2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Humira®	**Volume:**	
Name of Active Ingredient: Adalimumab	**Page:**	
Title of Study: A Multicenter, Randomized, Single-Blind Crossover Study of the Safety and Tolerability of Two Adalimumab Formulations in Adult Subjects with Rheumatoid Arthritis		
Investigator: Dr. Johan VanHoof, [redacted] Belgium		
Study Site: Six sites enrolled subjects. Sites were located in Belgium and the Czech Republic.		
Publications: None		
Studied Period (Years): First Subject First Visit: 28 March 2012 Last Subject Last Visit: 09 November 2012	**Phase of Development:** 2	

Objectives:

The primary objective of this study was to compare, immediately after injection, the injection site–related pain profile of a [redacted] adalimumab formulation in the prefilled [redacted] syringe with that of the commercially available adalimumab (HUMIRA®) formulation [redacted]

The secondary objective of this study was to compare the safety and injection site reaction adverse events (AEs) between the 2 formulations.

Methodology:

This was a Phase 2, randomized, single-blind, 2-period, crossover study designed to assess the injection site–related pain, safety, and tolerability of a [redacted] adalimumab formulation in the prefilled [redacted] syringe versus that of commercially available adalimumab in the current prefilled syringe.

Approximately 60 subjects with rheumatoid arthritis (RA) were to be recruited at approximately 6 sites within Belgium and Czech Republic. Subjects were either current on-label users of adalimumab who rated their average injection-site pain (in the last month) as at least 3 cm on a pain visual analogue scale (VAS), and had had at least 6 consecutive doses of adalimumab prior to Screening or were biologic-naïve subjects who required initiation of on-label treatment with adalimumab.

Subjects were randomly assigned in equal numbers to 2 sequences of adalimumab administration (CD and DC) following the schedule of their next 2 planned consecutive doses.

Sequence CD: first dose [redacted] of current adalimumab formulation ("C") in the [redacted] prefilled syringe and second dose [redacted] of [redacted] adalimumab formulation ("D") in the [redacted] syringe.

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Methodology (Continued):

Sequence DC: first dose with [redacted] adalimumab ("D") formulation in the [redacted] syringe and the second dose with [redacted] current adalimumab formulation ("C") in the [redacted] prefilled syringe.

Subjects recorded their subjective assessments of pain associated with the administered adalimumab injections at Visits 1 and 2 using the Short-Form McGill Pain Questionnaire (MPQ-SF) immediately after injection and approximately 15 minutes after each injection. Qualified study site staff recorded their assessments of injection site reactions associated with adalimumab injections at Visits 1 and 2 using the Draize scale approximately 10 minutes after each injection and approximately 30 minutes after each injection.

The end of the study was defined as the date of the last subject's last visit or the actual date of follow-up contact, whichever was later.

Number of Subjects (Planned and Analyzed):

Sixty subjects were planned and 62 subjects were analyzed for injection site-related pain (crossover analyses), 63 subjects were analyzed for other safety analyses.

Diagnosis and Main Criteria for Inclusion:

Subjects were males or females 18 years of age or older, who required adalimumab [redacted] subcutaneously every other week or every week for the treatment of RA, in accordance with the local adalimumab label.

An eligible subject had to be a current, on-label user of adalimumab who rated his or her average adalimumab injection site–related pain (in the last month) as at least 3 cm on a pain VAS and had at least 6 consecutive doses of adalimumab prior to Screening, or a biologic-naïve subject who required initiation of on-label treatment with adalimumab.

Subjects had to be judged to be in good health and had to have a negative tuberculosis (TB) Screening assessment or, if the subject had evidence of a latent tuberculosis infection, the subject had to have initiated and completed a minimum of 2 weeks of anti-TB therapy or have documented completion of a course of anti-TB prior to Baseline.

Test Product:	[redacted] adalimumab [redacted]
Dose:	One dose of [redacted] adalimumab [redacted] in the [redacted] syringe on the subject's on-label adalimumab dosing schedule
Mode of Administration:	Subcutaneous injection
Bulk Lot Number:	09-026087

Duration of Treatment:

Study participation encompassed the time needed for 2 regularly scheduled doses of adalimumab as per the subject's regular on-label dosing schedule (every other week or every week [eow or ew]), as applicable.

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Reference Therapy:	Currently marketed adalimumab [redacted]
Dose:	One dose of the current formulation of adalimumab [redacted] in the current pre-filled syringe on the subject's on-label adalimumab dosing schedule
Mode of Administration:	Subcutaneous injection
Lot Number:	10-001959

Criteria for Evaluation:

Related Pain:

Pain Assessment Module was administered to the subject twice after each injection: immediately following the injection and at approximately 15 minutes following the injection.

Efficacy: Efficacy was not assessed.

Safety/Tolerability:

Safety: Safety was evaluated on the basis of assessment of adverse events, vital signs, physical examinations, and laboratory tests.

Tolerability: Draize scale was completed by a qualified study site staff member for each subject twice after each injection: at approximately 10 minutes and at approximately 30 minutes following the injection.

Statistical Methods:

Efficacy: Efficacy was not assessed.

Safety: The number and percentage of subjects reporting treatment-emergent AEs was tabulated by MedDRA preferred term and system organ class with a breakdown by formulation group. Tabulations were also provided in which the number of subjects reporting an AE is additionally broken down by rating (mild, moderate, or severe) and by degree of relationship to study drug.

Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were defined.

