2.0 Synopsis

AbbVie Corporation/AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Humira and Methotrexate		
Name of Active Ingredient: Adalimumab and Methotrexate		
Title of Study: Concomitant longitudinal evaluation of adalimumab with methotrexate in the real world: the CLEAR study		
Principal Investigator: [redacted]		
Study Sites: 12 Canadian sites enrolled at least 1 subject		
Publications: None		
Studied Period (Years): First Subject First Visit: 05 August 2014 Last Subject Last Visit: 17 March 2017	**Phase of Development:** 3b	

Objectives:

Primary Objective:

The primary objective was to determine the proportion of primary and secondary sub-optimal responders to adalimumab (ADA) monotherapy (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) with a physician's global assessment (PGA) ≥ 3 and a Psoriasis Area Severity Index (PASI) ≥ 5 who have a satisfactory response after 16 weeks of treatment with ADA/methotrexate (MTX) combination therapy, based on Investigator and subject satisfaction assessments.

Objectives (Continued):

Secondary Objectives:

1. To determine the proportion of primary and secondary sub-optimal responders to ADA monotherapy (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) with a PGA ≥ 3 and a PASI ≥ 5 who reach PASI 50, PASI 75, and PASI 90 16 weeks after initiation of ADA/MTX combination therapy.
2. To define the demographic and clinical profile of subjects benefiting from ADA/MTX combination therapy.
3. To determine the magnitude, timing and maintenance of the benefit of adding MTX to ADA by assessing Investigator/subject satisfaction with treatment, PGA, PASI and Dermatology Life Quality Index (DLQI) at 8, 16, and 24 weeks after addition of MTX to therapy.
4. To determine change in DLQI from Baseline in subjects initiated on ADA/MTX treatment.
5. To determine change in serum levels of ADA following addition of MTX and to characterize a possible correlation with changes in Investigator/subject satisfaction with treatment, PGA, PASI, and DLQI over the study period. Serum levels were evaluated at Baseline (initiation of ADA + MTX) and at Weeks 8, 16, and 24.

Methodology:

This was a multicenter, single-arm, open-label longitudinal study. The study entailed a screening period up to 35 days, a 24-week treatment period, and a 70-day safety follow-up period. Subjects, who in the opinion of the Investigator were not responding optimally to ADA monotherapy (40 mg every other week [eow] or greater) at least 16 weeks after initiating treatment (primary sub-optimal responder) or who, after an initial positive response to ADA monotherapy (40 mg eow or greater) failed to maintain an optimal level of response (secondary sub-optimal responders) (sub-optimal responders defined as subjects with an unsatisfactory response to treatment based on Investigator assessment) and who had a PGA score of ≥ 3 and a PASI of ≥ 5 were potentially eligible for participation in the study.

Starting at the Baseline visit (Day 0), subjects continued to self-administer ADA (40 mg eow) and had oral MTX added to their treatment at a dose defined by the Investigator (between 10 mg and 25 mg per week). All subjects also received the non-investigational medicinal product oral folic acid as a dietary supplement, since MTX acts as a folic acid antagonist.

Applied to subjects who did not continue on Humira treatment, the 70-day safety follow-up period began from the last dose of ADA. Subjects were discontinued from the study if they withdrew consent or if they were deemed unsuitable to continue for any reason by the Investigator in consultation with the AbbVie Medical Monitor.

Number of Subjects (Planned and Analyzed):

The study was initially designed to enroll 200 subjects. Due to low recruitment rate, the study population sample size was reviewed to approximately 50 to meet scientific objectives without enrolling an undue number of subjects in alignment with ethical considerations. Of the 56 subjects screened, 46 were included in the ITT population, from 12 sites.

