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 to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration		
Investigator: [redacted], MD		
Study Site(s)**:** The Maintenance Study included 59 sites in Austria, Belgium, Canada, Czech Republic, Denmark, France, Germany, Israel, Italy, Netherlands, Poland, Romania, Spain, Switzerland, Ukraine, United Kingdom, and the United States.		
Publications: 1		
Studied Period (Years): First Subject First Visit: 01 May 2014 Last Subject Last Visit: 30 January 2020	**Phase of Development:** 3	

Objective(s):

The primary objective of Study M14-115 was to assess the efficacy and safety of 2 adalimumab induction regimens in achieving clinical remission based on Crohn's Disease Activity Index (CDAI) < 150 at Week 4 and endoscopic response defined as decrease in Simplified Endoscopic Score for Crohn's Disease (SES-CD) > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) at Week 12, in subjects with moderately to severely active Crohn's Disease (CD) and evidence of mucosal ulceration at Baseline. Additional objectives included:

- Assessing the efficacy and safety of 2 adalimumab induction regimens in reducing signs and symptoms of CD at Week 12.
- Assessing the efficacy and safety of 2 adalimumab maintenance regimens in reducing signs and symptoms of CD at Week 56.
- Assessing pharmacokinetics and immunogenicity of 2 adalimumab induction regimens following subcutaneous (SC) administration.

Methodology:

Study M14-115 consists of an Induction Study and a Maintenance Study. No placebo arm was planned because there is well documented efficacy of adalimumab in CD. The aim of Study M14-115 (Induction Study) was to investigate if better efficacy (clinical remission and endoscopic response) would be achieved with the higher dose regimen than the standard dose regimen. The exploratory Maintenance Study was designed to assess the safety and efficacy of two double-blinded exploratory treatment regimens (adalimumab clinically adjusted [CA] regimen and adalimumab therapeutic drug monitoring [TDM] regimen) at maintaining clinical and endoscopic improvements at Week 56.

At Week 12, subjects were re-randomized into the Maintenance Study in a 1:1 ratio to either the CA or the TDM regimen. The re-randomization at Week 12 was stratified by induction treatment regimen, clinical response (CR-70) status at Week 12, and decrease in SES-CD > 50% from Baseline per the site investigator reading at Week 12. Among subjects achieving SES-CD > 50% from Baseline at Week 12, the randomization was further stratified by achievement of SES-CD ≤ 4 and at least a 2-point reduction versus Baseline and no subscore greater than 1 in any individual variable, using the Week 12 SES-CD value provided by the site.

Clinically Adjusted (CA) Regimen

Subjects randomized to the clinically adjusted regimen received 40 mg adalimumab eow beginning at Week 12. The adalimumab dose was escalated to every week (ew) starting as early as Week 14 if the subject's CDAI is ≥ 220 or high-sensitivity C-reactive protein (hs-CRP) ≥ 10 mg/L (using results from the prior or current visit). These subjects were allowed to escalate at unscheduled visits that may occur only at Weeks 16, 18, 22, 24, 30, 32, 36, 38, 44, 46, 50, 52 and 54. Once subjects in the CA regimen were dose escalated, they continued to receive adalimumab 40 mg ew dosing.

Therapeutic Drug Monitoring (TDM) Regimen

At Weeks 14, 28, and 42, the adalimumab dose for subjects randomized to the TDM was determined by a dose adjustment criteria table. Doses were determined using blinded serum concentrations at the prior visit (Weeks 12, 26 and 40, respectively) as well as the CDAI or hs-CRP values from the current or prior visit. For subjects who met criteria for dose escalation at Weeks 14, 28, or 42, they received 40 mg weekly.

This clinical study report (CSR) includes data up through 30 January 2020 and covers the 44-week DB Maintenance Study and the 70-day follow-up call.

Number of Subjects (Planned and Analyzed): Approximately 500 subjects planned for Study M14-115.

A total of 184 subjects (Modified Intent-to-Treat [mITT] Population) (218 subjects [Safety Population]) were enrolled and randomized in the Maintenance Study. A total of 92 subjects (mITT Population) (109 subjects [Safety Population]) were randomized to receive the CA regimen, and 92 subjects (mITT Population) (109 subjects [Safety Population]) were randomized to receive the TDM regimen. The mITT Population includes all ITT subjects who achieved clinical response (CR-70) at Week 12. This is the primary population for the efficacy analysis for the Maintenance Study.

