

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Adalimumab	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Adalimumab	<b>Page:</b>	
<b>Title of Study:</b> A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis		
<b>Coordinating Investigator:</b> ██████████, MD		
<b>Study Site(s):</b> The Induction Study of the Japan Substudy included 22 sites in Japan. The Induction Study of the Main Study included 120 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Romania, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, and the United States (US).		
<b>Publications:</b> 1		
<b>Studied Period (Years):</b> First Subject First Visit: 22 July 2014 (Japan Substudy) 27 March 2014 (Main Study) Last Subject Last Visit: 21 September 2017 (Induction – Japan Substudy) 09 December 2018 (Last 70-day follow-up phone call for Induction – Main Study) 11 November 2019 (Last 70-day follow-up phone call for Study M14-033)	<b>Phase of Development:</b> 3	
<b>Objective:</b> The study objective of the Japan Induction Study was to evaluate the safety and efficacy of higher induction and maintenance dosing regimens in subjects with moderately to severely active ulcerative colitis (UC) and to show the consistency of efficacy between the Japanese population and the Integrated population of the study (Japanese and global study subjects enrolled outside of Japan).		

**Methodology:**

Study M14-033 consists of the Main Study (conducted in global subjects enrolled outside of Japan) and a Japan Substudy, both of which are composed of an Induction Study and a Maintenance Study. Higher induction and maintenance dosing regimens were to be compared to the standard approved adalimumab induction and maintenance regimens. Adult subjects with moderately to severely active UC who met all of the inclusion criteria and none of the exclusion criteria were planned for enrollment into the Japan Substudy.

This clinical study report (CSR) is an interim report that covers the 8-week double blind (DB) M14-033 Japan Induction Study and comprises all subjects enrolled in Japan and subjects enrolled at sites globally (integrated data). The initial Japan Induction CSR comprised data up to Week 8; this revision of the original CSR adds the 70-day follow-up safety data for subjects who discontinued from the Induction Study and did not start commercially available Humira<sup>®</sup> following study discontinuation. The data cutoff date is 09 December 2018. In this report, Japan results are highlighted, and their consistency with the integrated data is noted. A separate Induction CSR (R&D/18/1110) is available with results for subjects enrolled outside of Japan (Main Induction Study).

**Number of Subjects (Planned and Analyzed):** 100 subjects planned

The Japan Intent-to-Treat (J-ITT) and Japan Safety Population were the same, with 100 subjects for the Induction Study (Japan) (61 subjects were randomized and received the higher induction dosing regimen and 39 subjects were randomized and received the standard induction dosing regimen).

**Diagnosis and Main Criteria for Inclusion:**

Key eligibility criteria for Study M14-033 included: subject was male or female  $\geq 18$  and  $\leq 75$  years of age at the Baseline visit; had a diagnosis of UC for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period with exclusion of current infection, dysplasia, and/or malignancy; had active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed via a central reading protocol) despite concurrent or prior treatment with a full and adequate course, in the opinion of the Investigator, of at least 1 of the oral corticosteroids or immunosuppressants as defined in the protocol (may have been included if subject had previously experienced a benefit for UC from infliximab and discontinued its use due to a subsequent loss of response or intolerance [confirmed documentation indicating loss or response or lack of tolerability was required]); if female, was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or was of childbearing potential and was practicing an approved (per protocol) method of birth control throughout the study and for 150 days after last dose of study drug; if female, was not breast-feeding throughout the study and for 150 days after last dose; had a negative tuberculosis screening assessment; and was judged to be in otherwise good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead electrocardiogram performed during Screening.

Key exclusion criteria for Study M14-033 included: diagnosis and/or history of Crohn's disease or diagnosis of indeterminate colitis; current diagnosis of fulminant colitis and/or toxic megacolon; disease limited to the rectum (ulcerative proctitis) during the screening endoscopy; and history of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or planning bowel surgery.

