

## 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> D2E7	<b>Page:</b>	
<b>Title of Studies:</b> <u>Study M13-390:</u> Study to Assess Pharmacokinetic, Pharmacodynamic, Safety and Immunogenicity of a New Adalimumab Formulation in Subjects with Active Rheumatoid Arthritis (RA) <u>Study M13-692:</u> A Phase 2b, Multicenter, Open-Label Study in Rheumatoid Arthritis Subjects Who Completed Preceding Study M13-390 with Adalimumab		
<b>Coordination Investigator:</b> Marilú Colón-Soto, MD		
<b>Study Sites:</b> 21 sites in US, Puerto Rico and Europe		
<b>Publications:</b> None		
<b>Studied Period (Years):</b> First Subject First Visit: 02 May 2012 (Study M13-390) 17 December 2012 (Study M13-692) Last Subject Last Visit: 17 May 2013 (Study M13-390) 22 October 2013 (Study M13-692)		<b>Phase of Development:</b> 2b
<b>Objectives:</b> <u>Study M13-390:</u> The study objectives were to compare the new adalimumab formulation ( ) to the currently marketed adalimumab formulation (50 mg/mL) in a dosing regimen of 40 mg every other week (eow) for 24 weeks, with respect to the following parameters: <ul style="list-style-type: none"> <li>• Pharmacokinetics following multiple dosing</li> <li>• Pharmacodynamic variables (Disease Activity Score 28 [DAS28] [C-Reactive Protein (CRP)] and American College of Rheumatology [ACR] 20/50 responder rates) at Weeks 12 and 24</li> <li>• Physical function at Weeks 12 and 24, using Health Assessment Questionnaire-Disability Index (HAQ-DI)</li> <li>• Health Survey assessment at Weeks 12 and 24 using Short Form-36 questionnaire</li> <li>• Immunogenicity following multiple dosing</li> <li>• Safety and tolerability over 24 weeks</li> </ul> <u>Study M13-692:</u> The study objective was to further assess the safety, tolerability, efficacy and immunogenicity of the new adalimumab formulation ( ).		

**Methodology:**

Study M13-390:

This was a 24-week multicenter, randomized, double-blind, double dummy study with a parallel group design to assess pharmacokinetics, pharmacodynamics, safety and immunogenicity of the new adalimumab formulation (██████████) compared to the currently marketed formulation (50 mg/mL) in subjects with active RA. The study targeted 100 adult male and female subjects who fulfilled the study eligibility requirements within 21 sites in North America and Europe. Subjects from each dosing regimen were to receive 12 subcutaneous (sc; eow dosing for 24 weeks) injections of adalimumab 40 mg by a pre-filled syringe in parallel with a placebo injection (double dummy technique). Qualifying study subjects were randomized in a 1:1 ratio to the two treatment groups with stratification by concomitant use of MTX (with or without). At least 40%, but no more than 60% of the subjects were to have concomitant MTX. Within each stratum (with or without MTX), subjects were randomly assigned to the two formulation groups in approximately equal numbers.

Study drug was administered at the site at Weeks 0, 4, 8, 10, 12, 16, and 20. Study drug was administered at home at Weeks 2, 6, 14, 18, and 22. No study drug was administered at the final visit (Week 24 or Premature Discontinuation Visit).

Blood samples for adalimumab analysis were collected by venipuncture at Weeks 0, 4, 8, 10, 12, 16 and 20 prior to injection and also at Week 10 + 3 days, Week 11 and Week 11 + 3 days, and also at Week 24 or upon subject discontinuation. Blood samples for anti-adalimumab assay (AAA) were collected by venipuncture at Weeks 0, 4, 8, 12, 16, and 20 prior to injection and also at Week 24 or upon discontinuation.

Study M13-692:

This was an open-label study to further assess the safety, tolerability, efficacy and immunogenicity of the new adalimumab formulation (██████████) in subjects with RA who had completed in the previous adalimumab Study M13-390. The study enrolled 88 adult male and female subjects at 20 sites in North America and Europe who completed Study M13-390 and fulfilled the study eligibility requirements. Subjects were evaluated for entry into this study at the final visit (Week 24) of Study M13-390, which was the Week 0 (Day 1) visit for open-label extension (OLE) Study M13-692 (henceforth referred as Weeks 24 through 48). Subjects were to receive 12 subcutaneous (sc) injections (eow dosing for 24 weeks) of the new adalimumab formulation (██████████) via a pre-filled syringe.

