

## 2.0 Synopsis

<b>AbbVie Inc.</b>	<b>Individual Study Table Referring to Part of Dossier:</b>  <b>Volume:</b>  <b>Page:</b>	<b>(For National Authority Use Only)</b>
<b>Name of Study Drug:</b> Adalimumab		
<b>Name of Active Ingredient:</b> Adalimumab		
<b>Title of Study:</b> A Multicenter, Open-Label Study to Evaluate the Long Term Efficacy, Safety, and Tolerability of Repeated Administration of Adalimumab in Subjects with Crohn's Disease		
<b>Investigator:</b> ██████████		
<b>Study Sites:</b> 69 sites in the US, Canada, Israel, and Europe		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> First Subject First Visit: 12 August 2014 Last Subject Last Visit: 03 November 2017	<b>Phase of Development:</b> 3	
<p><b>Objectives:</b></p> <p>The primary objective of this study was to evaluate the long-term efficacy, safety, and tolerability of repeated administration of adalimumab in subjects with Crohn's disease (CD) who participated in and successfully completed the induction phase of up to Amendment 3 of Study M14-115.</p> <p>The secondary objective was to assess pharmacokinetics (PK) and immunogenicity of adalimumab following subcutaneous (SC) administration.</p>		
<p><b>Methodology:</b></p> <p>This was a Phase 3, multicenter, 40-week, OLE study designed to evaluate the long-term efficacy, safety, and tolerability of adalimumab. Approximately 300 adult subjects with moderately to severely active CD, who met all of the inclusion criteria and none of the exclusion criteria, and who participated and successfully completed through Amendment 3 of the lead-in study, Study M14-115, including the Week 12 ileocolonoscopy, were eligible to enroll into this study.</p> <p>Subjects were to be evaluated for entry into Study M14-347 at the Week 12 study visit of Study M14-115. The Week 12 visit of Study M14-115 was to be considered Week 0 (Baseline) of Study M14-347. In Study M14-347, study visits for clinical and safety assessments were to be performed at Weeks 0, 8, 16, 24, 32, and 40/Premature Discontinuation (PD). A subject's participation in the study was anticipated to be up to 40 weeks. Subjects who ended study participation early were to have a PD visit. All subjects were to have a follow-up phone call approximately 70 days after the last administration of study drug to obtain information on any new or ongoing adverse events (AEs). The 70-day follow-up phone call was not to be required for any subject who initiated commercial adalimumab.</p>		

**Methodology (Continued):**

All subjects were to receive open-label (OL) adalimumab 40 mg SC every other week (eow) beginning at Week 0. The Week 0 visit date was the date when the first dose of Study M14-347 study drug was received and is referred to as Day 1 or Week 0. The Week 0 value for a variable was defined as the last nonmissing value on or before the date of the first dose of Study M14-347 study drug.

No dose was to be administered at Week 40. Subjects may have been escalated to adalimumab 40 mg every week (ew) at or after Week 1 if the subject met the criteria for inadequate response, or de-escalated to 40 mg eow according to Protocol Figure 1. Subjects who dose-escalated to weekly adalimumab were considered non-responders at Week 40 of Study M14-347.

For subjects taking corticosteroids at Baseline of Study M14-115, adalimumab dose escalation was considered in lieu of increases in steroid dose. Subjects who continued to experience inadequate response on 40 mg ew who were taking corticosteroids at Baseline of Study M14-115 may have had their steroid dose increased, per the Investigator's discretion, in order to manage the symptoms. Any subject who continued to experience inadequate response on 40 mg ew may have been discontinued from the study at the investigator's discretion after discussion with the study designated physician (SDP). Subjects who dose escalated to adalimumab 40 mg ew had 1 opportunity to de-escalate adalimumab dose to 40 mg eow provided the following criteria had been met: CDAI < 200 and a high-sensitivity C-reactive protein (hs-CRP) value equal to or lower than that observed at the time of dose escalation. Subjects who experienced inadequate response after dose de-escalation (using the same criteria outlined above), may again have been escalated to 40 mg ew. A subject had only 1 opportunity to dose de-escalate and 1 opportunity to re-escalate to ew adalimumab dosing.