<p><b>Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:</b></p> <p>For the 8-Week DB Japan Induction Study, randomization was stratified by previous infliximab use and Baseline corticosteroid use. The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6, provided a total adalimumab dose over 8 weeks that was approximately twice that of the standard induction dose regimen (720 mg versus 320 mg).</p> <p>Subjects assigned to the higher induction dosing regimen were to receive adalimumab 160 mg (4 syringes) at Weeks 0, 1, 2, and 3, followed by adalimumab 40 mg (1 syringe) at Weeks 4 and 6. Subjects assigned to the standard induction dosing regimen were to receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and placebo (4 syringes) at Week 1, both adalimumab 80 mg (2 syringes) and placebo (2 syringes) at Week 2, placebo at Week 3 (4 syringes), and adalimumab 40 mg at Weeks 4 and 6 (1 syringe).</p> <p>Adalimumab lot numbers: 13-005618, 15-005080, and 16-001720 (Japan); 13-000648, 13-005618, 14-006602, 15-000609, 16-001720, 16-005133, and 17-002006 (Main)</p> <p>Placebo lot numbers: 12-007038 and 16-000470 (Japan); 12-007038, 14-002885, 15-005865, 16-000470, 16-004292 (Main)</p>
<p><b>Duration of Treatment:</b> 8 weeks</p>
<p><b>Criteria for Evaluation</b></p> <p><b>Efficacy:</b></p> <p>The primary efficacy variable for the Japan Induction Study was the proportion of subjects achieving clinical remission (defined as a Full Mayo score <math>\leq 2</math> with no subscore <math>&gt; 1</math>) at Week 8. Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Japan Induction Study were:</p> <ol style="list-style-type: none"> <li>1. Proportion of subjects achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 8.</li> <li>2. Proportion of subjects with fecal calprotectin below 150 mg/kg at Week 8.</li> <li>3. Proportion of subjects with Inflammatory Bowel Disease Questionnaire (IBDQ) response (increase of IBDQ <math>\geq 16</math> from Baseline) at Week 8.</li> <li>4. Proportion of subjects achieving clinical response (per Full Mayo score) at Week 8.</li> <li>5. Proportion of subjects achieving endoscopic remission (endoscopic subscore of 0) at Week 8.</li> <li>6. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score <math>\geq 6</math>) at Week 8.</li> <li>7. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score <math>\geq 1</math>) at Week 8.</li> </ol> <p><b>Pharmacokinetic:</b></p> <p>To be provided in a final separate report.</p> <p><b>Safety:</b></p> <p>The following safety evaluations were performed during the study: incidence of adverse events (AEs) and changes in vital signs, physical examination results, and clinical laboratory data.</p>

### **Statistical Methods**

#### **Efficacy:**

For the Japan Induction Study, the primary efficacy analysis was performed using the J-ITT analysis set. The efficacy analysis used the non-responder imputation (NRI) method to impute the missing values at Week 8 for the Japan Induction Study. Analyses for the Induction Study compared data for the adalimumab higher induction dosing regimen to the standard adalimumab induction dosing regimen in the J-ITT analysis set. The difference between induction dosing regimens in the proportion of subjects achieving clinical remission at Week 8 was assessed using Cochran-Mantel-Haenszel (CMH) test adjusted for previous infliximab use and baseline corticosteroid use. A CMH-based two-sided 95% confidence interval for the difference in the proportions between the induction dosing regimens was calculated. Logistic regression adjusting for the effect of randomization stratification factors, baseline immunosuppressant use, baseline C-reactive protein value, baseline disease severity and region Integrated Intent-to-Treat [I-ITT] only) was performed for the primary endpoint as sensitivity analyses.

#### **Safety:**

For the Japan Induction Study, all safety analyses were performed using the Japan Safety set. The safety variables were summarized by induction dosing regimen according to the regimen that the subject actually received. Induction dosing regimen differences in safety parameters were evaluated using two-sided tests at the significance level of 0.05.

Unless otherwise specified, the induction dosing regimen differences in continuous safety variables (e.g., change from baseline to final observation on laboratory tests) were assessed using an Analysis of Variance (ANOVA) model with the term of induction dosing regimen; the induction dosing regimen differences in categorical safety variables were evaluated using a Fisher's exact test.