Study drug was administered at the site at Weeks 24 and 36. Study drug was administered at home at Weeks 26, 28, 30, 32, 34, 38, 40, 42, 44, and 46. No study drug was administered at the final visit (Week 48 or Premature Discontinuation Visit).

Blood samples for adalimumab analysis and AAA assay were collected by venipuncture prior to injection at Weeks 24, 36, and 48 or upon subject discontinuation.

Study M13-390 and Study M13-692:

Adalimumab concentrations in serum were determined using a validated enzyme-linked immunosorbent assay (ELISA) method. The lower limit of quantitation (LLOQ) for adalimumab in serum was ██████████. Serum samples were analyzed for screening and confirmatory AAA assay using a validated double antigen immunoassay. The LLOQ for AAA in serum was ██████████.

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

Study M13-390: Planned: 100; Enrolled: 100; Analyzed: 100

Study M13-692: Enrolled: 88; Analyzed: 88

**Diagnosis and Main Criteria for Inclusion:**

1. Male or female subject, 18 years or older who had a diagnosis of RA as defined by the 1987-revised ACR-classification criteria or the new ACR/European League Against Rheumatism (EULAR) diagnostic criteria for RA 2010-classification criteria and had a disease duration for a minimum of 3 months.
2. Subject was naïve to biologic therapy.
3. Subject met the following criteria for the joint assessment:
  - At least 6 swollen joints out of 66 assessed;
  - At least 6 tender joints out of 68 assessed.
4. If a subject was on MTX, the doses were to be stable for at least 4 weeks prior to Screening and follow standard recommendations for MTX treatment (i.e., according to the packaging insert). The subject was to continue with the same dose of MTX throughout the study.
5. Prior DMARD therapy:
  - Subjects not on MTX at baseline remained without MTX throughout the study. Subjects on prior MTX discontinued at least 28 days prior to Week 0 (Day 1);
  - Subjects on DMARD therapy other than MTX (except prednisone/prednisolone 10 mg) discontinued it for at least 28 days before the first dose of investigational product at Week 0 (Day 1).

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

Study M13-390:

	<b>Regimen A (Test)</b>	<b>Regimen B (Reference)</b>	<b>Placebo for Regimen A</b>	<b>Placebo for Regimen B</b>
	<b>New Formulation</b>	<b>Currently Marketed Formulation</b>	<b>Placebo for New Formulation</b>	<b>Placebo for Currently Marketed Formulation</b>
	<b>██████████ in PFS</b>	<b>50 mg/mL in PFS</b>	<b>Formulation in PFS</b>	<b>Formulation in PFS</b>
Strength	██████████ PFS	40 mg/0.8 mL PFS	0 mg/██████████ PFS	0 mg/0.8 mL PFS

Study M13-692:

	<b>New Adalimumab Formulation (██████████) in PFS</b>
Strength	██████████

PFS = pre-filled syringe

**Duration of Treatment:**

Study M13-390: 24 weeks; Study M13-692: 24 weeks

### **Criteria for Evaluation**

#### **Efficacy:**

The pharmacodynamic variables assessed as efficacy are listed below.

#### Study M13-390:

- Change from baseline in disease activity score [DAS28 (CRP)] at Weeks 12 and 24.
- Response defined by ACR 20/50/70/90/100 criteria at Weeks 12 and 24.
- Change in HAQ-DI and the percentage of subjects with HAQ improvements at or exceeding the clinically minimal important difference at Weeks 12 and 24.
- Change in Short Form-36 Health questionnaire at Weeks 12 and 24 from baseline in Physical Component Summary score and Mental Component Summary score.

#### Study M13-692:

- Change from Baseline in DAS28-CRP at Weeks 36 and 48 with Baseline being Study M13-390 Week 0 visit.
- Response defined by American College of Rheumatology (ACR) 20/50/70/90/100 criteria at Weeks 36 and 48 with Baseline being Study M13-390 Week 0 visit.
- Change from Baseline in HAQ-DI score and the percentage of subjects with HAQ improvements at or exceeding the clinically minimal important difference at Weeks 36 and 48 with Baseline being Study M13-390 Week 0 visit.