Diagnosis and Main Criteria for Inclusion:

1. Subjects who had been on ADA monotherapy (40 mg eow or greater) for at least 16 weeks but who in the opinion of the Investigator had shown a sub-optimal response to treatment and had a PGA of $\geq$ 3 and a PASI of $\geq$ 5; or
2. Subjects who after an initial positive response to ADA monotherapy (40 mg eow or greater) had failed to maintain an optimal level of response, based on the opinion of the Investigator, and had a PGA of $\geq$ 3 and a PASI of $\geq$ 5;
3. Subjects who were receiving 40 mg ADA once weekly must have been on ADA 40 mg eow for 8 weeks prior to screening;
4. Subjects with at least a 6-month history of chronic plaque psoriasis (Ps);
5. Subjects greater than or equal to 18 years of age;
6. If female, subject was either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile or was of childbearing potential and was practicing birth control;
7. The results of the serum pregnancy test performed during the Screening Period and urine pregnancy test performed at the Baseline Visit must have been negative;
8. Subject was judged to be in good general health as determined by the Principal Investigator;
9. Subjects must have been evaluated for latent tuberculosis (TB) infection;
10. Subjects must have been able and willing to provide written informed consent and comply with the requirements of the study protocol;
11. Subjects must have been willing and able to self-administer subcutaneous (SC) injections or had a qualified person available to administer SC injections.

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

- Investigational Products: ADA and MTX
- Doses: ADA: 40 mg eow beginning at study Week 0 through Week 22
  MTX: Dose is up to the discretion of the investigator but recommended dose should be between 10 and 25 mg/week, beginning at Week 0 through Week 23. The minimum initial dose of MTX should be 10 mg/week. MTX dose can be increased at any time over the study period, based on the clinical judgment of the Investigator.
- Mode of Administration: ADA: SC injections self-administered by subjects via pens.
  MTX: Oral administration.

Duration of Treatment: Subjects were advised to self-administer ADA eow starting at the Baseline visit (Week 0) through Week 24; last injection was at Week 22.

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:
Not applicable.

Criteria for Evaluation

Efficacy:

Primary efficacy variables:

- Based on Investigator assessment, the proportion of subjects (primary and secondary sub-optimal responders at Baseline) achieving a satisfactory response to ADA + MTX treatment after 16 weeks (satisfactory response defined as highly or completely satisfied with subject's therapy based on responses to the satisfaction questionnaire);
- Based on subject self-assessment, the proportion of subjects (primary and secondary sub-optimal responders at Baseline) achieving a satisfactory response to ADA + MTX treatment after 16 weeks (satisfactory response defined as highly or completely satisfied with therapy based on responses to the satisfaction questionnaire).

Secondary efficacy variables:

- Based on Investigator assessment, the proportion of subjects achieving a satisfactory response at scheduled visits other than Week 16 (Not in the protocol; added to the statistical analysis plan [SAP])
- Based on subject self-assessment, the proportion of subjects achieving a satisfactory response at scheduled visits other than Week 16 (Not in the protocol; added to the SAP)
- Proportion of subjects achieving PASI 50/75/90/100 at all scheduled visits
- Change and percent change from Baseline in PASI at all scheduled visits (Not in the protocol; added to the SAP)
- Proportion of subjects achieving a clinical response defined as a PGA of "Clear" or "Minimal" at all scheduled visits
- Change and percent change from Baseline in DLQI at all scheduled visits
- Based on Investigator assessment, the proportion of subjects at each of the five categories of satisfaction at all scheduled visits
- Based on subject self-assessment, the proportion of subjects at each of the five categories of satisfaction at all scheduled visits
- Proportion of subjects achieving a DLQI score of 0 or 1 at all scheduled visits.
- Change and percent change from Baseline in body surface area (BSA) at all scheduled visits (Not in the protocol; added to the SAP)
- Change from Baseline in highly sensitive C-reactive protein (hs-CRP) at all scheduled visits (Not in the protocol; added to the SAP)

Efficacy Subgroup Analyses:

PASI 50/75/90/100 endpoints were also analyzed in the following subgroup: Subjects on ADA 40 mg eow prior to Baseline or 40 mg once weekly prior to wash-out.

