 subject (with non-perianal fistulas), B2 subject with fibrotic strictures, or B2 subject with inflammatory strictures and symptoms of obstruction. Subjects with perianal disease (fistulas) were allowed, but were to be excluded if actively draining or if an abscess was present.
- Any fibrotic stricture, passable or non-passable, even if dilated during Screening ileocolonoscopy and regardless of symptoms.
- Greater than one major surgery for CD in medical history, or planned or recent (< 6 months of Screening) surgery for CD.

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

Adalimumab, 160 mg (4 – 40 mg/0.8 mL injections), 80 mg (2 – 40 mg/0.8 mL injections), or 40 mg (1 – 40 mg/0.8 mL injection); SC administration, self-administered

Lot numbers: 10-001960, 11-003870, 11-005882, 13-000648, 13-005618, 14-006602, 15-000609

Duration of Treatment: 56 weeks

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

Prednisone burst (40 mg/day) and taper; oral administration, self-administered

Lot numbers: 10-001968, 11-000096, 11-003737, 12-000744, 12-006223, 13-001749, 13-003949, 14-002671, 14-004394, 15-000295 (5 mg tablets); 10-001969, 11-003739, 11-000469, 12-000745, 13-000236, 14-002673, 15-000294 (20 mg tablets)

Azathioprine (AZA) 2.5 mg/kg/day (rounded to the nearest tablet strength) in subjects with normal TPMT enzyme activity; 1.25 mg/kg/day in subjects with intermediate TPMT enzyme activity; oral administration, self-administered

Lot numbers: 10-002074, 11-005622, 12-006644, 13-002914, 14-004395, 15-001469 (25 mg tablets); 10-002075, 11-005623, 12-006645, 13-002915, 14-002665, 15-001470 (50 mg tablets)

Criteria for Evaluation

Efficacy:

The primary efficacy variable was the proportion of subjects with mucosal healing (CDEIS < 4) and no deep ulcerations on ileocolonoscopy (absence of all deep ulcerations in all segments explored in CDEIS) at 48 weeks after randomization (48 weeks after the first key visit).

Key secondary efficacy variables included the proportion of subjects who achieved deep remission (CDAI < 150, discontinuation from steroids for at least 8 weeks, absence of draining fistula, CDEIS < 4, and no deep ulcerations), biologic remission (hs-CRP < 5 mg/L, fecal calprotectin < 250 μg/g, and CDEIS < 4), mucosal healing (CDEIS < 4) on ileocolonscopy, mucosal healing (CDEIS < 4) and CDEIS < 4 in every segment on ileocolonscopy, complete mucosal healing (CDEIS = 0), and endoscopic response (CDEIS decrease > 5) at 48 weeks after randomization.

Additional secondary efficacy variables included steroid-free remission (CDAI < 150 and discontinuation from steroids for at least 8 weeks), number of major CD-related surgeries, change in Inflammatory Bowel Disease Questionnaire (IBDQ) scores, and change in CD behavior according to Montreal Classification from Screening to 48 weeks after randomization.

Pharmacokinetic:

Pharmacokinetic determinations from the samples collected included serum concentrations of adalimumab and anti-adalimumab antibodies.

Safety: AEs, laboratory data, and vital signs were assessed throughout the study.

Statistical Methods

Efficacy:

All statistical tests were 2-tailed with a significance level of 0.05. Descriptive statistics were provided: number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables; counts and percentages for discrete variables. Analyses were performed using SAS® (SAS Institute Inc., Cary, NC, USA). For endpoints that were binary variables, nonresponder imputation (NRI) was used to impute missing values; last observation carried forward (LOCF) analysis was used as a sensitivity analysis. Both LOCF and observed case analyses were performed for continuous endpoints, with the LOCF analysis considered primary for inferential purposes.

All efficacy analyses were conducted using modified intent-to-treat (mITT) population, which consisted of subjects who were randomized (Week 9 or Early Randomization); subjects were analyzed as randomized.

