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ORIGINAL RESEARCH

Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Patients with Rheumatoid Arthritis

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ABSTRACT

Introduction: Adalimumab, an anti-tumor necrosis factor antibody, is currently available in a 40 mg/0.8 mL formulation. The objective of this analysis was to evaluate injection site-related pain, safety, and tolerability of a 40 mg/0.4 mL formulation of adalimumab that had fewer excipients, a smaller volume, and a delivery presentation with a smaller gauge needle, versus the current 40 mg/0.8 mL formulation in patients with rheumatoid arthritis (RA).

Methods: Two identically designed, phase 2, randomized, single-blind, two-period crossover studies were conducted in Belgium and the Czech Republic (Study 1) and Australia, Canada, and Germany (Study 2). In both studies, adults with RA [biologic-naive or current users of 40 mg/0.8 mL adalimumab with an average injection site-related pain rating $\geq$3 cm on a visual analog scale (VAS; 0–10 cm)] were randomized to receive 40 mg/0.8 mL or 40 mg/0.4 mL adalimumab at visit 1. After 1–2 weeks (depending on patient medication schedule),

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patients received the other formulation at visit 2. A pain VAS [McGill Pain Questionnaire (MPQ-SF)] and the Draize scale were evaluated immediately after injection and 15 min postinjection. The primary endpoint was immediate pain after injection.

Results: 64 and 61 patients were randomized in Studies 1 and 2, respectively. Both studies found a clinically relevant and statistically significant lower immediate pain after injection for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation. The mean difference on the VAS for the pooled data (−2.48 cm) was also clinically relevant. Most other endpoints in both studies favored the 40 mg/0.4 mL formulation, and its tolerability and safety profile were consistent with 40 mg/0.8 mL adalimumab.

Conclusion: A 40 mg/0.4 mL adalimumab formulation was well tolerated and associated with less injection site-related pain than the 40 mg/0.8 mL adalimumab formulation.

Trial registration: ClinicalTrials.gov identifier, NCT01561313 and NCT01502423.

Funding: AbbVie.

Keywords: Injections; Pain; Quality of life; Rheumatoid arthritis; Tumor necrosis factor inhibitors

INTRODUCTION

Adalimumab (Humira®; AbbVie, North Chicago, IL, USA) is a fully human, highly specific, high-affinity anti-tumor necrosis factor α monoclonal antibody approved for the treatment of patients with rheumatoid arthritis (RA) as well as other immune-mediated inflammatory diseases in over 90 countries worldwide [1–3].

Adalimumab is administered via subcutaneous injection. In placebo-controlled clinical trials in adult patients with RA, the most common adverse event (AE) with adalimumab was injection site reactions, including erythema and/or itching, hemorrhage, related pain, and swelling [4–8]. The overall incidence of such reactions was 20.3% in patients who received adalimumab versus 13.8% who received placebo; these reactions are the most commonly reported AE across all indications [4].

Pain related to subcutaneous injection can be influenced by various factors, including the inactive ingredients of the formulation (e.g., citrate buffer) [9–11], injection volume [12, 13], and needle size and sharpness [14]. A 40 mg/0.4 mL formulation of adalimumab was developed to address pain associated with injection. The active ingredient in both formulations remains adalimumab derived from the same master cell bank using identical isolation processes [15].

The 40 mg/0.4 mL formulation differs from the current formulation of adalimumab in that it has fewer excipients (Supplementary Table 1); particularly, there is no citrate buffer. Further, the citrate-free formulation has a higher concentration of adalimumab that allows a smaller injection volume (40 mg adalimumab delivered in 0.4 mL instead of 0.8 mL), and the 40 mg/0.4 mL formulation is delivered via a syringe that has a smaller (29 vs 27 gauge) needle than the 40 mg/0.8 mL formulation.