#### **Pharmacokinetic:**

Summary statistics for adalimumab serum concentration at each time of scheduled sampling were calculated.

#### **Safety:**

The following safety evaluations were performed during the study: adverse event monitoring and vital signs, physical examination, ECG and laboratory tests assessments. In addition, injection site-related pain immediately after the injection was evaluated for the first dose of study drug.

### **Statistical Methods**

#### **Efficacy (Pharmacodynamics):**

Subjects who were administered at least one adalimumab dose were included for the analysis.

#### Study M13-390:

##### *1. DAS28-CRP:*

Descriptive statistics were provided for each scheduled time of measurement after randomization with a breakdown by formulation and MTX use (whether or not included in the therapy). The descriptive statistics were given for the Baseline values, the data at the given time during study drug treatment and for the change from Baseline. For Weeks 12 and 24, the descriptive statistics were given with and without imputation of missing values by the last observation carried forward (LOCF) method.

The difference in means between the two formulations at Weeks 12 and 24 were estimated in the framework of a 2-way analysis of covariance with classification by formulation and MTX use, using the Baseline measure as a covariate and including an effect for the interaction between formulation and MTX use. For subjects that prematurely discontinued before the Week 12 and Week 24 assessment, a replacement for missing values was given by using the last observation obtained from the subject.

**Statistical Methods (Continued)**

**Efficacy (Pharmacodynamics) (Continued):**

Study M13-390 (Continued):

A secondary repeated measures analysis was also performed across the scheduled times of measurement in Study M13-390, with observations classified by formulation, MTX use, and time of measurement, with effects for all potential 2-way interactions between the 3 factors. An appropriate structure was selected for the covariance matrix for the observations from a subject.

*2. ACR20 and Other ACR Definitions of Response*

For each of ACR20, ACR50, ACR70, ACR90 and ACR100, the percentage of subjects who were responders was reported for each scheduled time of assessment with a breakdown by formulation and by MTX class (whether or not included in the therapy). For subjects that prematurely discontinued, for all times of assessment after the termination, the subject was counted as a non-responder. A secondary analysis was performed in which only actual assessments were included (no imputation).

*3. HAQ-DI and Short Form-36 Health Questionnaires*

The methodology described for DAS28-CRP was used for HAQ-DI and SF-36 variables. Also, the percentage of subjects with HAQ-DI improvements at or exceeding the minimal clinically important difference (defined as HAQ-DI change from Baseline of  $-0.22$  and widely adopted by internal and external clinical trials in RA) was tabulated by formulation and by MTX use (whether or not included in the therapy).

Study M13-692:

*1. DAS28 (CRP):*

Summary statistics were provided for each scheduled time of assessment (Week 36 and Week 48 or premature discontinuation). For reference, the summary statistics were also provided for the Week 24 visit (Week 0 [Day 1] for Study M13-692). Summary statistics were provided for both the value itself and for the change from the Baseline value. The Baseline value was the last measurement obtained prior to the first dose of Study M13-390 (intended to be the value on Day 1 in Study M13 390). Descriptive statistics were provided with a breakdown jointly by adalimumab formulation in Study M13-390 and by MTX use. MTX use was defined as whether MTX was included in the subject's therapy for at least 2 weeks.

*2. ACR20 and Other ACR Definitions of Response*

For ACR20 and each of the other ACR response definitions, the percentage of responders was reported for Week 24, Week 36, Week 48 and the Final Visit (Week 48 or premature discontinuation). The Baseline value for these determinations was the same as for Study M13-390.

*3. HAQ-DI and Short Form-36 Health Questionnaires*

For HAQ-DI, descriptive statistics were provided as for DAS28-CRP. Percentage of subjects with a HAQ-DI improvement at or exceeding the minimal clinically important difference was reported as for ACR20.

**Statistical Methods (Continued)**

**Pharmacokinetic:**

Study M13-390:

For each scheduled time of measurement, summary statistics were provided for the adalimumab serum concentration data by formulation (new or current) and by MTX use (whether or not included in the therapy).

The percentage of subjects positive for AAA (AAA+) in Study M13-390 was reported by formulation and by whether MTX was included in the therapy. Serum samples were considered to be AAA+ if the following criteria were met: the measured AAA concentration was > 20 ng/mL and confirmed by confirmatory assay; and the serum sample was collected within 30 days after an adalimumab dose.