Statistical Methods (Continued)

Efficacy (Continued):

The number/percentage of subjects who achieved each response endpoint was presented by treatment group. The comparison between treatment groups was performed using the Cochran-Mantel-Haenszel test stratified by screening smoking status (yes or no) and weight (< 70 kg or ≥ 70 kg). Change from Baseline was summarized using descriptive statistics. The treatment difference in mean change from Baseline was analyzed using an analysis of covariance model that included factors for treatment, screening smoking status (yes or no), and weight (< 70 kg or ≥ 70 kg), and Baseline value as covariate.

Pharmacokinetic:

Not applicable.

Safety:

Safety analyses, based on the safety population (all subjects who were randomized [same as the mITT population]) included treatment-emergent AEs (TEAEs) reported, clinical laboratory values, and changes in vital signs. A TEAE was defined as an AE with onset or worsening on or after the date of randomization and up to 70 days after the last dose of study drug. AEs were summarized using the Medical Dictionary for Drug Regulatory Affairs (MedDRA®) version 19.0 by system organ class (SOC) and preferred term (PT). In addition, a summary of AEs by severity and relationship to study drug were presented. A subject who reported ≥ 2 AEs in different SOCs was counted only once in the overall total. A subject who reported ≥ 2 AEs with different PTs in the same SOC was counted only once in the SOC total. A subject who reported ≥ 2 AEs with the same PT was counted only once for that PT using the most extreme incident (i.e., most severe for severity and most related for relationship). Treatment group differences in the overall incidence of TEAEs were assessed with Fisher's exact test for each PT. The event rate per 100 patient years was provided for general AE categories and the AEs of special interest categories. For AEs of interest, PT incidence was provided by maximum relationship to study drug and, for infection and serious infection, by severity also.

Clinical laboratory data were summarized using descriptive statistics for mean change from Baseline over time. In addition, shifts from Baseline to minimum, maximum, and final values according to the normal reference range and the proportion of subjects who had potentially clinically significant values (PCS) according to Common Toxicity Code (CTC) ≥ Grade 3 during treatment were provided. Each subject's low and high values in reference to the normal range and PCS (CTC ≥ Grade 3) values were flagged in listings.

Vital signs were assessed using descriptive statistics for mean change from Baseline and identification of PCS values during treatment.

Summary/Conclusions

Demographic characteristics were similar between the Clinically Driven and Tight Control treatment groups (mITT population), with no statistically significant differences observed. Baseline disease characteristics reflected a population with moderate to severely active CD. At Baseline, the mean age of subjects was 31.6 years, mean duration of CD was 0.95 years, and 57.8% were female. According to the Montreal classification, most subjects had colonic or ileocolonic CD that was nonstricturing or nonpenetrating at Screening, and no subject had an abdominal or perianal fistula at Baseline.

Summary/Conclusions (Continued)

Efficacy Results:

A statistically significantly higher proportion of subjects (mITT population) had mucosal healing (CDEIS < 4) and no deep ulcerations on ileocolonoscopy in the Tight Control group compared with the Clinically Driven group at 48 weeks after randomization (45.9% versus 30.3%; *P* = 0.010), which was the primary efficacy endpoint of the study.

Across several key secondary efficacy endpoints, at 48 weeks after randomization compared with the Clinically Driven group, a statistically significantly higher proportion of subjects in the Tight Control group achieved deep remission (36.9% versus 23.0%; *P* = 0.014), biologic remission (29.5% versus 15.6%; *P* = 0.006), and mucosal healing (CDEIS < 4 [45.9% versus 30.3%]; *P* = 0.010). Similar proportions of subjects in each group achieved the endpoints of mucosal healing (CDEIS < 4) in every segment (29.5% versus 23.8%) and complete mucosal healing (CDEIS = 0 [18.0% vs 16.4%]; *P* = NS). In addition, at 48 weeks after randomization, a numerically higher proportion of subjects in the Tight Control group compared with the Clinically Driven group had an endoscopic response (CDEIS decrease > 5 [50.8% versus 40.2%]; *P* = NS), and a statistically significantly higher proportion of subjects in the Tight Control group compared with the Clinically Driven group achieved steroid-free remission (CDAI < 150 and discontinuation from steroids for at least 8 weeks [59.8% versus 39.3%], *P* < 0.001). The number and event rate per 100 patient-years (E/100 PYs) of major CD-related surgeries after randomization was numerically higher for the Tight Control group (6 [5.6/100 PYs]) than the Clinically Driven group (3 [2.0/100 PYs]), although the rate of surgeries was low in both groups. From Screening to 48 weeks after randomization, a smaller percentage of subjects in the Tight Control group compared with the Clinically Driven group had deterioration in CD behavior according to the Montreal classification (any increase in the behavior index or the development of perianal disease). In the patient-reported health outcome IBDQ, greater improvement in disease (numerically greater score from Baseline [LOCF]) was consistently demonstrated during the study in the Tight Control group compared with the Clinically Driven group.