Diagnosis and Main Criteria for Inclusion:

Key eligibility criteria for Study M14-115 included: Male or female ≥ 18 and ≤ 75 years of age at the Baseline visit; diagnosis of colonic, ileocolonic, or ileal CD for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before Baseline with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the investigator, must have been available; SES-CD ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader; CDAI ≥ 220 and ≤ 450 at Baseline 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 and/or immunosuppressants or both as defined below):

- Subject taking oral corticosteroids, excluding budesonide:
  - Oral corticosteroid dose ≤ 40 mg/day (prednisone or equivalent);
    - For subjects with a dose > 10 and ≤ 40 mg/day, dose had been stable for at least 7 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.
  - For subjects with a dose ≤ 10 mg/day, dose had been stable for at least 10 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.
- Subject taking oral budesonide:
  - Dose must not exceed 9 mg/day;
    - For subjects with a dose ≥ 6 mg/day, dose had been stable for at least 7 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.
    - For subjects with a dose < 6 mg/day, dose had been stable for at least 10 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.

or,

- At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-thioguanine nucleotide (6-TGN) level of at least 230 pmol/8 × 10^8 red blood cells (RBCs) to clarify a therapeutic level was achieved on the current dosing regimen or MTX ≥ 15 mg/week (SC/Intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

  Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.

or,

Diagnosis and Main Criteria for Inclusion (Continued):

- Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability;

Subjects were permitted to be included if they had previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD-related symptoms) or intolerance (in the opinion of the investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability was required.

Key exclusion criteria for Study M14-115 included: subjects with a current diagnosis of ulcerative colitis or indeterminate colitis; subjects on azathioprine, 6-MP, methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who had not been on these medications for at least 42 days prior to Baseline; or had not been on stable doses of these medications for at least 28 days prior to Baseline; or had discontinued these medications within 14 days of Baseline; Subject on oral aminosalicylates who had not been on stable doses of these medications for at least 28 days prior to Baseline; or discontinued use of aminosalicylates within 14 days of Baseline; Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide > 9 mg/day; or

- Subject taking an oral corticosteroid (excluding budesonide):
  - dose > 10 mg/day, but had not been on a stable dose for at least 7 days prior to Baseline; or
  - dose > 10 mg/day, but had not been on a current steroid course for at least 14 days prior to Baseline; or
  - dose ≤ 10 mg/day or equivalent, but had not been on a stable dose for at least 10 days prior to Baseline; or
  - dose ≤ 10 mg/day or equivalent but had not been on a current steroid course of at least 14 days in duration prior to Baseline, or
- Subject taking budesonide:
  - dose ≥ 6 mg/day, but had not been on a stable dose for at least 7 days prior to Baseline; or
  - dose ≥ 6 mg/day, but had not been on a current steroid course for at least 14 days prior to Baseline; or
  - dose < 6 mg/day dose but had not been on a stable dose of at least 10 days prior to Baseline; or
  - dose < 6 mg/day but the current course had not been at least 14 days in duration prior to Baseline; or

Had been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of inhalers.

Duration of Treatment: 52 Weeks

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

Adalimumab 40 mg/0.8 mL for SC injection

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

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

Criteria for Evaluation

Efficacy:

All efficacy endpoints for Maintenance Study are non-ranked.

- Proportion of subjects who achieve endoscopic response (SES-CD > 50% from Induction Baseline [or for an Induction Baseline SES-CD of 4, at least a 2-point reduction from Induction Baseline]) at Week 56 among subjects with endoscopic response at Week 12
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic remission at Week 12.
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects with endoscopic response at Week 12.
- Proportion of subjects who achieve sustained clinical remission, CDAI < 150 at Week 56 among subjects with CDAI < 150 at Week 12.
- Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 56.
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable) at Week 56.
- Proportion of subjects who achieve SES-CD ≤ 2 at Week 56.
- Proportion of subjects with deep remission, CDAI < 150 at Week 56 and SES-CD ≤ 4 and at least 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable at Week 56.
- Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 56 among subjects taking corticosteroid at Induction Baseline.
- Proportion of subjects with endoscopic response (decrease > 50% SES-CD from Induction Baseline [or for an Induction Baseline SES-CD of 4, at least a 2-point reduction from Induction Baseline]) at Week 56.
- Change from Induction Baseline in fecal calprotectin level at Week 56.
- Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g at Week 56.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at Week 56.
- Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 56.
- Proportion of subjects with endoscopic response, and ≥ 50% decrease from Induction Baseline in hs-CRP or fecal calprotectin at Week 56.