### **Summary/Conclusions**

Study M14-033 included a Japan Induction Study with 100 randomized subjects and a Main Induction Study with 852 randomized subjects.

#### **Efficacy Results:**

For the Japan Induction Study at Baseline, the overall mean duration of UC was 7.7 years, and over half of the subjects had extensive UC/pancolitis. Baseline characteristics were generally well balanced between the induction dosing regimen groups and consistent with a subject population with moderate to severe UC. The proportion of subjects achieving clinical remission (defined as a Full Mayo score  $\leq 2$  with no subscore  $> 1$ ) at Week 8 was not greater for subjects receiving the higher induction dosing regimen compared with standard induction dosing regimen. Overall, subgroup analysis results were consistent with the primary analysis. The ranked secondary endpoints, with the exception of IBDQ-based endpoints, were numerically higher in subjects receiving the higher induction than standard induction dosing regimen. Overall, the efficacy for Japanese subjects was consistent with that of the integrated population of the study (Japanese subjects and global study subjects enrolled outside of Japan).

#### **Pharmacokinetic Results:**

To be provided in a final separate report.

### **Summary/Conclusions (Continued)**

#### **Safety Results:**

The safety profile of subjects receiving the higher induction dosing regimen was comparable to subjects receiving the standard induction dosing regimen and was consistent with the known safety profile of adalimumab; no new safety signals or unexpected trends were identified.

Overall, 50% of subjects had 1 or more treatment-emergent AEs (TEAEs). No deaths were reported in the study. The overall incidence of serious AEs and AEs leading to discontinuation were low ( $\leq 5$  subjects [5.0%]) and comparable between subjects receiving the higher induction dosing regimen and the standard induction dosing regimen. AEs were most frequently reported in the system organ class of infections and infestations. The most frequently reported ( $\geq 5\%$  of subjects overall) TEAEs by preferred term were nasopharyngitis, injection site reaction, and pyrexia. Additional AEs reported by  $\geq 5\%$  of subjects in the standard dosing regimen were rash, anaemia, arthralgia, and colitis ulcerative. No additional AEs were reported by  $\geq 5\%$  of subjects in the higher dosing regimen. Most TEAEs were mild or moderate in severity with no reasonable possibility of relationship to study drug as assessed by the investigator. For AEs of special interest, infection AEs were reported in 23.0% of subjects receiving the higher induction dosing regimen and 10.3% of subjects receiving the standard induction dosing regimen. The proportion of subjects with other AEs of special interest was generally low for each induction dosing regimen and relatively balanced across induction dosing regimens.

There were no notable mean changes from Baseline for shifts from Baseline in laboratory parameter values (hematology, clinical chemistry, and urinalysis) from Baseline. Shifts in hematology, clinical chemistry, and urinalysis values from normal or high at Baseline to low at the final value or normal or low at Baseline to high at the final value were infrequent and not considered clinically meaningful. No subject had an elevated laboratory value that resulted in discontinuation of study drug; no subject met the criteria for a Hy's law case.

There were no notable mean changes from Baseline in vital signs values.

No pregnancies and no product complaints with a safety component were reported during the Japan Induction Study or the Main Induction Study, including the added 70-day follow-up period during which no study drug was administered.

#### **Conclusions:**

In the Japan Induction Study, the efficacy of the higher induction dosing regimen of adalimumab in inducing clinical remission (defined as a Full Mayo score  $\leq 2$  with no subscore  $> 1$ ) at Week 8 was not significantly superior to the standard induction dosing regimen of adalimumab. The higher induction dosing regimen, therefore, did not provide greater benefit to subjects with moderately to severely active UC, indicating the current labeled induction dose (160 mg/80 mg) remains the appropriate induction dosing regimen for subjects with moderate to severe UC. Clinical remission rates at Week 8 demonstrated the consistency of efficacy between the Japanese population and both the population of global study subjects enrolled outside of Japan (Main Study) and the Japan/Main Induction Studies integrated population. The safety profile for subjects receiving the higher induction dosing regimen was consistent with subjects receiving the standard induction dosing regimen, the integrated population of the study (Japanese subjects and global study subjects enrolled outside of Japan), the known safety profile of adalimumab based upon decades of data from global clinical studies, and post-marketing surveillance in the treatment of UC and other diseases. No new safety signals or trends were observed. Overall, the benefit-risk profile of the adalimumab standard induction dosing regimen in this patient population remains unchanged.