This report details the results of two phase 2, randomized crossover studies in patients with RA that assessed injection site-related pain, safety, and tolerability of the 40 mg/0.4 mL adalimumab formulation versus the 40 mg/0.8 mL formulation.

METHODS

Study Designs

Two phase 2, randomized, single-blind, two-period crossover studies of identical design were conducted (Fig. 1). Study 1 was conducted at six sites in Belgium and the Czech Republic between March and November 2012 (ClinicalTrials.gov identifier, NCT01561313), and Study 2 was conducted at seven sites in Australia, Canada, and Germany between January and November 2012 (ClinicalTrials.gov identifier, NCT01502423).

Independent ethics committees/institutional review boards reviewed and approved all study-related documents, including study protocols and any amendments, per Good Clinical Practice requirements. Studies were conducted with ethical principles in accordance with the Declaration of Helsinki. All patients provided informed consent before participating in any study-related procedures.

Formulations

Components of the 40 mg/0.8 mL and 40 mg/0.4 mL adalimumab formulations are listed in Supplementary Table 1. The 40 mg/0.8 mL formulation is delivered via a prefilled syringe with a 27-gauge needle. The 40 mg/0.4 mL presentation uses a prefilled syringe with a 29-gauge needle, a latex-free needle shield, and a plunger stopper that is coated to minimize leaching (Physiolis™; Becton, Dickinson and Company, Franklin Lakes, NJ, USA).

Patients

Injection site pain is a commonly reported AE across all populations for which adalimumab is indicated; patients with RA were selected as a representative population to investigate pain on injection for the two formulations. Eligible patients were men and nonpregnant, nonlactating women $\geq$18 years of age with a diagnosis of RA, as defined by the 1987 revised American College of Rheumatology (ACR) classification criteria [16] or the ACR/European League Against Rheumatism 2010 criteria [17], and who required adalimumab 40 mg every other week (eow) or every week (ew), per the local adalimumab label. Patients were either biologic-naive, or current users of 40 mg/0.8 mL adalimumab. The latter group had rated their average injection site-related pain as $\geq$3 cm on a pain visual analog scale (VAS) of 0–10 cm in the past month and had received $\geq$6 consecutive doses of adalimumab before screening. All patients had a negative tuberculosis (TB) screening assessment as determined by a tuberculin skin test (QuantiFERON-TB Gold® test; Cellestis, Inc., Valencia, CA, USA) or equivalent test, and a chest radiograph. If there was evidence of a latent TB infection, patients had to have completed $\geq$2 weeks of anti-TB therapy before baseline assessment. All patients must have been able and willing to
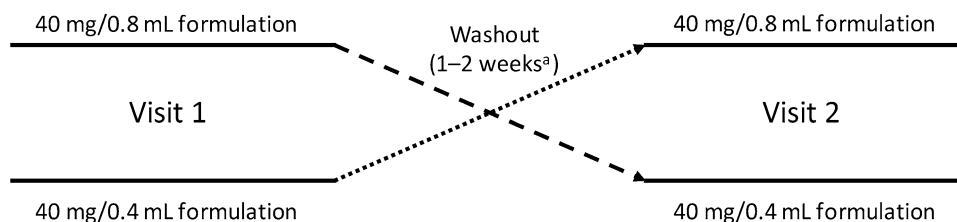

Fig. 1 Study design. ^aDependent on patient's prescribed on-label dosing schedule

provide written informed consent and comply with the requirements of the protocol. Patients were ineligible if they had an infection requiring intravenous anti-infectives within 30 days of, or oral anti-infectives within 14 days of, the first study visit; chronic recurrent infections; hepatitis B infection; an active systemic viral infection or any active infection that would make the patient an unsuitable candidate for the study based on the investigator's assessment. Patients were excluded if they had a history of invasive infection; human immunodeficiency virus; demyelinating disease; heart disease (including moderate to severe heart failure or recent cerebrovascular accident); dysplasia or malignancy (except for successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma or localized carcinoma in situ of the cervix); or clinically significant hematologic, renal, or liver disease. Patients were also excluded if they had received any live vaccine within 3 months of the study or if they had prior exposure to natalizumab or efalizumab. Patients who were receiving chronic medications prior to the study, including nonbiologic disease-modifying antirheumatic drugs or nonsteroidal anti-inflammatory drugs, continued on medications at their same prestudy doses.

