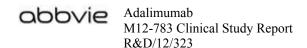


# 2.0 Synopsis

AbbVie Inc.	Individual St to Part of Do	tudy Table Referring	(For National Authority Use Only)
Name of Study Drug: Humira®	Volume:		
Name of Active Ingredient: Adalimumab	Page:		
<b>Title of Study:</b> A Multicenter, Randomized, Single-Blind Crossover Study of the Safety and Tolerability of Two Adalimumab Formulations in Adult Subjects with Rheumatoid Arthritis			
${\bf Investigator:}\ \ {\bf Dr.\ Johan\ Van Hoof},$			Belgium
Study Site: Six sites enrolled subject	ts. Sites were l	ocated in Belgium and tl	he Czech Republic.
Publications: None			
Studied Period (Years):		Phase of Development: 2	
First Subject First Visit: 28 March 2012			
Last Subject Last Visit: 09 Noven	nber 2012		
Objectives:			
The primary objective of this study w site—related pain profile of a syringe with that of the commercially  The secondary objective of this study events (AEs) between the 2 formulations.	adal available adali was to compar	imumab formulation in mumab (HUMIRA®) fo	the prefilled rmulation
Methodology:			
This was a Phase 2, randomized, sing site-related pain, safety, and tolerabile syringe versus that of common Approximately 60 subjects with rheur within Belgium and Czech Republic. rated their average injection-site pain	ity of a nercially availal matoid arthritis Subjects were	adalimumab ble adalimumab in the co (RA) were to be recruit either current on-label u	o formulation in the prefilled current prefilled syringe.  ed at approximately 6 sites users of adalimumab who
(VAS), and had had at least 6 consecunaïve subjects who required initiation	ative doses of a of on-label tre	dalimumab prior to Scre atment with adalimumal	eening or were biologic-
Subjects were randomly assigned in e (CD and DC) following the schedule	of their next 2 1	planned consecutive dos	es.
	of current adali of	mumab formulation ("C adalimumab form	"") in the prefilled nulation ("D") in the

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Methodology (Continued):	
Sequence DC: first dose with syringe and the prefilled syringe.	adalimumab ("D") formulation in the the second dose with current adalimumab formulation ("C") in
injections at Visits 1 and 2 usin after injection and approximate their assessments of injection si	ve assessments of pain associated with the administered adalimumab g the Short-Form McGill Pain Questionnaire (MPQ-SF) immediately ly 15 minutes after each injection. Qualified study site staff recorded ite reactions associated with adalimumab injections at Visits 1 and 2 mately 10 minutes after each injection and approximately 30 minutes after
The end of the study was define contact, whichever was later.	ed as the date of the last subject's last visit or the actual date of follow-up
Number of Subjects (Planned	and Analyzed):
Sixty subjects were planned and analyses), 63 subjects were ana	d 62 subjects were analyzed for injection site-related pain (crossover lyzed for other safety analyses.
Diagnosis and Main Criteria	for Inclusion:
	18 years of age or older, who required adalimumab
adalimumab injection site-relat	current, on-label user of adalimumab who rated his or her average ed pain (in the last month) as at least 3 cm on a pain VAS and had at least mab prior to Screening, or a biologic-naïve subject who required with adalimumab.
assessment or, if the subject had	in good health and had to have a negative tuberculosis (TB) Screening devidence of a latent tuberculosis infection, the subject had to have num of 2 weeks of anti-TB therapy or have documented completion of a line.
Test Product:	adalimumab

# **Duration of Treatment:**

**Bulk Lot Number:** 

**Mode of Administration:** 

Dose:

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.

One dose of

Subcutaneous injection

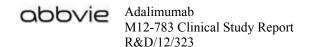
schedule

09-026087

adalimumab

adalimumab syringe on the subject's on-label adalimumab dosing

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Reference Therapy:

One dose of the current formulation of adalimumab
the current pre-filled syringe on the subject's on-label adalimumab
dosing schedule

Mode of Administration:
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.

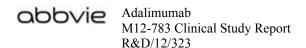
Laboratory test values and vital signs measurements that were potentially clinically significant, according to predefined criteria, were defined.

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**

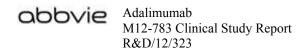
Seventy-one subjects were screened for the study, 64 subjects were randomized, and 63 subjects received at least 1 dose of the study drug at 6 sites in Belgium and the Czech Republic. Twenty subjects were biologic-naïve and 44 subjects were currently on adalimumab treatment. who was currently adalimumab user and randomized to CD, received one dose of study drug (current adalimumab) and discontinued because of an adverse event (pharyngitis) and 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 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 adalimumab (1.6 cm) than for current adalimumab (3.3 cm), with a mean within-subject difference of 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 adalimumab (0.9 cm) than for current adalimumab (1.0 cm) with a mean within-subject difference of adalimumab minus current adalimumab of -0.09 cm (95% CI [-0.40, 0.23], P = 0.581). adalimumab reduced injection-related pain by Immediately after the injection, 79.2% (median within-subject injection site pain difference) relative to current adalimumab. Fifteen minutes after the injection, the reduction in pain with 50.0% (median within-subject percent injection site pain difference) relative to current adalimumab. The mean present pain intensity was significantly lower for adalimumab than for current adalimumab immediately after the dose (0.7 versus 1.3), with a mean within-subject difference of 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 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 adalimumab than for current adalimumab immediately after the dose (2.0 versus 4.0), with a mean within-subject difference of 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 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 adalimumab and for current adalimumab both immediately after the dose (0.4 versus 0.3), with a mean within-subject difference of 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 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 adalimumab than for current adalimumab immediately after the dose (2.4 versus 4.4), with a mean within-subject difference of 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 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 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 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 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 adalimumab than following current adalimumab. Safety data were consistent with the known profile for current adalimumab and no additional safety concerns were identified for adalimumab.

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Date of Report: 17May2013