Pharmacokinetic Results:

Results of pharmacokinetic analyses will be presented in a separate report.

Safety Results:

Overall, a similar number of subjects in each treatment group experienced AEs, SAEs, and AEs leading to discontinuation of adalimumab. Notably, all event rates were lower for the Tight Control group (643.1, 32.4, and 18.2/100 PYs, respectively) than for the Clinically Driven group (694.4, 49.3, and 27.4/100 PYs, respectively).

Treatment-emergent AEs most frequently reported (by ≥ 10% of subjects overall) were CD (aggravated), nasopharyngitis, arthralgia, headache, abdominal pain, nausea. Treatment-emergent SAEs were reported in approximately 19% of subjects overall, with a similar proportion of subjects in each treatment group. The most frequently reported SAEs occurred in the MedDRA SOCs of Gastrointestinal Disorders, Infections and Infestations, and Investigations.

Summary/Conclusions (Continued)

Safety Results (Continued):

Serious infections were reported by 7.4% of subjects overall; the percentage and rate of serious infection was lower in the Tight Control group (4.9%; 7.1/100 PYs) than the Clinically Driven group (9.8%; 16.4/100 PYs). One subject (Tight Control group) had a serious case of active tuberculosis (TB) (pulmonary TB) that led to the subject's discontinuation from the study. One subject (Tight Control group) had a malignancy (neuroendocrine tumor), and 1 subject (Tight Control group) had a demyelinating disorder (Guillain-Barré syndrome), which began posttreatment, was serious, and resolved.

There were no reports in the following AE of special interest categories: opportunistic infections excluding oral candidiasis and TB; parasitic infection; legionella infection; malignancies: lymphoma, nonmelanoma skin cancer, hepatosplenic T-cell lymphoma, melanoma, or leukemia; lupus-like reactions and systemic lupus erythematosus; cutaneous vasculitis; Stevens-Johnson syndrome; sarcoidosis; myocardial infarction; congestive heart failure; pulmonary embolism; interstitial lung disease; diverticulitis; erythema multiforme; amyotrophic lateral sclerosis; progressive multifocal leukoencephalopathy; reversible posterior leukoencephalopathy syndrome; reactivation of hepatitis B; autoimmune hepatitis; and Humira® administration-related medication error. No deaths were reported in this study.

Mean changes in laboratory parameter values (hematology, clinical chemistry, urinalysis) over time from Baseline to 48 weeks after randomization and the final value, except for normal expected improvement, showed no clinically remarkable changes. Shifts in liver function test values during the study were infrequent. No subject met the criteria for a Hy's law case, indicating no drug-induced liver injury with study drug treatment. Mean changes from Baseline values for vital sign parameters, except for the improvement in weight, were not considered clinically meaningful.

Conclusions:

Study M11-271 was a prospective, open-label, multicenter, active-controlled Phase 3 study designed to assess the benefit of tight control (intent-to treat approach driven by biomarkers and symptoms) versus standard clinical management (approach driven by clinical symptoms only) of CD. The results from this study demonstrated that tight control of CD activity using the stringent criteria (hs-CRP, fecal calprotectin, CDAI, and prednisone use) was superior to clinical management using less stringent criteria (CDAI, prednisone use). The efficacy data from Study M11-271 demonstrated superior endoscopic and deep remission outcomes with the treat-to-target approach versus the clinical symptoms only approach. The safety profile observed in this study was consistent with the known safety profile of the drugs used in this study (prednisone, AZA, and adalimumab), and no new safety signals were observed.

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