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<b>Name of Study Drug:</b> Adalimumab	<b>Volume:</b>	
<b>Name of Active Ingredient:</b> Adalimumab	<b>Page:</b>	
<b>Title of Study:</b> A Double-Blind, Randomized, Multicenter Study of Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Ulcerative Colitis		
<b>Investigator:</b> [REDACTED], MD		
<b>Study Site(s):</b> 22 sites in Japan, and 115 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Netherlands, Poland, Romania, Slovakia, Spain, Switzerland, Ukraine, United Kingdom, and the United States.		
<b>Publications:</b> 1		
<b>Studied Period (Years):</b> First Subject First Visit: 22 July 2014 for Japan Substudy; 27 March 2014 for Main Study Last Subject Last Visit: 23 July 2018 for Japan Substudy; 11 November 2019 for Main Study	<b>Phase of Development:</b> 3	
<b>Objective:</b> The study objective of the Japan Substudy is to evaluate the safety and efficacy of higher induction and maintenance adalimumab dosing regimens in subjects with moderately to severely active ulcerative colitis (UC) and to show the consistency of efficacy between the Japan Population and the Integrated Population of the study (Japanese subjects and global study subjects enrolled outside of Japan).		
<b>Methodology:</b> Study M14-033 comprises a Main Study and a Japan Substudy, each of which consists of an Induction Study and a Maintenance Study. This clinical study report (CSR) presents results of the Maintenance Study from sites in Japan (Japan Population) and from all sites (Japan and outside of Japan; Integrated Population) through the last 70-day follow-up. The Maintenance Study began when the first subject completed the first Week 8 visit of the study (04 June 2014 for the Main Study and 01 October 2014 for the Japan Substudy). Histologic results will be presented in the final Maintenance CSR. In the Maintenance Study, the higher maintenance dosing regimen was compared to the standard approved adalimumab maintenance regimen; an exploratory dosing regimen that used a therapeutic drug monitoring (TDM) strategy was included in the Integrated Population only. All subjects were to have moderately to severely active UC who met all of the inclusion criteria and none of the exclusion criteria were eligible to participate in the Maintenance Study for both the Main Study and the Japan Substudy. Results for the 8-week double-blind (DB) Induction Study were previously reported in the Study M14-033 Induction CSR Main and Study M14-033 Induction CSR Japan Substudy.		

**Number of Subjects (Planned and Analyzed):** 840 subjects were planned.

The Integrated intent-to-treat (I-ITT) and Safety Populations for the Integrated Population (Japanese subjects and global study subjects enrolled outside of Japan) were the same with 846 subjects re-randomized into the Maintenance Study (345 subjects receiving the every other week (eow) dose regimen; 350 subjects receiving the every week (ew) dose regimen; and 151 subjects receiving the TDM dose regimen). The TDM dose regimen is part of the Integrated Population only.

In the Japan Substudy the intent-to-treat (ITT) and Safety Populations were the same with a total of 89 subjects re-randomized into the Maintenance Study (43 subjects to receiving the 40 mg eow dose regimen and 46 subjects receiving the 40 mg ew dose regimen). These subjects are referred to in this CSR as the Japan Population (J-ITT).