**Number of Subjects (Planned and Analyzed):**

Approximately 300 subjects planned; 252 subjects analyzed

**Diagnosis and Main Criteria for Inclusion:**

Key eligibility criteria for Study M14-115 included: CDAI  $\geq 220$  and  $\leq 450$ ; evidence of mucosal ulceration by the Simplified Endoscopic Score for Crohn's disease (SES-CD)  $\geq 6$ , excluding the presence of narrowing component, or SES-CD  $\geq 4$ , excluding the presence of narrowing component, for patients with disease limited to the ileum, confirmed by a central reader. The specific subject population chosen was based on the unmet medical need for subjects with evidence of mucosal inflammation.

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

Adalimumab (40 mg/0.8 ml) subcutaneous, open-label administration of 40 mg eow or 40 mg ew for subjects whose disease was not controlled on 40 mg eow beginning at Week 0.

Lot numbers: 13-005618, 15-005080, 15-000609

**Duration of Treatment:** Up to 40 weeks

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

None

### Criteria for Evaluation

#### Efficacy:

*Primary Efficacy Endpoint:* Proportion of subjects with SES-CD  $\leq 4$  and at least a 2-point reduction vs. Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 40 among subjects with SES-CD  $\leq 4$  and at least a 2-point reduction vs. Study M14-115 Baseline and no subscore greater than 1 in any individual variable at Week 0 (NRI) of Study M14-347.

*Additional Efficacy Endpoints:* SES-CD secondary endpoints, Crohn's Disease Activity Index (CDAI) remission and response, Stool (liquid/soft) Frequency and Abdominal Pain Score (SFPS) remission, fecal calprotectin and high-sensitivity C-reactive protein endpoints, quality of life endpoints, symptomatic remission and response, and extra-intestinal manifestations and fistulas. See study protocol for detailed list of additional efficacy endpoints.

**Pharmacokinetic:** Provided in a separate report.

**Safety:** Treatment-emergent adverse events (TEAEs), physical examinations, vital signs, and laboratory data were assessed throughout the study.

### Statistical Methods

The Statistical Analysis Plan (SAP) for this study was completed prior to final database lock (version 1.0, dated 13 November 2017). The following changes were made to the planned analyses after finalization of the SAP.

SAP Section 10.2 Primary Efficacy Analysis: The OC method, not LOCF, was used as the sensitivity analysis. As there is only one post-baseline endoscopy in Study M14-347, there is no LOCF for Week 40 SES-CD.

SAP Section 9.1 Study Drug Exposure: Duration of exposure is defined for each subject as the number of days since first dose of study drug through the last study drug dose date + 14 days, not 70 days.

SAP Table 7, Criteria for Potentially Clinically Significant Vital Sign Findings: The cutoff for diastolic blood pressure (mmHg) has a typo. It should be 105 mmHg, instead of 100 mmHg.

SAP, Section 10.3, Additional Efficacy Analyses: includes the endpoint "Proportion of subjects who achieve CDAI remission and discontinue corticosteroid use at each visit among subjects who used corticosteroids at Week 0 of Study M14-347." Since many of the subjects had corticosteroids tapered during Study M14-115, a new endpoint "Proportion of subjects who achieve CDAI remission and discontinue corticosteroid use at each visit among subjects who used corticosteroids at Baseline of Study M14-115" was added.

SAP, Section 11.3, Analysis of Laboratory data: CTC Version 4.0 (or later) is listed. However, to keep consistence with other Humira CD studies, CTC Version 3.0 is used for the clinical study report (CSR) tables.

#### Efficacy:

The following efficacy evaluations were collected during the study to assess response and remission: endoscopy, laboratory tests, subject diary entries, physical examination, health-related quality of life, pain, and stool.

**Pharmacokinetic:** Provided in a separate report.

**Safety:** The following safety evaluations were performed during the study: monitoring of AEs, changes in vital signs, physical examination results, laboratory tests, and product complaints.

## Summary/Conclusions

### Efficacy Results:

The primary efficacy endpoint was a stringent evaluation of the maintenance of a low level of mucosal inflammation in subjects who achieved that same SES-CD cutoff at Week 12 of Study M14-115. Subjects who dropped out of Study M14-347 or dose-escalated to weekly adalimumab were considered non-responders for all efficacy endpoints in this study. The stringency of the SES-CD cutoff that was selected for the primary endpoint can be observed by the fact that approximately 30% of the subjects enrolled in Study M14-347 had achieved this cutoff upon study entry. The primary efficacy endpoint (i.e., maintenance of this mucosal inflammation cutoff) was achieved by one-third of subjects who entered with this degree of inflammation at Week 40. No differences were observed between most subgroups analyzed. A higher proportion of subjects who used IMMs at Baseline and a smaller proportion of subjects with Baseline hs-CRP > median 7.04 mg/L achieved the primary endpoint; however, the numbers of subjects were too small to draw any firm conclusions.