Treatment

After a screening visit (within 30 days of baseline), patients were centrally randomized using an interactive voice response system/interactive web response system in a 1:1 ratio to one of two sequences of adalimumab [either the 40 mg/0.8 mL or 40 mg/0.4 mL formulation at visit 1, followed by the other formulation at visit 2 in a blinded manner (Fig. 1)]. The timing of the second visit was based on the regularly

scheduled doses of adalimumab required by the patient's prescribed on-label dosing schedule (eow or ew).

Assessments

Patients reported injection site pain on the four-item short-form McGill Pain Questionnaire (MPQ-SF) [18], which included (1) a VAS on which the current pain level was marked on a scale from 0 cm (no pain) to 10 cm (worst possible pain); (2) evaluation of overall pain intensity on a six-point scale [no pain (0), mild (1), discomforting (2), distressing (3), horrible (4), excruciating (5)]; (3) sensory and affective dimensions of the pain experience, rated on a four-point scale from 0 (none) to 3 (severe) for each of 15 pain descriptors (sensory: throbbing, shooting, stabbing, sharp, cramping, gnawing, hot/burning, aching, heavy, tender, and splitting; affective: tiring/exhausting, sickening, fearful, and punishing/cruel); and (4) assessment of needle pain (yes, no), including cause of pain (needle entry or solution that was injected). On each visit, items 1–3 were administered twice: immediately (within 2 min) and 15 min after the injection. Item 4 was administered to the patient after completion of item 3, immediately after the injection.

Qualified site staff used the Draize scale to score injection site hemorrhage/petechiae, erythema, edema, and pruritus (scale details are found in Supplementary Material). Assessments were performed 10 and 30 min after the injections on both visits. The study site personnel who administered injections were different from those who administered the MPQ-SF, or completed the Draize scale.

Safety was evaluated on the basis of AEs, physical examinations, vital signs, and standard laboratory tests. Spontaneous reports of injection site pain or reactions were

considered AEs; any injection site pain or reactions reported/observed after the 30-min Draize scale evaluation was completed were also considered AEs.

Statistical Methods

Based on a prior investigation, it was reasonable to assume a mean pain level of 3.00 and 2.00 cm on the 10-cm VAS for 40 mg/0.8 mL and 40 mg/0.4 mL formulations, respectively, with a standard deviation of 2.60 for the difference. From this assumption, it was estimated that a two-sided level $\alpha = 0.05$ test for superiority with 83% power would require a total of 60 patients.

Injection site pain was analyzed in the crossover intent-to-treat population, defined as all patients who were randomized and completed both periods and received study drug in each period of the study. The primary endpoint was the patient's immediate pain after injection on the VAS. The 95% confidence intervals (CI) and *P* values for the difference between 40 mg/0.8 mL and 40 mg/0.4 mL formulations were calculated using a two-period crossover analysis of variance (ANOVA) model with period, sequence, and treatment as fixed effects, and subject as a random effect. The same statistical model was also used for the pooled analysis of injection site pain and for continuous endpoints in the individual studies. The two identical studies were pooled to obtain a more reliable estimate of the treatment effect. The percent difference between the two formulations in immediate pain after injection was calculated for each patient and analyzed using descriptive statistics. Based on a minimal clinically important difference (MCID) of 1.3 cm in VAS immediately following injection [19], the proportion of patients who achieved ≥1.3 cm less pain on the VAS while receiving the 40 mg/0.4 mL formulation than while receiving the 40 mg/0.8 mL formulation was calculated; a

two-sided exact binomial test was performed to assess whether this proportion differed from 50%. The exploratory analyses assessing percentage differences and proportion of patients who achieved MCID were performed post hoc.