Study M13-692:

Summary statistics were provided for the adalimumab serum concentration data at each scheduled time of measurement including Week 24 (Week 0 [Day 1] of Study M13-692), which was also the last time of measurement in Study M13-390. For each time, the summary statistics were provided in a 2-way classification by adalimumab formulation in Study M13-390 and by MTX use. MTX use was defined by whether MTX was included in the subject's therapy for at least 2 weeks. In addition to providing summary statistics in a 2-way classification by MTX use and the formulation assigned in Study M13-390 for adalimumab trough concentrations at Weeks 24, 36 and 48 in Study M13-692, summary statistics were also presented for adalimumab trough concentrations during Study M13-390 for all subjects (N = 88) enrolled in OLE Study M13-692.

The percentage of subjects with AAA+ results in Study M13-692 was reported in a fashion parallel to that of the summary statistics for adalimumab serum concentration. In addition to these percentages for the individual visits of Study M13-692, the percentage of AAA+ subjects at any time throughout Study M13-390 and the OLE Study M13-692 were reported. Immunogenicity was reported as a 2-way classification of subjects by the adalimumab formulation used in Study M13-390 and by MTX use. There were three MTX classes: MTX in the Study M13-390 therapy; no MTX in the therapy during Study M13-390 and the OLE Study M13-692; and no MTX in the therapy of Study M13-390, but added during this study. No subjects receiving monotherapy in Study M13-390 had MTX added to the therapy in OLE Study M13-692, although one subject had MTX withdrawn at the beginning of OLE Study M13-692. Therefore, MTX use was defined by whether a subject was on MTX for at least 2 weeks in Study M13-692.

**Statistical Methods (Continued)**

**Safety:**

Study M13-390:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by MedDRA preferred term and system organ class with a breakdown by formulation (new and currently marketed) and by MTX class (whether or not included in the therapy). Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA term) was additionally broken down by rating (mild, moderate or severe) and by degree of relationship to study drug. Serious adverse events (SAEs) were summarized as appropriate.

Laboratory test values and measurements of vital signs that were potentially clinically significant according to predefined criteria were identified. Descriptive statistics were provided for changes from Baseline of continuous laboratory variables and of vital signs for each scheduled time of assessment with a breakdown by formulation (new or currently marketed formulations) and by MTX use. The Baseline mean and visit mean were provided with the descriptive statistics for change from Baseline.

Descriptive statistics were provided for the data from the Patient's Injection Site-Related Pain VAS assessment. Note that each subject provided two assessments: one for the assigned active formulation injection and a second for the placebo injection of the other formulation. Descriptive statistics were provided separately for the four kinds of injections: the two active adalimumab formulations (new or currently marketed) and the two placebos. A 2-way analysis of variance was performed on the data for the active formulation injections with classification by formulation and by whether MTX was included in the therapy. The model included only main effects for these two factors.

Study M13-692:

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). There were two summaries of adverse events. The first was a summary of treatment-emergent adverse events only for the 24-week OLE Study M13-692. A second summary was provided, that included safety data from Study M13-390 for the subjects (N = 88) who were enrolled in Study M13-692, but included data from the complete 48-week exposure to study drug throughout Study M13-390 and OLE Study M13-692.

In the first summary of adverse events, the number and percentage of subjects reporting treatment-emergent adverse events were tabulated by MedDRA preferred term and system organ class with a breakdown by MTX use (whether or not included in the therapy during this study for at least 2 weeks). Tabulations were also provided in which the number of subjects reporting an adverse event (MedDRA term) was additionally broken down by rating (mild, moderate or severe) and by whether judged possibly related to study drug. Serious adverse events (SAEs) were summarized as appropriate.

The second summary of adverse events was like the first except that the tabulations were provided with a 2-way breakdown by the adalimumab formulation used in Study M13-390 and MTX use. MTX use was defined by whether or not MTX was included in the therapy for at least 2 weeks at any time after the first dose of Study M13-390.