**Diagnosis and Main Criteria for Inclusion:**

Key eligibility criteria for Study M14-033 included: Male or female  $\geq 18$  and  $\leq 75$  years of age at the Baseline visit; Subject with a diagnosis of UC for 90 days or greater prior to Baseline, confirmed by endoscopy (colonoscopy or flexible sigmoidoscopy) during the Screening Period with exclusion of current infection, dysplasia and/or malignancy; active UC with a Mayo Score of 6 to 12 points and endoscopy subscore of 2 to 3 (confirmed by central reader) despite concurrent or prior treatment with a full and adequate course, in the opinion of the Investigator, of at least one of the following (oral corticosteroids or immunosuppressants as defined in the protocol); subject may be included if they have previously experienced a benefit for their UC from infliximab and discontinued its use due to a subsequent loss of response or intolerance (confirmed documentation indicating loss of response or lack of tolerability was required); if female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or was of childbearing potential and was practicing an approved (per protocol) method of birth control throughout the study and for 150 days after last dose of study drug; if female, subject was not breast-feeding throughout the study and for 150 days after last dose; subject had a negative tuberculosis Screening Assessment; and the subject was judged to be in otherwise good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray, and a 12-lead electrocardiogram performed during Screening.

Key exclusion criteria for Study M14-033 included: subject with diagnosis and/or history of Crohn's disease or diagnosis of indeterminate colitis (IC); current diagnosis of fulminant colitis and/or toxic megacolon; subject with disease limited to the rectum (ulcerative proctitis) during the screening endoscopy; and history of subtotal colectomy with ileorectostomy or colectomy with ileoanal pouch, Kock pouch, or ileostomy or was planning bowel surgery.

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

For the 8-Week DB Induction Study, the randomization in both the Main Study and the Japan Substudy was to be stratified by previous infliximab use and Baseline corticosteroid use. Drug was to be subcutaneously self-administered at approximately the same time of the day. The higher induction dose regimen of 160 mg at Weeks 0, 1, 2, and 3, followed by 40 mg at Weeks 4 and 6 lead to a total adalimumab dose over 8 weeks that was approximately twice that of the standard induction dose regimen (720 mg versus 320 mg).

At Week 8, subjects in the Main Study were to be re-randomized via IRT to receive 1 of 3 DB adalimumab treatment maintenance regimens in a 2:2:1 ratio; in the Japan Substudy subjects were to be re-randomized via IRT in a 1:1 ratio to receive 1 of 2 DB adalimumab treatment maintenance regimens.

All subjects were to be re-stratified by treatment regimen in the Induction Study and response status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) at Week 8. For responders at Week 8, the re randomization was to be further stratified by remission status (per Full Mayo score utilizing the Week 8 endoscopy subscore provided by the site) determined at Week 8.

Subjects assigned to the higher induction dose regimen were to receive adalimumab 160 mg (4 syringes) at Weeks 0, 1, 2, and 3, followed by adalimumab 40 mg (1 syringe) at Weeks 4 and 6. Subjects assigned to the standard induction dose regimen were to receive adalimumab 160 mg (4 syringes) at Baseline (Week 0) and placebo (4 syringes) at Week 1, both adalimumab 80 mg (2 syringes) and placebo (2 syringes) at Week 2, placebo at Week 3 (4 syringes), and adalimumab 40 mg at Weeks 4 and 6 (1 syringe).

Adalimumab lot numbers: 13-000648, 13-005618, 14-006602, 15-000609, 15-005080, 16-001720, 16-005133, 17-002006

Placebo lot numbers: 12-007038, 14-002885, 16-000470, 15-005865, 16-004292

**Duration of Treatment:** 44 Weeks

**Criteria for Evaluation**

**Efficacy:**

The primary efficacy variable for the Maintenance Study was the proportion of Week 8 responders (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.

Ranked secondary efficacy variables (ranked hierarchically in decreasing order) for the Maintenance Study were:

1. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
2. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.
3. Proportion of Week 8 responders (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
4. Proportion of Week 8 remitters (per Full Mayo score) achieving clinical remission (per Full Mayo score) at Week 52.
5. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic improvement (endoscopic subscore of 0 or 1) at Week 52.
6. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days at Week 52.