For analysis of VAS results by category, injection site pain was classified as mild (≤3 cm), moderate (>3 to <7 cm) or severe (≥7 cm) [20]. For dichotomous endpoints, Fisher's exact version of the Mainland–Gart test was used for analysis. Demographic and baseline characteristics were summarized and compared between the two sequence groups. Homogeneity for continuous variables was assessed using a one-way ANOVA model using treatment arm as the independent factor. Homogeneity of discrete variables was evaluated using Fisher's exact test. Unless otherwise stated, all statistical tests were conducted at an $\alpha = 0.05$ level. The analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

The safety population consisted of all patients who received ≥1 dose of study drug. AEs were summarized. Treatment-emergent AEs were defined as those that began on or after the first dose of study drug and up to 70 days after the last dose of study drug.

RESULTS

Patients

In Study 1, 71 patients were screened and 64 were randomized, 33 to the sequence of 40 mg/0.8 mL to 40 mg/0.4 mL formulation and 31 to the sequence of 40 mg/0.4 mL to 40 mg/0.8 mL formulation. In Study 2, 68 patients were screened and 61 were randomized, 31 and 30 to the respective sequences of 40 mg/0.8 mL to 40 mg/0.4 mL and 40 mg/0.4 mL to 40 mg/

0.8 mL formulation (Fig. 2). One randomized patient in each study discontinued before receiving the first dose of study drug; one patient in Study 1 discontinued (due to pharyngitis) after receipt of the first dose of study drug (Fig. 2).

Demographic and clinical characteristics at baseline within each study were similar between the sequence groups, with the exception of age and duration of RA in Study 1 (Table 1).

Pain and Injection Site Assessment

Primary Endpoint: Immediate Pain After Injection

The primary endpoint was achieved in both studies. Patient-reported injection-related pain immediately after injection, as measured by VAS, was significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation in both studies. In Study 1, the mean difference was -1.74 (95% CI -2.33 to -1.16; $P < 0.001$), with a 79% median reduction and a 47% mean reduction in pain; in Study 2, the mean difference was -3.25 (95% CI -4.00 to -2.49;

$P < 0.001$) with an 89% median reduction and a 61% mean reduction in pain. The mean difference in immediate pain after injection for the pooled population was -2.48 (95% CI -2.97 to -2.00; $P < 0.001$; Fig. 3i) with an 84% median reduction and a 54% mean reduction in pain; 67% of patients experienced ≥ 1.3 cm less pain (MCID) following receipt of the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation ($P < 0.001$). No carryover effects between the two visits were noted in either study; carryover effects were not tested between pain immediately after injection and pain 15 min after injection.

