

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: Stephen Hall, Emeritus Research - Site Management Organisation, [REDACTED]		
Study Site: Seven sites enrolled subjects. Sites were located in Canada, Germany, and Australia.		
Publications: None		
Studied Period (Years): First Subject First Visit: 19 January 2012 Last Subject Last Visit: 07 November 2012	Phase of Development: 2	
Objective: <p>The primary objective of this study was to compare, immediately after injection, the injection site-related pain profile of a high-concentration adalimumab formulation in the prefilled Physiolis syringe with that of the commercially available adalimumab (HUMIRA®) formulation in the current prefilled syringe.</p> <p>The secondary objective of this study was to compare the safety and injection site reaction adverse events (AEs) between the 2 formulations.</p>		
Methodology: <p>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 high-concentration adalimumab formulation in the prefilled Physiolis syringe versus that of commercially available adalimumab in the current prefilled syringe.</p> <p>Approximately 60 subjects with rheumatoid arthritis were to be recruited at approximately 7 sites within Australia, Canada, and Germany. 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.</p> <p>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.</p> <p>Sequence CD: first dose with 40 mg of current adalimumab formulation in the 27-gauge prefilled syringe and second dose with 40 mg of high-concentration adalimumab formulation in the 29-gauge Physiolis syringe.</p>		

<p>Methodology (Continued):</p> <p>Sequence DC: first dose with 40 mg of high-concentration adalimumab formulation in the Physiolis 29-gauge syringe and the second dose with 40 mg adalimumab formulation in the 27-gauge prefilled syringe.</p> <p>Subjects recorded their subjective assessments of pain associated with the administered adalimumab injections at Visits 1 and 2 using the Short-Form McGill 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.</p> <p>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.</p>	
<p>Number of Subjects (Planned and Analyzed):</p> <p>Sixty subjects were planned and 60 subjects were analyzed.</p>	
<p>Diagnosis and Main Criteria for Inclusion:</p> <p>Subjects were males or females 18 years of age or older, who required adalimumab 40 mg subcutaneously every other week or every week for the treatment of rheumatoid arthritis (RA), in accordance with the local adalimumab label.</p> <p>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.</p> <p>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.</p>	
<p>Test Product:</p> <p>Dose:</p> <p>Mode of Administration:</p> <p>Bulk Lot Number:</p>	<p>High-concentration adalimumab [REDACTED]</p> <p>One dose of high-concentration adalimumab [REDACTED] in the Physiolis syringe on the subject's on-label adalimumab dosing schedule</p> <p>Subcutaneous injection</p> <p>09-026087</p>
<p>Duration of Treatment:</p> <p>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.</p>	

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:	10-001960 [REDACTED] 10-001959 [REDACTED]
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:	
Sixty-eight subjects were screened for the study; 61 subjects were randomized, and 60 subjects received at least 1 dose of the study drug at 7 sites in Australia, Canada, and Germany. Eighteen subjects were biologic-naïve, 43 subjects were currently on adalimumab treatment. Subject 1108, who was biologic-naïve and randomized to Sequence DC, discontinued from the study and never received study drug. Sixty subjects received at least 1 dose of adalimumab (ITT population). All of the subjects in the ITT population received study drug treatment in both study periods and, thus, were also included in the crossover ITT (cITT) population treatment. No subject discontinued study drug because of an AE.	

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 high-concentration adalimumab formulation with the current adalimumab formulation.