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Proportion of subjects with endoscopic remission, and ≥ 50% decrease from Induction Baseline in hs-CRP or fecal calprotectin at Week 56.
- Proportion of subjects with clinical remission, and ≥ 50% decrease from Induction Baseline in hs-CRP or fecal calprotectin at Week 56.
- Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Induction Baseline) at Week 56.
- Proportion of subjects with clinical response (decrease CDAI ≥ 70 points from Induction Baseline) at each scheduled visit in Maintenance Study.
- Proportion of subjects with enhanced clinical response (decrease CDAI ≥ 100 points from Induction Baseline) at each scheduled visit in Maintenance Study.
- Proportion of subjects who discontinue corticosteroid use at each scheduled visit in Maintenance Study among subjects taking corticosteroid at Induction Baseline.
- Proportion of subjects who achieve a composite subtotal score of CDAI components "Number of liquid or very soft stools" and "Abdominal pain" (Stool [liquid/soft] Frequency + Abdominal Pain Score; SFPS) (SFPS) < 50 at Week 56 who had an SFPS ≥ 100 at Induction Baseline.
- Proportion of subjects who achieve SES-CD ≤ 3 and at least a 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable at Week 56.
- Proportion of subjects with SES-CD = 0 at Week 56.
- Change from Induction Baseline in fecal calprotectin level at each scheduled visit in Maintenance Study.
- Change from Induction Baseline in hs-CRP at each scheduled visit in Maintenance Study.
- Change in Inflammatory Bowel Disease Questionnaire (IBDQ) total score and individual IBDQ domain scores (bowel, emotional, social, systemic) from Induction Baseline at each scheduled visit in Maintenance Study.
- Change in Work Productivity and Impairment Questionnaire (WPAI) from Induction Baseline at each scheduled visit in Maintenance Study.
- Change in European Quality of Life 5 dimensions (EQ-5D) from Induction Baseline at each scheduled visit in Maintenance Study.
- Change in CDAI from Induction Baseline at each scheduled visit in Maintenance Study.
- Change in SFPS from Induction Baseline at each scheduled visit in Maintenance Study.
- Change in Abdominal Pain Rating Scale score from Induction Baseline at each scheduled visit in Maintenance Study.
- Change in Bristol Stool Chart score from Induction Baseline at each scheduled visit in Maintenance Study.
- Proportion of subjects who achieve CDAI remission (CDAI < 150) at each scheduled visit in Maintenance Study.
- Proportion of subjects who achieve SFPS remission (SFPS < 50) at each scheduled visit in Maintenance Study.
- Proportion of subjects with major CD related event (e.g., hospitalization, bowel surgery, abscess drainage) in Maintenance Study.

Criteria for Evaluation (Continued)

Efficacy (Continued):

- Proportion of subjects with no draining fistulas at Week 56 among subjects with draining fistula at Induction Baseline.
- Proportion of subjects in each treatment group with > 50% reduction from Induction Baseline in the number of draining fistulas at Week 56 among subjects with draining fistula at Induction Baseline.
- Resolution of extra-intestinal manifestations at each scheduled visit in Maintenance Study.
- Proportion of subjects with an SES-CD decrease of ≥ 3 points compared to Induction Baseline at Week 56.
- Proportion of subjects who achieve symptomatic remission, defined as average daily stool frequency ≤ 2.8 (and not worse than Induction Baseline) and average daily abdominal pain ≤ 1.0 (and not worse than Induction Baseline), at each scheduled visit in Maintenance Study among subjects with Induction Baseline stool frequency (SF) ≥ 4.0 and/or AP ≥ 2.0.
- Proportion of subjects who achieve symptomatic response, defined as average daily stool frequency at least 30% reduction from Induction Baseline and average daily abdominal pain not worse than Induction Baseline or average daily abdominal pain at least 30% reduction from Induction Baseline and average daily stool frequency not worse than Induction Baseline, at each scheduled visit in Maintenance Study among subjects with Induction Baseline SF ≥ 4.0 and/or AP ≥ 2.0.
- Time to dose escalation in Maintenance Study.
- Proportion of subjects with IBDQ response (increase ≥ 16 points from Induction Baseline) at each scheduled visit in Maintenance Study.
- Proportion of subjects with IBDQ remission (IBDQ ≥ 170 points) at each scheduled visit in Maintenance Study.
- Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at each scheduled visit in Maintenance Study.
- Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at each scheduled visit in Maintenance Study.
- Proportion of subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve clinical remission (CDAI < 150) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve endoscopic response (decrease > 50% SES-CD from Induction Baseline [or for an Induction Baseline SES-CD of 4, at least a 2-point reduction from Induction Baseline]) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.
- Proportion of subjects who achieve endoscopic remission (SES-CD ≤ 4 and at least a 2-point reduction versus Induction Baseline and no subscore greater than 1 in any individual variable) at Week 56 among subjects requiring dose escalation to weekly dosing during Maintenance Study.