Pain Immediately After Injection by Category

Changes in patient pain perception were assessed by category based on VAS assessments of pain immediately after injection (Table 2). More patients who received the 40 mg/0.4 mL formulation reported mild pain on the VAS compared with patients who received the 40 mg/0.8 mL formulation (86.9% vs 42.6%). Most patients reported a reduction in pain to the mild
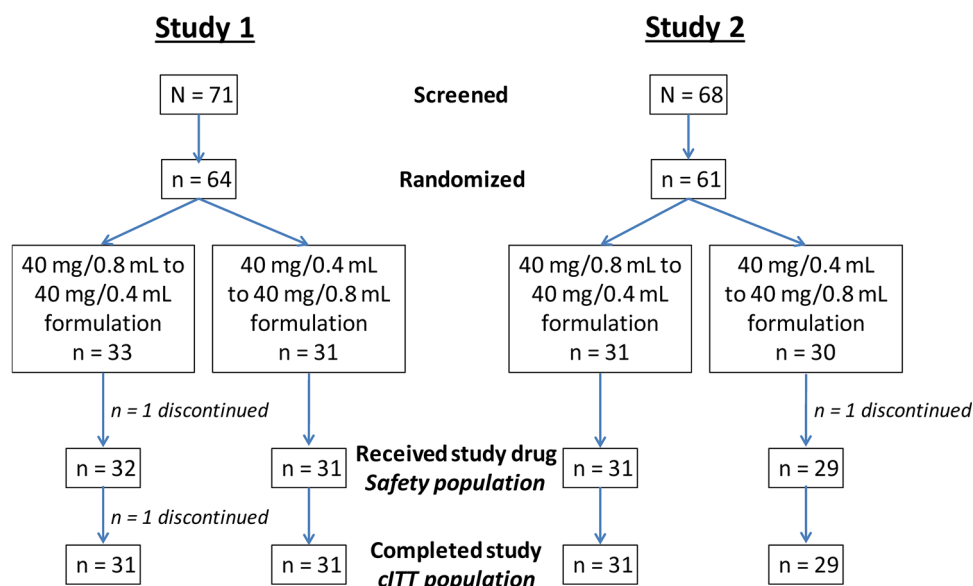

Fig. 2 Patient disposition. *cITT* crossover intent-to-treat

Table 1 Patients' baseline demographic and clinical characteristics (cITT population)

Characteristic	Study 1			Study 2		
	40 mg/0.8 mL to 40 mg/0.4 mL formulation (*n* = 31)	40 mg/0.4 mL to 40 mg/0.8 mL formulation (*n* = 31)	Total (*N* = 62)	40 mg/0.8 mL to 40 mg/0.4 mL formulation (*n* = 31)	40 mg/0.4 mL to 40 mg/0.8 mL formulation (*n* = 29)	Total (*N* = 60)
Sex, *n* (%)						
Female	21 (67.7)	21 (67.7)	42 (67.7)	24 (77.4)	23 (79.3)	47 (78.3)
Male	10 (32.3)	10 (32.3)	20 (32.3)	7 (22.6)	6 (20.7)	13 (21.7)
Age, y, mean (SD)	51.1 (12.6)[a]	58.6 (13.5)[a]	54.8 (13.5)	58.3 (11.6)	54.4 (14.1)	56.4 (12.9)
Duration of RA[b], y, mean (SD)	9.3 (7.6)[c]	16.8 (9.8)[c]	13.0 (9.5)	11.7 (8.0)	12.1 (11.3)	11.9 (9.6)
Biologic-naive, *n* (%)	10 (32.3)	9 (29.0)	19 (30.6)	10 (32.3)	7 (24.1)	17 (28.3)
Currently receiving adalimumab for ≥6 consecutive doses, *n* (%)	21 (67.7)	22 (71.0)	43 (69.4)	21 (67.7)	22 (75.9)	43 (71.7)
Injection site pain immediately after injection in the last month, cm, mean (SD)[d,e]	4.9 (1.6)	4.8 (1.4)	4.8 (1.5)	5.4 (1.9)	5.8 (2.0)	5.6 (1.9)
Adalimumab dosing frequency[d], *n* (%)						
Weekly	0	0	0	1 (4.8)	0	1 (2.3)
Every other week	21 (100)	22 (100)	43 (100)	19 (90.5)	21 (95.5)	40 (93.0)
Other	0	0	0	1 (4.8)	1 (4.5)	2 (4.7)

ANOVA analysis of variance, *cITT* crossover intent-to-treat, *RA* rheumatoid arthritis, *SD* standard deviation