**Criteria for Evaluation (Continued)**

7. Proportion of Week 8 remitters (per Full Mayo score) taking steroids at Baseline who are steroid-free for at least 90 days and in clinical remission (per Full Mayo score) at Week 52.
8. Proportion of Week 8 responders (per Full Mayo score) with IBDQ response (increase of IBDQ  $\geq 16$  from Baseline) at Week 52.
9. Proportion of Week 8 non-responders (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
10. Proportion of Week 8 non-remitters (per Full Mayo score) with clinical remission (per Full Mayo score) at Week 52.
11. Proportion of Week 8 responders (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
12. Proportion of Week 8 remitters (per Full Mayo score) achieving endoscopic subscore of 0 at Week 52.
13. Proportion of Week 8 responders (per Full Mayo score) with response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score  $\geq 6$  from Baseline) at Week 52.
14. Proportion of Week 8 responders (per Full Mayo score) with response in IBDQ fatigue item (increase of IBDQ fatigue item score  $\geq 1$  from Baseline) at Week 52.

**Pharmacokinetic:**

To be provided in a final separate report.

**Safety:**

The following safety evaluations were performed during the study: incidence of adverse events, changes in vital signs, physical examination results, and clinical laboratory data.

**Statistical Methods**

**Efficacy:**

For the Maintenance Study endpoints, the difference between the adalimumab 40 mg eow (hereafter referred to as the eow dose regimen) versus the adalimumab 40 mg ew (hereafter referred to as the ew dose regimen) was assessed. The secondary endpoints at Week 52 that are of the categorical type were analyzed using a two-sided Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen, and responder/remitter status at Week 8. Additionally, the CMH based two-sided 95% confidence interval for the difference in the proportions between the treatment groups was calculated.

**Pharmacokinetic:**

To be provided in a final separate report.

**Safety:**

All safety analyses were performed on the Safety Population set for the Maintenance Study. The safety variables were summarized by treatment regimen (for all 3 treatment arms) according to the treatment a subject actually received. Treatment group differences between the ew dose regimen and the eow dose regimen in safety parameters will be evaluated using two-sided tests at the significance level of 0.05.

Unless otherwise specified, the treatment group differences in continuous safety variables (e.g., change from baseline to final observation on laboratory tests) were assessed using an analysis of variance model with the term of treatment, and the treatment group differences in categorical safety variables were evaluated using a Fisher's exact test.

**Summary/Conclusions****Efficacy Results:**

For the Integrated Population, among Week 8 responders (per Full Mayo score, defined as a decrease in Full Mayo score of  $\geq 3$  points and  $\geq 30\%$  from Baseline plus a decrease in the rectal bleeding subscore [RBS]  $\geq 1$  or an absolute RBS of 0 or 1), the proportion of subjects receiving the ew dose regimen who achieved clinical remission (defined as a Full Mayo score  $\leq 2$  with no subscore  $> 1$ ) at Week 52 was statistically significantly higher than the proportion of subjects receiving the eow dose regimen per nonresponder imputation (NRI). Overall, subgroup analysis results for the Integrated Population were generally consistent with the primary analysis.

For those Week 8 responders in the Japan Population the proportion of subjects receiving the ew dose regimen who achieved clinical remission at Week 52 was numerically higher than the proportion of subjects receiving the eow dose regimen (NRI). Overall, subgroup analysis results for the Japan Population were generally consistent with the primary analysis except for: Baseline full Mayo score ( $\leq 9$ ,  $> 9$ ), Baseline full Mayo score ( $\leq$  median,  $>$  median), presence of pancolitis at Baseline, Baseline hs-CRP ( $\leq 5$  mg/L,  $> 5$  mg/L), and Baseline hs-CRP ( $\leq$  median,  $>$  median).

In the Integrated Population, for each of the ranked secondary efficacy endpoints, the proportion of subjects who achieved the endpoint was numerically higher among subjects receiving the ew dose regimen than subjects receiving the eow dose regimen.

In the Japan Population, for 8 of the ranked secondary efficacy endpoints, the proportion of subjects who achieved the endpoint was numerically higher among subjects receiving the ew dose regimen than subjects receiving the eow dose regimen.

**Pharmacokinetic Results:**

To be provided in a final separate report.