Criteria for Evaluation (Continued)

Pharmacokinetic:

To be provided in a separate report.

Safety:

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

Statistical Methods

Efficacy:

All efficacy endpoints for the Maintenance Study are non-ranked. For categorical endpoints, the non-responder imputation (NRI) method of imputation was used for the missing values. LOCF was used as a sensitivity analysis wherever applicable. Both last observation carried forward (LOCF) and observed case (OC) analyses were performed for continuous endpoints. The LOCF analysis was considered primary for inferential purposes. In additional, Mixed-Effect Model Repeated Measure (MMRM) were applied as a sensitivity analysis, wherever appropriate, for the longitudinal continuous endpoints.

For endoscopy related endpoints, there was no LOCF imputation as there was only one post-baseline endoscopy during Maintenance. OC was used as a sensitivity analysis.

The difference in proportions of subjects between treatment groups was analyzed using the two-sided Cochran-Mantel-Haenszel (CMH) test adjusted for induction treatment regimen, and decrease in SES-CD > 50% from Induction Baseline per central reading at Week 12. Additionally, the CMH-based two-sided 95% confidence interval (CI) for the difference in the proportions between the treatment groups will be calculated.

The difference in change from Induction Baseline between treatment groups was analyzed using an ANCOVA model including factors of treatment, induction treatment regimen, decrease in SES-CD > 50% from Induction Baseline per central reading at Week 12, and Induction Baseline values. Parameter estimates with 95% CI and P-value were provided.

Pharmacokinetic:

To be provided in a separate report.

Safety:

All safety analyses were performed on the safety analysis set. The safety variable was summarized by treatment according to the treatment a subject actually received.

Summary/Conclusions

Efficacy Results:

Results from the Maintenance Study demonstrated that both the CA and TDM maintenance treatment regimens led to similar results among key efficacy endpoints in reducing signs and symptoms of CD at Week 56. Both maintenance regimens demonstrated that adalimumab is efficacious for long-term treatment of CD as evidenced by the endpoints of clinical remission at Week 56, sustained clinical remission, steroid-free clinical remission, symptomatic remission and response, in addition to maintenance of endoscopic response and remission at Week 56 in subjects who achieved endoscopic and remission at Week 12, respectively. There was no statistically significant difference between the two treatment regimens for any endpoint.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Approximately two-thirds of the subjects in each treatment regimen achieved clinical remission at Week 56 indicating similar efficacy regardless of the treatment regimen a subject received. Among subjects with clinical remission at Week 12, greater than 70% achieved clinical remission at Week 56 in each treatment regimen, demonstrating maintenance of effect. The proportion of subjects who discontinued corticosteroid use and achieved clinical remission at Week 56, among subjects taking corticosteroids at Induction baseline, was greater than 70% for each treatment regimen.

Approximately 40% of subjects in each treatment regimen achieved endoscopic response at Week 56. The proportion of subjects who maintained endoscopic response at Week 56 among subjects with endoscopic response at Week 12 was 71.4% for the CA regimen, and 55.6% for the TDM regimen, however, there was no statistically significant difference between the treatment regimens.

Approximately one-third of subjects in each treatment regimen achieved endoscopic remission at Week 56. The proportion of subjects who maintained endoscopic remission at Week 56 among subjects with endoscopic remission at Week 12 was 70.0% for the CA regimen, and 51.5% for the TDM regimen, however, there was no statistically significant difference between the treatment regimens.