[a] *P* < 0.05 for difference between sequence groups using one-way ANOVA

[b] Calculated as (date of first study drug−date of diagnosis of RA)/365.25

[c] *P* ≤ 0.001 for difference between sequence groups using one-way ANOVA

[d] Only for patients currently receiving adalimumab

[e] Assessed on a 10-cm visual analog scale at screening (0 cm = no pain; 10 cm = worst possible pain)

category after receiving the 40 mg/0.4 mL formulation, including 15 of 17 patients who experienced severe pain and 42 of 53 patients who experienced moderate pain after receiving the 40 mg/0.8 mL formulation. Only four patients reported worse pain with the 40 mg/0.4 mL formulation than the 40 mg/0.8 mL formulation.
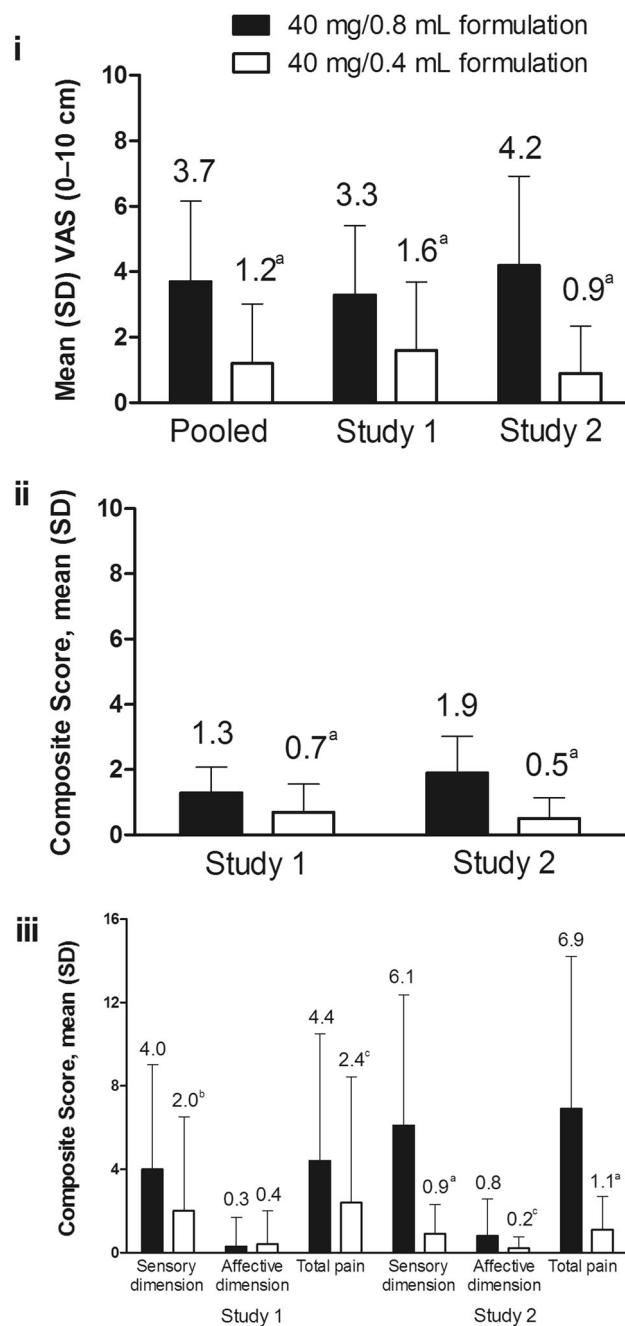
Fig. 3 Parameters assessed in the cITT population immediately after injection. Injection site pain for pooled data, Study 1, and Study 2 (**i**); present pain intensity in Study 1 and Study 2 (**ii**); and MPQ-SF total pain, sensory dimension, and affective dimension scores of pain experience scores in Study 1 and Study 2 (**iii**). *cITT* crossover intent-to-treat, *MPQ-SF* short-form McGill Pain Questionnaire, *SD* standard deviation, *VAS* visual analog scale. [a]$P < 0.001$. [b]$P = 0.001$. [c]$P = 0.009$

Other Endpoints

Injection-related pain 15 min after injection was significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation in Study 2 but not in Study 1 (Table 3). For the pooled population, the mean difference in pain 15 min