**Safety Results:**

The safety results of adalimumab in both subjects enrolled in Japan and subjects enrolled outside of Japan receiving the ew dose regimen, eow dose regimen, and TDM dose regimen (Integrated Population only) were comparable and consistent with the known safety profile of adalimumab; no new safety signals or unexpected trends were identified.

The majority of subjects in each dosing regimen in both the Integrated Population and the Japan Population had 1 or more treatment-emergent adverse events (TEAEs). There were 4 deaths in the study (Integrated Population), no deaths occurred in the Japan Population; 2 occurring in subjects receiving the ew dose regimen and 2 occurring in subjects receiving the eow dose regimen; all were assessed by the investigator and AbbVie as having no reasonable possibility of relationship to study drug. The rates of TEAEs and serious adverse events (SAEs) were comparable between the dosing regimens for both populations. In the Integrated Population a total of 103 subjects (12.2%) experienced SAEs; 92 subjects (10.9%) experienced TEAEs leading to discontinuation of study drug. In the Japan Population, a total of 6 subjects (6.7%) experienced SAEs; 7 subjects (7.9%) experienced TEAEs leading to discontinuation of study drug.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

In the Integrated Population the system organ class (SOC) with the most frequently reported TEAEs for all dose regimens were gastrointestinal disorders (33.1% of subjects receiving the ew dose regimen, 40.0% of subjects receiving the eow dose regimen, and 29.8% of subjects receiving the TDM dose regimen) and infections and infestations (38.3% of subjects receiving the ew dose regimen, 40.0% of subjects receiving the eow dose regimen, and 34.4% of subjects receiving the TDM dose regimen). The most frequently ( $\geq 5\%$  of subjects total) reported TEAEs by preferred term (PT) were colitis ulcerative, nasopharyngitis, arthralgia, upper respiratory tract infection, and headache.

In the Japan Population the SOC with the most frequently reported TEAEs for all dose regimens were infections and infestations (60.9% of subjects receiving the ew dose regimen, and 55.8% of subjects receiving the eow dose regimen), gastrointestinal disorders (28.3% of subjects receiving the ew dose regimen, 23.3% of subjects receiving the eow dose regimen), and skin and subcutaneous tissue disorders (21.7% of subjects receiving the ew dose regimen, 14.0% of subjects receiving the eow dose regimen). The most frequently ( $\geq 5\%$  of subjects total) reported TEAEs by PT were nasopharyngitis, anemia, influenza, colitis ulcerative, pyrexia, nausea, and cystitis.

For both the Integrated and the Japan Population, the proportions of subjects experiencing AESIs were generally low ( $< 5\%$  of subjects total); with the exception of infections and hematologic disorders. The occurrences of all AESIs were relatively balanced across dose regimens.

There were no notable mean changes in laboratory parameter values (hematology, clinical chemistry, and urinalysis) from Baseline. Shifts in hematology, clinical chemistry, and urinalysis values from normal or high at Baseline to low at the final value or normal or low at Baseline to high at the final value were infrequent and not considered clinically meaningful.

There were no notable mean changes from Baseline in vital signs values.

A total of 5 pregnancies were reported during Study M14-033 (Integrated Population); 4 resulted in live births without congenital anomaly and 1 resulted in a spontaneous abortion which occurred in the first trimester. No pregnancies occurred in the Japan Population.

No unexpected drug or device issues were identified during the study.

**Conclusions:**

During the Maintenance Study, for the Integrated Population among Week 8 responders, a statistically significantly higher proportion of subjects receiving the ew dose regimen achieved clinical remission per Full Mayo score at Week 52 than subjects receiving the eow dose regimen.

For the Japan Population, among Week 8 responders, a numerically higher proportion of subjects receiving the ew dose regimen achieved clinical remission per Full Mayo score at Week 52 than subjects receiving the eow dose regimen.

The safety results of the adalimumab maintenance treatment in both the Japan Population and Integrated Population were comparable and consistent with the known safety profile of adalimumab; no new safety signals or unexpected trends were identified. Overall, the benefit-risk profile of the adalimumab standard maintenance dosing regimen in this patient population remains unchanged.