Of those subjects who dose escalated to weekly dosing, greater than 50% of subjects in each treatment regimen achieved clinical remission at Week 56. Approximately one-third of subjects in the CA regimen, and one-fourth of subjects in the TDM regimen who dose escalated to weekly dosing achieved endoscopic response at Week 56. Similar results were observed for endoscopic remission at Week 56 study.

Adalimumab treatment lead to high rates of efficacy in symptomatic endpoints (symptomatic remission and response); at Week 56, approximately 55% of subjects in both treatment regimens achieved symptomatic remission, and greater than 70% of subjects in each treatment regimen achieved symptomatic response, as measured by stool frequency and abdominal pain.

The quality of life PRO measure of IBDQ remission was achieved by more than 55% of subjects in each treatment regimen at Week 56, and IBDQ response was achieved by more than 70% of subjects in each treatment regimen. Adalimumab treatment let to improvement in EIMs; among subjects that had EIMs at Induction Baseline, greater than 60% of subjects in both regimens had EIMs that resolved at Week 56.

Pharmacokinetic Results:

To be provided in a separate report.

Safety Results:

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

Summary/Conclusions (Continued)

Safety Results (Continued):

Approximately 70% of subjects in each treatment regimen had 1 or more treatment-emergent adverse events (TEAEs) in the Maintenance Study. There were no deaths in the Maintenance Study. The proportions of subjects who experienced at least 1 serious adverse event (SAE) or a TEAE leading to study drug discontinuation were low and comparable across treatment regimens. Most TEAEs were mild or moderate in severity as assessed by the investigator. The percentage of subjects who experienced TEAEs assessed by the investigator as having at least a reasonable possibility of being related to study drug was comparable for both treatment regimens (26.6% of subjects receiving the CA regimen and 30.3% of subjects receiving the TDM regimen). The proportion of subjects experiencing adverse events of special interest (AESIs) were comparable for both treatment regimens (37.6% of subjects receiving the CA regimen and 38.5% of subjects receiving TDM regimen). The occurrences of AESIs were relatively balanced across treatment 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.

No pregnancies were reported during the Maintenance Study.

Quality assurance personnel reviewed all product complaints associated with adalimumab during the clinical study, and no new safety risks have been identified.

Conclusions:

Results the from Maintenance Study indicate that both CA and TDM maintenance treatment regimens lead to similar results among key efficacy endpoints for subjects with moderate to severe CD. The addition of TDM as criteria for dose adjustment showed no clinical benefit over the use of clinical symptoms and biomarkers alone. Both treatment regimens evaluated in this study showed similar frequency, severity, and seriousness of safety events. No new safety signals were observed with either treatment regimen. Overall, the benefit-risk profile of adalimumab in this patient population remains unchanged.

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 to Evaluate Higher Versus Standard Adalimumab Dosing Regimens for Induction and Maintenance Therapy in Subjects with Moderately to Severely Active Crohn's Disease and Evidence of Mucosal Ulceration

Coordinating Investigator: [redacted]

Study Site(s)**:** The Induction Study included 93 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), including Puerto Rico.

Publications: None.

Studied Period (Years): First Subject First Visit: 01 May 2014 Last Subject Last Visit: 21 January 2019 (Last Subject Last Week 12 Visit)	**Phase of Development:** 3

Objective(s):

The primary objective of this study was to assess the efficacy and safety of 2 adalimumab induction regimens in achieving clinical remission (Crohn's Disease Activity Index [CDAI] < 150) at Week 4 and endoscopic response defined as decrease in Simplified Endoscopic Score for Crohn's Disease (SES-CD) > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) at Week 12, in subjects with moderately to severely active Crohn's Disease (CD) and evidence of mucosal ulceration at Baseline. Additional objectives included:

- Assessing the efficacy and safety of 2 adalimumab induction regimens in reducing signs and symptoms of CD at Week 12.
- Assessing the efficacy and safety of 2 adalimumab maintenance regimens in reducing signs and symptoms of CD at Week 56.
- Assessing pharmacokinetics (PK) and immunogenicity of 2 adalimumab induction regimens following subcutaneous (SC) administration.

Methodology

Study M14-115 consists of an Induction Study and a Maintenance Study. No placebo arm was planned because there is well documented efficacy of adalimumab in CD, and the aim of this study was to achieve better efficacy (clinical remission and endoscopic response) with the higher dose regimen than the standard dose regimen. Approximately 500 adult subjects with moderately to severely active CD who met all of the inclusion criteria and none of the exclusion criteria were eligible to participate in the Induction Study.