## Statistical Methods (Continued)

### Safety (Continued):

Laboratory test values and measurements of vital signs that were potentially clinically significant according to predefined criteria were identified. Descriptive statistics were provided for changes from Baseline of continuous laboratory variables and of vital signs for each scheduled time of assessment (Week 36 and Week 48 or premature discontinuation). For reference, the descriptive statistics were provided for Week 24, (Week 0 [Day 1] of Study M13-692). The Baseline value was the last measurement obtained prior to the first dose of Study M13-390 (intended to be the value on Day 1 in Study M13-390).

## Summary/Conclusions

### Efficacy Results:

#### Study M13-390:

DAS28-CRP values were not statistically significantly different ( $p > 0.516$ ) between the new formulation and the currently marketed formulation at Week 12 or Week 24, for both observed and LOCF analyses. Similar results were observed for the visits at Weeks 4, 8, 16 and 20 with the DAS28-CRP values not statistically significantly different ( $p = 0.091$ ) between the two formulations. When stratifying by concomitant MTX use, changes in DAS28-CRP between the two formulations were statistically significantly different for the populations with and without MTX (interaction p-value 0.004) at Week 12.

- Without MTX: The DAS28-CRP was significantly lower for the new formulation ( $p = 0.040$ ) compared to the currently marketed formulation, at Week 12.
- With MTX: The DAS28-CRP was significantly higher for the new formulation ( $p = 0.040$ ) compared to the currently marketed formulation at Week 12.

However, at Week 24, the DAS28-CRP values were not statistically significantly different between the new and currently marketed formulations, regardless of MTX use ( $p = 0.329$ ).

Similarly, the DAS28-CRP values stratified by MTX use were not statistically significantly different between the two formulations ( $p = 0.103$ ) for the visits at Weeks 4, 8, 16 and 20 with the exception of the Week 16 without MTX group comparison ( $p = 0.028$ ).

The ACR20/50/70 responses appeared to be similar between the new formulation and the currently marketed formulation at Week 12 and Week 24. Similarly, the ACR20/50/70 responses appeared to be comparable between the new and currently marketed formulations when accounting for MTX use.

#### Study M13-692:

The mean change from Baseline in DAS28-CRP values at Week 36 and Week 48 in OLE Study M13-692 was similar for subjects who received the new formulation or the currently marketed formulation in Study M13-390. Similarly, the mean change from Baseline in DAS28-CRP values at Week 36 and Week 48 in OLE Study M13-692 was similar for subjects who received the new formulation or the currently marketed formulation in Study M13-390 when stratified by MTX use. At Week 48, there appeared to be a trend towards improved response in the presence of MTX use.

The ACR20/50/70 responses at Week 36 and Week 48 in OLE Study M13-692 appeared to be similar between subjects who received the new formulation and currently marketed formulation in Study M13-390. Similarly, the ACR20/50/70 responses appeared to be comparable in Study M13-692 for subjects who received the new and currently marketed formulations in Study M13-390 when accounting for MTX use.



**Summary/Conclusions (Continued)**

**Other Pharmacodynamic Measures:**

Study M13-390:

HAQ-DI values were not statistically significantly different ( $p = 0.461$ ) between the new formulation and the currently marketed formulation at Week 12 or Week 24 for both LOCF and observed analyses. Similarly, HAQ-DI values were not statistically significantly different ( $p = 0.212$ ) between the new formulation and the currently marketed formulation at Week 12 or Week 24 when accounting for MTX use, for both LOCF and observed analyses. Furthermore, the percentage of subjects with HAQ-DI improvements at or exceeding the minimal clinically important difference (defined as HAQ-DI change from baseline of  $-0.22$ ) also appeared comparable between the two formulations at Weeks 12 or 24, irrespective of concomitant MTX use.

SF-36 (Physical Component) values were not statistically significantly different ( $p = 0.692$ ) between the new formulation and the currently marketed formulation at Week 12 or Week 24, for both LOCF and observed analyses. Similarly, SF-36 (Physical Component) values were not statistically significantly different ( $p = 0.192$ ) between the new formulation and the currently marketed formulation at Week 12 or Week 24 when accounting for MTX use, for both LOCF and observed analyses.

SF-36 (Mental Component) values were not statistically significantly different ( $p = 0.152$ ) between the new and the currently marketed formulations at Week 12 or Week 24, for both LOCF and observed analyses. Similarly, SF-36 (Mental Component) values were not statistically significantly different ( $p = 0.066$ ) between the two formulations at Week 12 or Week 24 when accounting for MTX use, for both LOCF and observed analyses.