Proportions of subjects who maintained other endpoint cutoffs of SES-CD were also evaluated. The endpoint with the highest denominator (N = 119) and the maintenance rate at Week 40 (45.4%) was proportion of subjects who maintained a decrease in SES-CD > 50% from Study M14-115 Baseline. This endpoint is most similar to the endoscopic endpoints being used in most current registrational clinical trials in CD in 2018. More stringent endpoints (i.e., maintenance of SES-CD ≤ 2 and SES-CD = 0) were associated with denominators of 50 or fewer subjects and maintenance rates of 34% or lower.

The efficacy of maintenance of clinical remission endpoints per CDAI observed in Study M14-347 was similar to that observed in prior adalimumab trials. Approximately two-thirds of subjects in CDAI remission and CDAI response at Week 0 of Study M14-347 maintained CDAI remission and CDAI response at Week 40 of Study M14-347, respectively. Study M14-347 also assessed several more stringent composite CDAI endpoints that included some or all of the following: hs-CRP < 5 mg/L and fecal calprotectin < 250 µg, and SES-CD ≤ 4 and at least a 2-point reduction from Study M14-115 Baseline and no subscore > 1 in any individual variable. The one-quarter to one-third of subjects entering Study M14-347 at Week 0 with these statuses maintained these endpoints at Week 40. More than one-half of subjects entering Study M14-347 with SFPS remission maintained this endpoint at Week 40. When considering the overall population (N = 252), the proportion of subjects in clinical remission per CDAI was generally stable over time (61.1% at Week 0 to 51.2% at Week 40). The results of Study M14-347 indicate that the currently approved maintenance dose of adalimumab (40 mg eow) is appropriate for maintenance of symptomatic remission in the overall population of patients treated with either the currently approved 160/80 mg induction dosing regimen or the investigational higher dosing regimen.

The endpoint of hs-CRP < 5 mg/L and fecal calprotectin < 250 µg at Week 40 among subjects with hs-CRP < 5 mg/L and fecal calprotectin < 250 µg at Week 0 was maintained by nearly one-half of subjects, indicating maintenance in resolution of inflammation. Modified symptomatic remission was achieved by nearly one-half of subjects. Improvement in quality of life outcome was maintained for two-thirds of subjects who achieved IBDQ remission and response, respectively. Most subjects with draining fistulas at Study M14-115 Baseline had no draining fistulas at Week 40 of Study M14-347. Among all types of EIMs reported at Study M14-115 Baseline, the prevalence of each type decreased at Week 40 in all instances. The proportion of subjects with the most commonly reported EIM, peripheral arthropathy, decreased by three-fold at Week 40 compared to Study M14-115 Baseline. The prevalence of other EIMs at Week 40 was low (≤ 2.4% of subjects).

**Summary/Conclusions (Continued)**

**Pharmacokinetic Results:** Results are presented in a separate report.

**Safety Results:** Adalimumab 40 mg eow was generally safe and well tolerated and no new safety signals were noted. No subjects died in this study. The majority of subjects experienced at least 1 TEAE with CD (worsening of CD) as the most frequently reported TEAE. The proportion of subjects who experienced either a treatment-emergent SAE or a TEAE leading to study drug discontinuation was low ( $\leq 10.7\%$ ). Most TEAEs were mild to moderate in severity and assessed by the investigator as having no reasonable possibility of relationship to study drug. The proportion of subjects experiencing an AESI was also low ( $\leq 4.0\%$ ).

**Conclusions:** In this OLE study, adalimumab demonstrated efficacy in the maintenance of SES-CD, CDAI, and SPFS and symptomatic remission over 40 weeks. These findings were supported by the maintenance of improvement in biomarkers of inflammation and in quality of life as measured by IBDQ response and remission.

Safety results demonstrate that adalimumab maintenance therapy was generally safe and well-tolerated over 40 weeks. The safety profile of adalimumab in this study was consistent with the overall safety profile observed for adalimumab based upon years of data from global clinical studies and post-marketing surveillance in the treatment of CD and other diseases.

Overall, these findings support the long-term safety, efficacy, and tolerability of adalimumab for the treatment of CD after either high dose or standard dose induction treatment in a population of subjects with moderate to severe CD by symptoms plus endoscopic activity.