Safety:

Safety analyses were performed on all subjects who received at least one dose of ADA and MTX. Incidence of adverse events (AEs) and changes in vital signs, physical examination results, and clinical laboratory tests (hematology, chemistry and urinalysis) were assessed.

Statistical Methods

The primary objective of the statistical analyses was to determine the proportion of subjects with Ps who had a satisfactory response to ADA + MTX treatment, based on a self-assessment by subjects and an assessment by the treating Investigator. Secondary objectives included an evaluation of the efficacy of ADA + MTX in subjects with Ps and characterization of the possible relationship between serum levels of ADA and efficacy outcomes. The impact of MTX on ADA serum levels were also assessed by defining the change in serum ADA from Baseline following the addition of MTX to therapy. Safety of ADA + MTX was also assessed.

Efficacy:

The primary and secondary efficacy analyses were conducted on the ITT population. The primary efficacy analyses were also conducted for the following sub-populations:

- Subjects defined as primary sub-optimal responders at Baseline, based on Investigator assessment;
- Subjects defined as secondary sub-optimal responders at Baseline, based on Investigator assessment.

Missing data were imputed using the following methods for the efficacy analyses:

- Non-Responder Imputation (NRI): The NRI analysis categorized any subject who has missing value at a specific visit as non-responder (or "dissatisfied" in satisfaction variables) for that visit. NRI was the primary approach in analyses of categorical variables.
- Mixed-effect Model Repeat Measurement (MMRM): A mixed-effect model was developed for continuous endpoint repeated measured at Baseline, Week 8, 16, and 24; controlling for time and subject ID. The fixed effects were used to report the visit means at corresponding visits. Change and percent change from baseline were determined accordingly. MMRM was the primary approach in analyses of continuous variables.
- Last Observation Carried Forward (LOCF): The LOCF analyses used the completed evaluation from the previous visit to impute missing data at later visits. Baseline efficacy evaluations were not carried forward. LOCF was a sensitivity approach in analyses of continuous variables and categorical variables.

Pharmacokinetic:

ADA serum concentrations were summarized at each time point using descriptive statistics including number of subjects, number of non-missing observations, mean, median, standard deviation, coefficient of variation (CV), minimum and maximum as appropriate. Mean and median concentration versus time plots was generated. Data were assessed for the following subgroups:

- Total recruited subjects;
- Subjects defined as primary sub-optimal responders at Baseline, based on Investigator assessment;
- Subjects defined as secondary sub-optimal responders at Baseline, based on Investigator assessment

To further characterize the relationship between ADA serum levels and treatment response, subjects were classified as non-responders (< 50% improvement in PASI from Baseline (Baseline defined as addition of MTX to ADA therapy); moderate responders ($\geq$ 50% to < 75% improvement in PASI from Baseline) or good responders ($\geq$ 75% improvement in PASI from Baseline) at 8, 16, and 24 weeks. At each visit, median ADA serum levels were evaluated by group and compared between groups.

In addition, exploratory analysis to determine possible associations between MTX dose and ADA serum levels was carried out.

Statistical Methods (Continued)

Safety:

All AEs, serious adverse events (SAEs), and AEs leading to discontinuation were collected during the study and up to 70 days after the last dose of ADA. Safety analyses were carried out using the Safety Population. A treatment- emergent AE was defined as an event with onset or worsening after the first dose of study drugs (ADA + MTX) and within 70 days after the last dose of ADA. The number and percent of subjects experiencing treatment-emergent AEs were tabulated using the Medical Dictionary for Drug Regulatory Activities (MedDRA®, Version 19.1) system organ class and preferred term. Summaries (including percentages and event per 100 patient-years) of SAEs, deaths, and AEs leading to discontinuation from the study were provided as well.