Table 2 Changes in patient perception of immediate pain on the VAS by category

VAS category, n (%)	40 mg/0.8 mL formulation (N = 122) Total	40 mg/0.4 mL formulation (N = 122)		
		Mild (≤3 cm)	Moderate (>3 to <7 cm)	Severe (≥7 cm)
Mild (≤3 cm)	52 (42.6)	49 (40.2)	2 (1.6)	1 (0.8)
Moderate (>3 to <7 cm)	53 (43.4)	42 (34.4)	10 (8.2)	1 (0.8)
Severe (≥7 cm)	17 (13.9)	15 (12.3)	2 (1.6)	0
Total	122 (100)	106 (86.9)	14 (11.5)	2 (1.6)

VAS visual analog scale

after injection for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation was −0.35 (95% CI −0.62 to −0.07; $P = 0.014$).

Present pain intensity immediately after injection was significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation in Study 1 and in Study 2 (Fig. 3ii); within-patient differences were −0.60 (95% CI −0.84 to −0.35) and −1.35 (95% CI −1.64 to −1.06), respectively ($P < 0.001$ for both). Present pain intensity scores 15 min after injection were significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation in Study 2 but not in Study 1 (Table 3).

In Study 1, MPQ-SF pain experience sensory dimension and total scores immediately after injection were significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation [within-patient differences of −2.05 (95% CI −3.25 to −0.85) and −2.03 (95% CI −3.53 to −0.54), respectively; $P \leq 0.009$ for both]. Affective dimension scores were not significantly different [0.02 (95% CI −0.36 to 0.39); $P = 0.932$; Fig. 3iii]. Immediately after injection in Study 2, sensory dimension, affective dimension, and total scores were significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation [within-patient

differences of −5.19 (95% CI −6.69 to −3.68), −0.65 (95% CI −1.13 to −0.17), and −5.84 (95% CI −7.63 to −4.05), respectively; $P \leq 0.009$ for all; Fig. 3iii]. Pain experience sensory dimension, affective dimension, and total scores 15 min after injection were not significantly lower for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation in Study 1, whereas sensory dimension and total scores were significantly lower in Study 2 (Table 3).

A subgroup of patients ($n = 55$ in each study) were able to discern between the pain of the needle entering the skin and the pain from the injected solution for ≥1 of the injections. In both studies, more patients attributed pain with the 40 mg/0.8 mL formulation to the solution rather than to the needle. Conversely, more patients attributed pain with the 40 mg/0.4 mL formulation to needle entry than to the solution (Supplementary Table 2).

Study staff completed the Draize scale at 10 and 30 min after injection. In both studies and with both formulations, the majority of patients had no hemorrhage/petechiae, no or very slight erythema, and no or very slight edema; pruritus was rarely observed (Supplementary Tables 3, 4).

Table 3 Pain parameters 15 min after injection

Assessment, mean (SD)	40 mg/0.8 mL formulation	40 mg/0.4 mL formulation	Within-patient difference[a] (95% CI)	P value[b]
Study 1	N = 62	N = 62		
Pain of injection	1.0 (1.52)	0.9 (1.66)	−0.09 (−0.40 to 0.23)	0.581
Present pain intensity	0.3 (0.54)	0.2 (0.48)	−0.05 (−0.22 to 0.13)	0.584
MPQ-SF pain experience				
Sensory dimension score	0.8 (1.83)	0.6 (2.14)	−0.13 (−0.73 to 0.48)	0.671
Affective dimension score	0.1 (0.65)	0.1 (0.58)	−0.03 (−0.24 to 0.17)	0.754
Total score	0.9 (2.32)	0.7 (2.64)	−0.16 (−0.93 to 0.61)	0.678
Study 2	N = 60	N = 60		
Pain of injection	1.0 (1.61)	0.4 (1.08)	−0.62 (−1.08 to −0.17)	0.008
Present pain intensity	0.7 (0.86)	0.2 (0.53)	−0.42 (−0.62 to −0.22)	<0.001
MPQ-SF pain experience				
Sensory dimension score	1.5 (2.84)	0.4 (0.92)	−1.17 (−1.81 to −0.52)	<0.001
Affective dimension score	0.1 (0.25)	0.1 (0.36)	0 (−0.09 to 0.10)	0.963
Total score	1.6 (2.88)	0.5 (1.03)	−1.17 (−1.81 to −0.52)	<0.001