The primary response variable, the injection-related pain measured immediately after injection on a 10-cm VAS scale, was analyzed using a crossover ANOVA model with period, treatment, and sequence as fixed effects and subject as random effect.

Summary/Conclusions

Seventy-one subjects were screened for the study, 64 subjects were randomized, and 63 subjects received at least 1 dose of the study drug at 6 sites in Belgium and the Czech Republic. Twenty subjects were biologic-naïve and 44 subjects were currently on adalimumab treatment. [redacted] who was currently adalimumab user and randomized to CD, received one dose of study drug (current adalimumab) and discontinued because of an adverse event (pharyngitis) and [redacted] who was biologic-naïve and randomized to CD discontinued before receiving any study drug.

Sixty-three subjects received at least 1 dose of adalimumab (ITT population). Sixty-two subjects in the ITT population received study drug treatment in both study periods and, thus, were also included in the crossover ITT (cITT) population. One subject discontinued due to an AE after one dose of study drug (current adalimumab) and was not included in the cITT population.

Summary/Conclusions (Continued)

Efficacy Results:

Efficacy in terms of influence on adalimumab formulations on the underlying RA disease was not assessed in this study. The primary objective of this study was to compare the injection site–related pain profile of a [redacted] adalimumab formulation with the current adalimumab formulation.

Results of the primary and secondary response variables are as follows:

- The mean injection site pain assessment on a VAS (0 to 10 cm) immediately after the dose was significantly lower for [redacted] adalimumab (1.6 cm) than for current adalimumab (3.3 cm), with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of –1.74 cm (95% confidence interval [CI] [–2.33, –1.16], $P < 0.001$). Thus, the primary objective of the study was achieved.
- Fifteen minutes after the dose, the mean injection site pain assessment on VAS (0 to 10 cm) was slightly lower for [redacted] adalimumab (0.9 cm) than for current adalimumab (1.0 cm) with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of –0.09 cm (95% CI [–0.40, 0.23], $P = 0.581$).
- Immediately after the injection, [redacted] adalimumab reduced injection-related pain by 79.2% (median within-subject injection site pain difference) relative to current adalimumab. Fifteen minutes after the injection, the reduction in pain with [redacted] adalimumab was 50.0% (median within-subject percent injection site pain difference) relative to current adalimumab.
- The mean present pain intensity was significantly lower for [redacted] adalimumab than for current adalimumab immediately after the dose (0.7 versus 1.3), with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of –0.60 (95% CI [–0.84, –0.35], $P < 0.001$).
- Fifteen minutes after the dose, the present pain intensity was slightly lower for [redacted] adalimumab than for current adalimumab (0.2 versus 0.3 with a mean within-subject difference of –0.05 (95% CI [–0.22, 0.13], $P = 0.584$).
- The mean sensory dimension score of pain experience from the MPQ-SF was significantly lower for [redacted] adalimumab than for current adalimumab immediately after the dose (2.0 versus 4.0), with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of –2.05 (95% CI [–3.25, –0.85], $P < 0.001$).
- Fifteen minutes after the dose, the sensory dimension score of pain experience was slightly lower for [redacted] adalimumab than for current adalimumab (0.6 versus 0.8 with a mean within-subject difference of –0.13 (95% CI [–0.73, 0.48], $P = 0.671$).
- The mean affective dimension score of pain experience from the MPQ-SF was very similar for [redacted] adalimumab and for current adalimumab both immediately after the dose (0.4 versus 0.3), with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of 0.02 (95% CI [–0.36, 0.39], $P = 0.932$), and 15 minutes after the dose (0.1 versus 0.1), with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of –0.03 (95% CI [–0.24, 0.17], $P = 0.754$).

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Summary/Conclusions (Continued)

Efficacy Results (Continued):

- The mean total score of pain experience from the MPQ-SF was significantly lower for [redacted] adalimumab than for current adalimumab immediately after the dose (2.4 versus 4.4), with a mean within-subject difference of [redacted] adalimumab minus current adalimumab of –2.03 (95% CI [–3.53, –0.54], $P = 0.009$).
- Fifteen minutes after the dose, the total score of pain experience was slightly lower (0.7 versus 0.9), with a within-subject difference of [redacted] adalimumab minus current adalimumab of –0.16 (95% CI [–0.93, 0.61], $P = 0.678$).
- Pain experience scores for biologic-naïve and current adalimumab users were generally similar as those reported for the cITT population.

Safety Results:

Both adalimumab formulations were well tolerated among this RA population. Treatment-emergent AEs were reported in 2 subjects following treatment with current adalimumab and 1 subject following [redacted] adalimumab. All treatment-emergent AEs were mild in severity. A potentially drug-related treatment-emergent AE was reported in 1 of these subjects following treatment with [redacted] adalimumab (mild erythematous rash considered probably related).

One AE, mild pharyngitis that was considered probably not related to study drug, led to study drug discontinuation. No deaths, serious AEs, or severe AEs were reported. There were no clinically meaningful differences between the treatment groups in hematology, clinical chemistry, or vital signs.

Conclusions:

The results of this Phase 2, randomized, single-blind, 2-period, crossover study in RA subjects who were biologic-naïve or current adalimumab users successfully demonstrated the superiority of [redacted] adalimumab with regard to injection site pain assessment, measured with VAS, immediately after the injection. Subjects generally reported a lower degree of injection site pain for all variables following [redacted] adalimumab than following current adalimumab. Safety data were consistent with the known profile for current adalimumab and no additional safety concerns were identified for [redacted] adalimumab.

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