The injection site-related pain (ISP), based on VAS scores, was statistically significantly lower for the new formulation compared to the currently marketed formulation ( $p < 0.001$ ), irrespective of concomitant MTX use. Also, the ISP associated with the new active formulation was lower than the ISP for the placebo of the new and currently marketed formulations ( $p = 0.002$ ).

Study M13-692:

The mean change from Baseline in HAQ-DI values at Week 36 and Week 48 in OLE Study M13-692 was similar for subjects who received the new formulation or the currently marketed formulation in Study M13-390. Similarly, the mean change from Baseline in HAQ-DI values at Week 36 and Week 48 in OLE Study M13-692 was similar for subjects who received the new formulation or the currently marketed formulation in Study M13-390 when accounting for MTX use.

### Summary/Conclusions (Continued)

#### Pharmacokinetic Results:

##### Study M13-390:

##### *Pharmacokinetics*

Overall, the mean adalimumab trough concentration values for the new formulation appeared to be similar to the currently marketed formulation. Furthermore, mean adalimumab concentration values appeared to be comparable between the two formulations within the dosing interval starting at Week 10, i.e., at Week 10 + 3 days, Week 11 and Week 11 + 3 days; mean adalimumab concentration values at Week 10 + 3 days (maximum observed concentration) were 7.66 µg/mL and 7.32 µg/mL for the new and currently marketed formulations, respectively.

When stratifying the mean adalimumab concentrations by concomitant MTX use, the concentration values showed some differences between the two formulations.

- Adalimumab Monotherapy: Mean adalimumab trough concentrations for the new formulation appeared to be higher than the currently marketed formulation; mean adalimumab concentrations at Week 24 were 4.97 µg/mL and 2.94 µg/mL for the new and the currently marketed formulation, respectively. The mean adalimumab concentrations within the dosing interval starting at Week 10 were slightly higher for the new formulation; adalimumab concentrations at Week 10 + 3 days were 7.24 µg/mL (new formulation) and 5.51 µg/mL (currently marketed formulation).
- Adalimumab with MTX: In contrast to the monotherapy groups, mean adalimumab concentration values for the new formulation appeared to be slightly lower than the currently marketed formulation; mean adalimumab concentrations at Week 24 were 6.81 µg/mL and 8.24 µg/mL for the new and currently marketed formulation, respectively. Similarly, mean adalimumab concentrations at Week 10 + 3 days appeared to be slightly lower for the new formulation (8.02 µg/mL) compared to currently marketed formulation (9.78 µg/mL).

##### *Immunogenicity*

The AAA+ rate appeared to be comparable between the new formulation (7/50, 14%) and the currently marketed formulation (8/50, 16%). Similar results were observed when stratifying by concomitant MTX use. The AAA+ rate in subjects with MTX also appeared to be similar between new formulation (1/27, 3.7%) and currently marketed formulation (1/29, 3.4%). The AAA+ rate in subjects on adalimumab monotherapy appeared to be similar between new formulation (6/23, 26%) and currently marketed formulation (7/21, 33%), with a difference of one subject between formulations. The AAA+ rates were lower in subjects on concomitant MTX (~3%) than in those not on concomitant MTX (~26% – 33%).

**Summary/Conclusions (Continued)**

**Pharmacokinetic Results:**

Study M13-692:

*Pharmacokinetics*

Results from subjects (N = 88) participating in the OLE Study M13-692 demonstrated that the trends observed in Study M13-390 continued when all subjects received the new formulation (██████████) for an additional 24 weeks. Mean adalimumab trough concentrations in the OLE Study M13-692 were similar to trough concentrations observed in Study M13-390 upon achievement of steady state at approximately Week 12. Differences in adalimumab concentrations observed during Study M13-390 between subjects assigned to the new formulation (██████████) and currently marketed formulation (50 mg/mL) when stratified by MTX use also were observed in OLE Study M13-692 even though all subjects received the new formulation (██████████) in the OLE Study M13-692.