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

- The subject's mean injection site pain assessment on a VAS (0 to 10 cm) immediately after the dose was significantly lower for high-concentration adalimumab (0.9 cm) than for current adalimumab (4.2 cm), with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -3.25 (95% confidence interval [CI] $[-4.00, -2.49]$, $P < 0.001$). Thus, the primary objective of the study was achieved.
- At 15 minutes after the dose, the subject's mean injection site pain assessment on VAS (0 to 10 cm) was significantly lower for high-concentration adalimumab (0.4 cm) than for current adalimumab (1.0 cm) with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -0.62 (95% CI $[-1.08, -0.17]$, $P = 0.008$).
- Immediately after the injection, the median percentage reduction (within subject) in injection-related pain with high-concentration adalimumab was 88.9% relative to current adalimumab. Similarly, 15 minutes after the injection, the median percentage reduction (within subject) in pain with high-concentration adalimumab was 80.6% relative to current adalimumab.
- The present pain intensity (PPI) was significantly lower for high-concentration adalimumab than for current adalimumab both immediately (0.5 cm versus 1.9 cm), with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -1.35 (95% CI $[-1.64, -1.06]$) as well as 15 minutes after the dose (0.2 cm versus 0.7 cm), with a mean within-subject difference of high-concentration adalimumab of -0.42 (95% CI $[-0.62, -0.22]$) ($P < 0.001$ for both).
- The sensory dimension score of pain experience from the MPQ-SF was significantly lower for high-concentration adalimumab than for current adalimumab, both immediately after the dose (0.9 cm versus 6.1 cm), with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -5.19 (95% CI $[-6.69, -3.68]$) and 15 minutes after the dose (0.4 cm versus 1.5 cm), with a mean within-subject difference of -1.17 (95% CI $[-1.81, -0.52]$) ($P < 0.001$ for both).
- The affective dimension score of pain experience from the MPQ-SF was significantly lower for high-concentration adalimumab than for current adalimumab immediately after the dose (0.2 cm versus 0.8 cm with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -0.65 (95% CI $[-1.13, -0.17]$, $P = 0.009$), while it was similar for high-concentration adalimumab (0.1 cm) and current adalimumab (0.1 cm) 15 minutes after the dose with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of 0.00 (95% CI $[-0.09, 0.10]$, $P = 0.963$).

Summary/Conclusions (Continued):

Efficacy Results (Continued):

- The total score of pain experience from the MPQ-SF was significantly lower for high-concentration adalimumab than for current adalimumab, both immediately after the dose (1.1 cm versus 6.9 cm), with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -5.84 (95% CI $[-7.63, -4.05]$) and 15 minutes after the dose (0.5 cm versus 1.6 cm), with a mean within-subject difference of high-concentration adalimumab minus current adalimumab of -1.17 (95% CI $[-1.81, -0.52]$) ($P < 0.001$ for both).
- The results in the biologic-naïve and current adalimumab users subgroups were generally similar to those of the combined group. It is of note that, in subjects who were current users of adalimumab, pain of injection and the sensory dimension score of pain immediately after injection for current adalimumab was numerically higher than for biologic-naïve subjects (4.8 cm versus 2.6 cm and 7.3 cm versus 2.9 cm, respectively), but this difference was not apparent in the group for high-concentration adalimumab (0.8 cm versus 1.3 cm and 1.0 cm versus 0.7 cm, respectively). Correspondingly, the subjects' difference was higher for subject's pain on injection and the sensory dimension score of pain for current adalimumab users compared to biologic-naïve subjects (-4.0 cm versus -1.4 cm and -6.3 versus -2.2 cm). This indicates that pain on injection does not diminish over time, and that the relatively reduced pain on injection with high-concentration adalimumab should become even more clinically relevant over time.

Safety Results:

Both adalimumab formulations were well tolerated among this RA population. Treatment-emergent AEs were reported in 8 subjects following treatment with current adalimumab and 4 subjects following high-concentration adalimumab. Drug-related treatment-emergent AEs were reported in 2 subjects following treatment with current adalimumab and 3 subjects following high-concentration adalimumab. The frequency of moderate AEs was similar following current adalimumab and high-concentration adalimumab. Possibly or probably drug-related treatment-emergent AEs were reported for similar numbers of subjects following treatment with current adalimumab and high-concentration adalimumab.

No deaths, serious AEs, severe AEs, or AEs leading to discontinuation 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 high-concentration adalimumab with regard to injection site pain assessment, measured with VAS, immediately after the dose and at 15 minutes after the dose. Subjects consistently reported a lower degree of injection site pain for all variables following high-concentration adalimumab than following current adalimumab. Safety data were consistent with the known profile for current adalimumab and no additional safety concerns were identified for high-concentration adalimumab.

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