Methodology (Continued):

This clinical study report (CSR) includes data up through 10 April 2019 and covers the 12-week double-blind (DB) Induction Study.

Number of Subjects (Planned and Analyzed): Approximately 500 subjects planned.

The Intent-to-Treat (ITT) and Safety Populations were the same, with 514 subjects for the Induction Study (308 subjects receiving the higher induction dosing regimen and 206 subjects receiving the standard induction dosing regimen).

Diagnosis and Main Criteria for Inclusion:

Key eligibility criteria for Study M14-115 included: Male or female ≥ 18 and ≤ 75 years of age at the Baseline visit; diagnosis of colonic, ileocolonic, or ileal Crohn's disease for ≥ 3 months prior to Baseline and confirmed by endoscopy during the Screening period or endoscopy performed within 45 days before Baseline with exclusion of current infection, dysplasia, and/or malignancy. Appropriate documentation of biopsy results consistent with the diagnosis of CD, in the assessment of the Investigator, must have been available; SES-CD ≥ 6, excluding the presence of narrowing component, or SES-CD ≥ 4, excluding the presence of narrowing component, for patients with disease limited to the ileum, on screening endoscopy or endoscopy performed within 45 days before Baseline, confirmed by a central reader; CDAI ≥ 220 and ≤ 450 at Baseline 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 and/or immunosuppressants or both as defined below):

- Subject taking oral corticosteroids, excluding budesonide:
  - Oral corticosteroid dose ≤ 40 mg/day (prednisone or equivalent);
    - For subjects with a dose > 10 and ≤ 40 mg/day, dose had been stable for at least 7 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.
    - For subjects with a dose ≤ 10 mg/day, dose had been stable for at least 10 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.
- Subject taking oral budesonide:
  - Dose must not exceed 9 mg/day;
    - For subjects with a dose ≥ 6 mg/day, dose had been stable for at least 7 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.
    - For subjects with a dose < 6 mg/day, dose had been stable for at least 10 days prior to Baseline and the duration of the current steroid course had been at least 14 days prior to Baseline.

or,

Diagnosis and Main Criteria for Inclusion (Continued):

- At least a consecutive 42-day course of azathioprine, 6-mercaptopurine (6-MP), or injectable methotrexate (MTX) prior to Baseline, with a stable dose for at least 28 days prior to Baseline of azathioprine ≥ 1.5 mg/kg/day or 6-MP ≥ 1 mg/kg/day (rounded to the nearest available tablet or half tablet formulation) or a documented 6-thioguanine nucleotide (6-TGN) level of at least 230 pmol/8 × 10^8 red blood cells (RBCs) to clarify a therapeutic level was achieved on the current dosing regimen or MTX ≥ 15 mg/week (subcutaneous [SC]/Intramuscular [IM]), or a dose that is the highest tolerated by the subject (e.g., due to leukopenia, elevated liver enzymes, nausea) during that time.

  Note: If a subject is taking both an oral corticosteroid and an immunosuppressant listed above, BOTH of the drugs need to meet the above criteria. Oral MTX use is allowed during the study (at a stable dose for 28 days prior to Baseline) however current or prior use of oral MTX is not sufficient for inclusion into the study.

or,

- Concurrent therapy with oral corticosteroids or immunosuppressants (azathioprine, 6-MP or SC/IM MTX) is not required for subjects not currently taking these medications who were previously treated during the past 1 year and have confirmed documentation of failure to respond, or were previously treated during the past 5 years and have confirmed documentation indicating lack of tolerability.

Subject were permitted to be included if they had previously experienced a benefit from infliximab and discontinued its use due to a subsequent loss of response (judged by the Investigator to have responded to infliximab in the past and subsequently experienced an overall lack of improvement or worsening of CD-related symptoms) or intolerance (in the opinion of the Investigator therapy was discontinued as a result of a significant acute or delayed infusion/administration reaction to the medication) to the agent. Confirmed documentation indicating loss of response or lack of tolerability was required.