*Immunogenicity*

Ten of the 15 (10/15, 67%) AAA+ subjects in Study M13-390 were enrolled in the OLE Study M13-692. Five AAA- subjects in Study M13-390 became AAA+ in Study M13-692; three subjects were on adalimumab monotherapy (current formulation in Study M13-390), while two were on adalimumab with MTX (new formulation in Study M13-390). One AAA+ subject in Study M13-390 did not meet AAA+ criteria (AAA concentration > 20 ng/mL and confirmed by the confirmatory assay) in Study M13-692, but was considered AAA+ in the combined analysis due to historic criteria of a single AAA+ determination. Throughout the 48-week period of Study M13-390 and OLE Study M13-692, the AAA+ rates were lower in subjects on concomitant MTX (3.4% – 11%) than in subjects on monotherapy (26% – 49%).

**Safety Results:**

Study M13-390 and Study M13-692:

No deaths occurred during the study and no serious infections reported during the study for both studies.

Mean change from Baseline to final value in hematology, chemistry, and urinalysis laboratory parameters was clinically unremarkable for both formulation groups with or without MTX.

The majority of seated systolic and diastolic BP changes were transient and resolved during the study. The mean changes from Baseline in seated systolic and diastolic BP were clinically unremarkable and there was no trend across the groups. There were no significant changes in pulse, respiratory rate, body temperature, body weight or ECG.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

Study M13-390:

A total of 65 subjects (65%) reported at least one AE. Two subjects experienced a SAE, three subjects prematurely discontinued from the study due to an AE, and one subject experienced an event that was considered severe by the investigator. A total of 38 subjects (38%) had AE of infection. There was no trend observed between the formulations. The AEs that were most frequently reported by at least 5% of subjects in any group were nasopharyngitis and upper respiratory tract infection. The proportion of subjects who reported these AEs was similar between the two formulations. There was no obvious trend among the groups to be observed due to small subject numbers with AEs.

A total of 27 subjects reported an AE that was considered by the investigator as having a reasonable possibility of being related to the study drug. There were no trends observed across groups in the types of AEs with reasonable possibility of being related to study drug. The majority of the AEs reported by subjects were considered by the investigator to be mild to moderate in severity. Only one subject reported a severe AE (thoracic vertebral fracture) in the currently marketed formulation group.

Two subjects reported at least one SAE during the study (transitional cell carcinoma and thoracic vertebral fracture due to accidental fall). Both SAEs were considered by the investigator with no reasonable possibility related to the study drug. Three subjects experienced at least one AE that led to discontinuation from study drug (injection site reaction and fever, transitional cell carcinoma and swelling face).

There were 38 subjects that reported at least one treatment-emergent AE of infection with 18 receiving the new formulation and 20 receiving the currently marketed formulation. The two most frequently reported infections related to the study drug were nasopharyngitis and upper respiratory infection.

Of the special interest AEs that were examined, there were no reports of treatment-emergent TB, diverticulitis, HBV, lupus-like syndrome reactions or systemic lupus erythematosus, vasculitis, sarcoidosis, cardiovascular and cerebrovascular events, pulmonary embolism, intestinal perforation; pancreatitis, Stevens-Johnson syndrome and erythema multiforme-related events, worsening and new onset psoriasis, demyelinating disease, amyotrophic lateral sclerosis, leukoencephalopathy, liver failure or other liver events, medication errors or maladministration events during the study.

The special interest AEs were reported by five subjects with injection site reaction, two subjects with hematological disorder-related event, one subject with malignancy, one subject with leukaemia and one subject with allergic reaction. There were no trends across groups in the types of events observed. The incidents were few and scattered among the groups.

There were four subjects who had at least one clinically significant abnormality in their hematology laboratory values, nine subjects who had at least one clinically significant abnormality in their chemistry laboratory values, and 7 subjects who had potentially clinically significant abnormalities in their liver function tests. None of them discontinued the study because of their abnormal hematology or chemistry values.

**Summary/Conclusions (Continued)**

**Safety Results (Continued):**

Study M13-692 (Including Data from Study M13-390):

Eighty-eight (88) subjects entered the OLE Study M13-692 from Study M13-390. The majority of the AEs reported by subjects were considered by the investigator to be mild to moderate in severity. For these 88 subjects, two sets of safety analyses were performed to evaluate the safety data. The first was a summary of treatment-emergent adverse events exclusively during the 24-week OLE Study M13-692. A second summary included data from the complete 48-week exposure to study drug throughout Study M13-390 and OLE Study M13-692 for the 88 subjects that participated in Study M13-692. Only the complete 48-week exposure data are discussed in the text.