Summary/Conclusions

Efficacy Results:

Forty-six subjects were included in the ITT population (6 subjects were primary sub-optimal responders, and 40 subjects were secondary sub-optimal responders). The majority of subjects in the study were male (4 [66.7%] subjects in the primary sub-optimal group and 31 [77.5%] subjects in the secondary sub-optimal group), White (4 [66.7%] subjects in the primary sub-optimal group and 31 [77.5%] subjects in the secondary sub-optimal group), and all but 1 (2.5%) subject in the secondary sub-optimal group were non-Hispanic or Latino. The mean age (± standard deviation [SD]) was 41.0 ± 13.84 years (range: 20 – 62 years) in the primary sub-optimal group and 47.3 ± 11.91 years (range: 24 – 68 years) in the secondary sub-optimal group. A large proportion of subjects had a BMI ≥ 30 (3 [50.0%] subjects in the primary sub-optimal group and 24 [60.0%] subjects in the secondary sub-optimal group).

The median duration of Ps was 19.920 years (range: 5.83 – 32.79 years) in the primary sub-optimal group and 20.665 years (range: 4.92 – 42.97 years) in the secondary sub-optimal group. Most subjects did not have PsA: 1 subject from the primary sub-optimal group with PsA duration of 8.830 years and 17 subjects from the secondary sub-optimal group with median PsA duration of 10.650 years (range: 0.81 – 38.65 years). Approximately half of the subjects had family history of Ps (3 [50.0%] subjects in the primary sub-optimal group and 22 [55.0%] subjects in the secondary sub-optimal group).

Other disease characteristics at Baseline are summarized below:

- PASI (mean ± SD): 10.1 ± 3.84 in the primary sub-optimal group and 10.5 ± 5.17 in the secondary sub-optimal group
- PGA-S (mean ± SD): All subjects in the primary sub-optimal group had a PGA-S of 4.0, and the mean in the in the secondary sub-optimal group was 4.3 ± 0.51
- BSA (mean ± SD): 11.0 ± 5.62 in the primary sub-optimal group and 11.3 ± 11.78 in the secondary sub-optimal group

At baseline, the mean DLQI was 11.5 ± 5.86 (range: 4.0 – 18.0) in the primary sub-optimal group and 9.6 ± 7.37 (range: 0.0 – 30.0) in the secondary sub-optimal group. The mean hs-CRP was 4.0 ± 5.19 (range: 0.5 – 14.3) in the primary sub-optimal group and 5.0 ± 8.20 (range: 0.2 – 44.6) in the secondary sub-optimal group.

Summary/Conclusions (Continued)

Efficacy Results (Continued)

For the primary endpoints, based on the investigator assessment, 33.3% (2/6) of subjects from the primary sub-optimal group and 52.5% (21/40) of subjects from the secondary sub-optimal group achieved a satisfactory response at Week 16. Similar response rates were observed based on the subject self-assessment – 16.7% (1/6) of subjects from the primary sub-optimal group and 52.5% (21/40) of subjects from the secondary sub-optimal group, respectively.

Meaningful results related to the secondary efficacy endpoints are summarized as follows:

- The proportion of subjects achieving a satisfactory response continued to increase after Week 16 in the secondary sub-optimal group. At Week 24, 60% (24/40) of subjects achieved a satisfactory response, based on both the Investigator assessment and the subject self-assessment. The response rate in the primary sub-optimal group maintained at Week 24.
- At Week 24, 66.7% of subjects in the primary sub-optimal group and 65.0% of subjects in the secondary sub-optimal group reached a PASI 50. A PASI 75 was reached by 16.7% of subjects in the primary sub-optimal group and 42.5% of subjects in the secondary sub-optimal group. A proportion of 16.7% of subjects in the primary sub-optimal group and 30.0% of subjects in the secondary sub-optimal group reached a PASI 90. A proportion of 16.7% of subjects in the primary sub-optimal group and 27.5% of subjects in the secondary sub-optimal group reached a PASI 100.
- Overall, PASI scores improved at each visit; the change from Baseline (Least squares means [LS means] ± SE) decreased from –4.6 (± 2.07) to –3.1 (± 3.17) in the primary sub-optimal group, and increased from –4.6 (± 0.65) to –6.3 (± 0.68) in the secondary sub-optimal group, from Week 8 to Week 24.
- A proportion of 16.7% (1/6) of subjects in the primary sub-optimal group achieved a clinical response defined as a PGA of "clear" or "minimal" over the 24-week period. In the secondary sub-optimal group, the proportion increased from 27.5% (11/40) of subjects at Week 8 to 47.5% (19/40) of subjects at Week 24.
- From Week 8 to Week 24, the change from Baseline (LS means ± SE) in DLQI score decreased in the primary sub-optimal group, from –5.0 (± 1.40) to –1.7 (± 4.29), and it increased in the secondary sub-optimal group, from –4.8 (± 0.71) to –6.3 (± 0.69).
- A proportion of 16.7% (1/6) of subjects in the primary sub-optimal group achieved a DLQI score of 0 or 1 over the 24-week period. In the secondary sub-optimal group, the proportion increased from 7.5% (3/40) of subjects at Baseline to 40.0% (16/40) of subjects at Week 16 and Week 24.
- Overall, the changes from Baseline (LS means ± SE) in BSA increased from Week 8 to Week 16 and slightly decreased from Week 16 to Week 24 in the primary sub-optimal group and in the secondary sub-optimal group.
- The change from Baseline (LS means ± SE) in hs-CRP at Week 24 was –2.6 ± 0.47 for the primary sub-optimal group and 0.1 ± 1.52 for the secondary sub-optimal group.

Examining subgroups, in the ADA 40 mg once weekly prior to wash-out subgroup, the proportion of subjects achieving a response were 67% in PASI 50 and in PASI 75, and 0% in PASI 90 and 100. In the ADA 40 mg eow prior to Baseline subgroup, the proportion was 61% at PASI 50 and 12% at PASI 100.

Of note, findings among the primary sub-optimal group should be interpreted with caution due to the limited number of subjects (N = 6).

Summary/Conclusions (Continued)

Pharmacokinetic Results:

Mean serum ADA concentrations for all subjects were at steady-state of approximately 4 µg/mL, for the whole study.

Secondary sub-optimal responder achieved a higher mean serum ADA concentration than the primary sub-optimal responder over the whole study.

Subjects with investigator/subject satisfaction assessment at Week 16 had higher mean serum ADA concentrations during the study than those that did not achieve investigator/subject satisfaction assessment.

Mean serum ADA concentrations were higher in subjects who were PGA responders than those non-responders from Week 8 to Week 24.

Mean serum ADA concentrations were higher in subjects who achieved PASI 50, 75, 90 and 100 than those who didn't from Week 8 to Week 24.

DLQI responders had higher mean serum ADA concentrations compared to non-responders from Baseline to Week 24.

Safety Results:

The median duration of exposure to ADA was 168.0 days (range: 14.0 – 171.0 days), and the median duration of exposure to MTX was 168.0 days (range: 7.0 – 175.0 days).

Overall, the mean treatment compliance was high across the entire study period, at 97.7% and 97.4% for ADA and MTX, respectively.

No deaths were reported during the study.

Twenty-seven (58.7%) subjects experienced at least one treatment-emergent adverse events (TEAEs) during the study period. Four SAEs were reported by 1 (2.2%) subject: cardiac arrest, generalized tonic-clonic seizure, loss of consciousness, and hypercapnia. All SAEs were considered by the Investigator to be not reasonably possibly related to either ADA or MTX. One (2.2%) subject experienced polymyalgia rheumatica, a TEAE of special interest, that led to study discontinuation. This TEAE was considered by the Investigator to be not reasonably possibly related to either ADA or MTX.