Key exclusion criteria for Study M14-115 included: subjects with a current diagnosis of ulcerative colitis or indeterminate colitis; subjects on azathioprine, mercaptopurine (6-MP), methotrexate (MTX), or another immunosuppressant (e.g., thalidomide) who had not been on these medications for at least 42 days prior to Baseline; or had not been on stable doses of these medications for at least 28 days prior to Baseline; or had discontinued these medications within 14 days of Baseline; Subject on oral aminosalicylates who had not been on stable doses of these medications for at least 28 days prior to Baseline; or discontinued use of aminosalicylates within 14 days of Baseline; Subject on oral corticosteroid > 40 mg/day (prednisone or equivalent) or subjects on budesonide > 9 mg/day; or

- Subject taking an oral corticosteroid (excluding budesonide):
  - dose > 10 mg/day, but had not been on a stable dose for at least 7 days prior to Baseline; or
  - dose > 10 mg/day, but had not been on a current steroid course for at least 14 days prior to Baseline; or
  - dose ≤ 10 mg/day or equivalent, but had not been on a stable dose for at least 10 days prior to Baseline; or
  - dose ≤ 10 mg/day or equivalent but had not been on a current steroid course of at least 14 days in duration prior to Baseline, or

Diagnosis and Main Criteria for Inclusion (Continued):

- Subject taking budesonide:
  - dose ≥ 6 mg/day, but had not been on a stable dose for at least 7 days prior to Baseline; or
  - dose ≥ 6 mg/day, but had not been on a current steroid course for at least 14 days prior to Baseline; or
  - dose < 6 mg/day dose but had not been on a stable dose of at least 10 days prior to Baseline; or
  - dose < 6 mg/day but the current course had not been at least 14 days in duration prior to Baseline; or

Had been taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of inhalers.

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

Subjects were randomized in a 3:2 ratio to receive a higher adalimumab induction regimen or standard adalimumab induction regimen during the DB Induction Study. Subjects in the Induction Study were stratified by Baseline high-sensitivity C-reactive protein (hs-CRP), prior infliximab use, and CD activity at Baseline.

Subjects assigned to the higher induction regimen received blinded adalimumab 160 mg at Baseline, Week 1, Week 2, and Week 3. At Week 4, subjects received 40 mg every other week (eow) through Week 12. Subjects assigned to the standard adalimumab induction regimen received blinded adalimumab 160 mg at Baseline and matching placebo at Week 1, adalimumab 80 mg and matching placebo at Week 2, and then matching placebo at Week 3, and then adalimumab 40 mg eow starting at Week 4 through Week 12.

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

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

Duration of Treatment: 12 Weeks

Criteria for Evaluation

Efficacy:

Induction Study Co-Primary Efficacy Endpoints:

- Proportion of subjects who achieve a CDAI < 150 at Week 4.
- Proportion of subjects with decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) at Week 12.

Induction Study Ranked Secondary Endpoints:

1. Proportion of subjects with sustained clinical remission (CDAI < 150) at both Weeks 4 and 12.
2. Proportion of subjects with CDAI < 150 at Week 4 and decrease in SES-CD > 50% from Baseline (or for a Baseline SES-CD of 4, at least a 2-point reduction from Baseline) at Week 12.
3. Proportion of subjects with clinical remission (CDAI < 150) at Week 12.
4. Proportion of subjects who discontinued corticosteroid use and achieved clinical remission (CDAI < 150) at Week 12 among subjects taking corticosteroids at Baseline.
5. Proportion of subjects with endoscopic remission (SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable) at Week 12.

Criteria for Evaluation (Continued)

6. Change from Baseline in fecal calprotectin level at Week 4.
7. Proportion of subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg/g at Week 4.
8. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, and fecal calprotectin < 250 µg/g at Week 4.
9. Proportion of subjects with CDAI < 150, hs-CRP < 5 mg/L, SES-CD ≤ 4 and at least a 2-point reduction versus baseline and no subscore > 1 in any individual variable, and fecal calprotectin < 250 µg/g at Week 12.
10. Proportion of subjects who achieve an SES-CD ≤ 2 at Week 12.
11. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 4.
12. Proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from baseline) at Week 12.
13. Proportion of subjects achieving response in Inflammatory Bowel Disease Questionnaire (IBDQ) Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 4.
14. Proportion of subjects achieving response in IBDQ Bowel Symptom domain (increase of IBDQ bowel symptom domain score ≥ 8) at Week 12.
15. Proportion of subjects achieving response in IBDQ fatigue item (increase of IBDQ fatigue item score ≥ 1) at Week 12.