A total of 60 subjects (68%, 60/88) reported at least one AE, 23 subjects (26%) reported an AE that was considered by the investigator as having a reasonable possibility of being related to the study drug.

Three subjects experienced a SAE (iron deficiency anemia, osteoarthritis and atrial fibrillation), one subject prematurely discontinued from the study due to an AE, and three subjects experienced an event that was considered severe by the investigator. A total of 37 subjects (42%) had AE of infection. There appeared to be no trend of AEs observed in the different formulation groups. The AEs that were most frequently reported AEs in any group were nasopharyngitis and upper respiratory tract infection.

The special interest AEs were reported by four subjects with injection site reaction, three subjects with hematological disorder-related events, one subject with worsening/new onset of psoriasis, and one subject with allergic reaction.

There were 37 subjects that reported at least one treatment-emergent AE of infection; 18 received the new formulation in Study M13-390 and 19 received the currently marketed formulation in Study M13-390. The two most frequently reported infections related to the study drug were nasopharyngitis and upper respiratory infection.

Three subjects reported at least one SAE during the study (iron deficiency anemia, osteoarthritis and atrial fibrillation). The three serious/severe AEs were considered by the investigator as having no reasonable possibility of being related to the study drug. One subject experienced at least one AE that led to discontinuation from study drug (iron deficiency anemia).

Of the special interest AEs that were examined, there were no reports of treatment-emergent TB, diverticulitis, HBV, malignancy, lupus-like syndrome reactions or systemic lupus erythematosus, vasculitis, sarcoidosis, cardiovascular and cerebrovascular events, pulmonary embolism, interstitial lung disease, intestinal perforation, pancreatitis, Stevens-Johnson syndrome and erythema multiforme-related events, demyelinating disease, amyotrophic lateral sclerosis, leukoencephalopathy, liver failure or other liver events, medication errors or maladministration events during the study.

The special interest AEs were reported by four subjects with injection site reaction, three subjects with hematological disorder-related event, one subject with onset of psoriasis and one subject with allergic reaction. There was no trend across groups in the types of events observed. The incidents were few and scattered among the groups.

There were four subjects who had at least one clinically significant abnormality in their hematology laboratory values, four subjects who had at least one clinically significant abnormality in their chemistry laboratory values, and eight subjects who had potentially clinically significant abnormalities in their liver function tests. None of them discontinued the study because of their abnormal hematology or chemistry values.

**Summary/Conclusions (Continued)**

**Conclusions:**

Study M13-390 was designed to compare the new adalimumab formulation ( ) to the currently marketed adalimumab formulation (50 mg/mL) using a dosing regimen of 40 mg eow for 24 weeks, with respect to pharmacokinetics, efficacy, safety and immunogenicity. PK/PD measures were assessed for an additional 24 weeks in the OLE Study M13-692 in which all subjects received the new formulation ( ). Pharmacokinetics of the two formulations were previously investigated in healthy volunteers in a pilot bioavailability study where the two showed similar bioavailability, and a pivotal bioequivalence study, in which the new formulation met the prespecified bioequivalence criteria compared to the currently marketed formulation.

When examining the effect of the formulation, the results of these studies provided useful comparisons of the PK, PD, and safety of the new adalimumab formulation relative to the currently marketed adalimumab formulation in subjects with RA. Overall, PK, PD, immunogenicity and safety measures were similar for the two formulations. Numerous PD measures were assessed throughout the study (DAS28-CRP, HAQ-DI, SF-36 Physical and Mental Components), with no differences observed between formulations when stratified by MTX use, with no differences observed between formulations when stratified by MTX use, with the exception of a temporary difference in DAS28-CRP values between Weeks 12 and 16. Some differences in adalimumab concentrations were observed between formulations when stratified by MTX use; however, these differences persisted in the OLE Study M13-692 when all subjects received the new formulation. Therefore, the differences observed in the concentrations of adalimumab and Week 12 DAS28-CRP response between the new and currently marketed formulations, when the data was stratified by MTX use, are likely attributed to the relatively small sample size of subjects in each group and to sample selection and random assignment as well as random variation over time, rather than a formulation-related effect.

Adalimumab was generally safe and well tolerated throughout Study M13-390 and OLE Study M13-692 with no obvious trends in AEs among groups.