Of the 20 (43.5%) subjects reporting at least one infectious AE, 2 (4.3%) subjects experienced infectious AEs that were considered by the Investigator to be reasonably possibly related to ADA (one subject experienced a moderate nasopharyngitis, a mild urinary tract infection, and a mild sinusitis; and 1 subject experienced a mild nasopharyngitis), 8 (17.4%) subjects experienced moderate infectious AEs, and no subjects experienced serious infectious AEs.

Of all the TEAEs of special interest assessed in this study, there were no reports of the following: legionella infection, diverticulitis, opportunistic infection, excluding an oral candidiasis and TB, oral candidiasis, TB either active or latent, parasitic infection, reactivation of hepatitis B, progressive multifocal leukoencephalopathy, malignancy, lymphoma, hepatosplenic T-Cell lymphoma, non-melanoma skin cancer, melanoma, leukaemia, malignancy other than lymphoma, hepatosplenic T-cell lymphoma (HSTCL), leukaemia, non-melanoma skin cancer (NMSC), or melanoma, allergic reaction including angioedema/anaphylaxis, lupus-like reactions and systemic lupus erythematosus, cutaneous vasculitis, sarcoidosis, autoimmune hepatitis, myocardial infarction, cerebrovascular accident, congestive heart failure, pulmonary embolism, interstitial lung disease, intestinal perforation,

Summary/Conclusions (Continued)

Safety Results (Continued):

pancreatitis, Stevens-Johnson syndrome, erythema multiforme, worsening/new onset of Ps, demyelinating disorder, amyotrophic lateral sclerosis, reversible posterior leukoencephalopathy syndrome, hematologic disorders including pancytopenia, liver failure or another liver event, Humira-administration-related medication error, or injection site reactions.

Mean change from Baseline to each study visits in hematology, chemistry, and urinalysis laboratory variables was clinically unremarkable. No subjects met criteria for potentially clinically significant hematology values during the study. Potentially clinically significant chemistry values were observed for: glucose (hyperglycemia) (4 subjects; note: one subject was prematurely discontinued), uric acid (hyperuricemia) (1 subject), and triglycerides (hypertriglyceridemia) (1 subject). These values were reviewed and analyzed, and none of those have been clinically significant during the study duration.

Conclusions:

Responding to the primary objective of this study, it was observed that the proportion of primary and secondary sub-optimal responders to ADA monotherapy with a PGA ≥ 3 and a PASI ≥ 5 who have a satisfactory response after 16 weeks of treatment with ADA/MTX combination therapy, based on Investigator and subject satisfaction assessments, was approximately 50% in the secondary sub-optimal group for both assessments at Week 16. In the primary sub-optimal group, the satisfaction assessments varied between 17% and 33%, respectively for the subject self-assessment and the Investigator assessment. The number of subject in the primary sub-optimal group was too low (N = 6) to make clinically meaningful conclusions among this group.

Overall, findings from this study suggest that a combination therapy with ADA and MTX in subjects with Ps who have failed to achieve an optimal response to initial ADA therapy or have not maintained an initial positive response to treatment is safe and effective.

While efficacy was noticeable at Week 8, the endpoints used in this study – including subject satisfaction with therapy as a primary endpoint in order to incorporate the patient-centered approach in alignment with the most recent Canadian Ps treatment guidelines – showed a continued improvement at Week 16 and Week 24, suggesting a continuous benefit of the combination therapy with time. As such at Week 24 in the secondary sub-optimal group, both the Investigators and the subjects assessed that a proportion of 60% of subjects were satisfied with therapy, and the PASI 90 and PASI 100 reached approximately 30% of subjects, which are comparable to results from the CHAMPION Study.

No new safety signals were detected during the study. The compliance with both ADA and MTX was approximately of 97% during the study. A proportion of 89% continued a treatment with ADA after the study and 61% continued with the combination therapy with ADA and MTX.