Pharmacokinetic:

To be provided in a separate report.

Safety:

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

Statistical Methods

Efficacy:

The primary efficacy analysis used the ITT analysis set for the Induction Study. The efficacy analysis used the non-responder imputation (NRI) method to impute the missing CDAI values at Week 4 or missing SES-CD values at Week 12 for the Induction Study. The comparisons between treatment groups on the two co-primary efficacy variables were performed using the Cochran-Mantel-Haenszel (CMH) adjusted for hs-CRP at Baseline (< 10 and ≥ 10 mg/L), prior infliximab use (or prior anti-TNF use for subjects randomized under original protocol), and Crohn's disease severity (CDAI ≤ 300, > 300) at Baseline. A CMH based two-sided 95% confidence interval (CI) for the difference between the treatment groups was calculated.

Pharmacokinetic:

To be provided in a separate report.

Safety:

All safety analyses were performed on the safety analysis set. The safety variable was summarized by treatment according to the treatment a subject actually received.

Summary/Conclusions

Efficacy Results:

Subjects receiving the higher induction dosing regimen did not demonstrate significantly greater efficacy of clinical remission at Week 4 (43.2% vs. 43.7%, $P = 1.00$), or endoscopic response at Week 12 (42.5% vs. 39.3%, $P = 0.509$), over subjects receiving the standard induction dosing regimen. The stratification factors of hs CRP (< 10 mg/L and ≥ 10 mg/L) at Baseline, previous use of infliximab (yes, no), and CD severity (CDAI ≤ 300, > 300), were not associated with significant differences between treatment regimens in the proportion of subjects who achieved clinical remission at Week 4 or endoscopic response at Week 12.

The ranked secondary endpoints did not achieve statistical significance between higher and standard induction dose regimens based on the prespecified fixed sequence multiple testing procedure. Two of the secondary endpoints had nominal *P*-values < 0.05: proportion of subjects achieving clinical remission at Week 12 (62.3% of subjects receiving the higher induction dosing regimen vs. 51.5% of subjects receiving the standard induction dosing regimen, nominal $P = 0.008$) and proportion of subjects achieving clinical response at Week 12 (83.4% of subjects receiving the higher induction dosing regimen vs. 74.8% of subjects receiving the standard induction dosing regimen, nominal $P = 0.015$).

Pharmacokinetic Results:

To be provided in a separate report.

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.

Slightly more than 60% of subjects in each treatment regimen had 1 or more treatment-emergent adverse events (TEAEs) in the Induction Study. One subject died during Screening due to cardiac arrest; there were no other deaths in the study. The proportions of subjects who experienced at least 1 serious adverse event (SAE) or a TEAE leading to study drug discontinuation were low and comparable across treatment regimens. Most TEAEs were mild or moderate in severity. The percentage of subjects who experienced TEAEs assessed by the investigator as having at least a reasonable possibility of being related to study drug was comparable for both treatment regimens (24.0% of subjects receiving the higher induction dosing regimen and 26.2% of subjects receiving the standard induction dosing regimen). The proportions of subjects experiencing adverse events of special interest (AESIs) were comparable for both dosing regimens (31.5% of subjects receiving the higher induction dosing regimen and 34.5% of subjects receiving the standard induction dosing regimen). The occurrences of AESIs were relatively balanced across dosing 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.

One pregnancy was reported during the study with an outcome of maternal elective termination with no fetal congenital anomalies reported.

Quality assurance personnel reviewed all product complaints associated with adalimumab during the clinical study, and no new safety risks have been identified.

Conclusions:

The efficacy of the higher induction dosing regimen of adalimumab in inducing clinical remission at Week 4 and endoscopic response at Week 12 was not significantly superior from the standard dosing regimen of adalimumab. The higher induction dosing regimen of adalimumab, therefore, did not provide greater benefit to subjects with moderately to severely active CD, indicating the standard adalimumab induction dosing regimen remains the appropriate regimen for subjects with moderate to severe CD. The safety profile of subjects receiving the higher induction dosing regimen was consistent with subjects receiving the standard induction dosing regimen and the overall safety profile of adalimumab; no new safety signals or trends were observed. Overall, the benefit-risk profile of the standard induction dose of adalimumab in this patient population remains unchanged.