ANOVA analysis of variance, *CI* confidence interval, *MPQ-SF* short-form McGill Pain Questionnaire, *SD* standard deviation

[a] Within-patient difference for 40 mg/0.4 mL adalimumab–40 mg/0.8 mL adalimumab from the crossover ANOVA model with period, sequence, and treatment as fixed effects, and subject as a random effect

[b] For differences between treatment groups from ANOVA with period, sequence, and treatment as fixed effects, and subject as a random effect

Safety

There were few AEs in Studies 1 and 2 (Table 4). In Study 1, there were three AEs; none were serious or severe. One patient discontinued after visit 1 (after receiving the 40 mg/0.8 mL formulation of adalimumab) because of mild pharyngitis. One AE in Study 1 was considered to be at least possibly related to adalimumab [erythematous rash (mild) in a patient after receiving the 40 mg/0.8 mL formulation of adalimumab].

Eleven AEs were observed in Study 2. Most were mild in severity and five were moderate [injection site reaction in one patient after receiving 40 mg/0.4 mL adalimumab; upper respiratory tract infection (URTI) in one patient after receiving the 40 mg/0.8 mL formulation of adalimumab; and lower respiratory tract infection, URTI, upper limb

Table 4 Adverse event summary

AE, n (%)	Study 1 (N = 63)			Study 2 (N = 60)		
	40 mg/ 0.8 mL formulation	40 mg/ 0.4 mL formulation[a]	Total	40 mg/ 0.8 mL formulation	40 mg/ 0.4 mL formulation	Total
Any AE	2 (3.2)	1 (1.6)	3 (4.8)	8 (13.3)	4 (6.7)	11 (18.3)
Any AE at least possibly drug-related	1 (1.6)	0	1 (1.6)	2 (3.3)	3 (5.0)	4 (6.7)
Any severe or serious AE	0	0	0	0	0	0
Any AE leading to discontinuation of study drug	1 (1.6)	0	1 (1.6)	0	0	0
AEs of special interest						
Any infection	1 (1.6)	0	1 (1.6)	6 (10.0)	1 (1.7)	7 (11.7)
Injection site reaction	0	0	0	0	2 (3.3)	2 (3.3)

AE adverse event

[a] n = 62; one patient discontinued the study before receiving the 40 mg/0.4 mL formulation

fracture, and asthma, all in one patient after receiving the 40 mg/0.8 mL formulation of adalimumab]. No AEs were serious, severe, or resulted in study discontinuation. Five events (in four patients) were considered by the investigator to be at least possibly related to adalimumab. After receiving the 40 mg/0.8 mL formulation of adalimumab, urinary tract infection and headache each occurred in one patient. After receiving the 40 mg/0.4 mL formulation, injection site pruritus, injection site reaction, and URTI were reported in one patient each. The injection site reaction in one patient was of moderate intensity and lasted 4 days, resolving with diphenhydramine treatment. The patient, a current adalimumab user with a history of injection site reactions, did not report any pain on the VAS at the time of the injection or 15 min post-dose. On the Draize scale, well-defined erythema was reported 10 and 30 min post-dose, and constant pruritus was reported 30 min after the injection. The second patient (biologic-naive) reported injection site reaction pruritus, which lasted for 30 min. No pain was reported on the VAS at the time of injection or 15 min after, and there was no pruritus at 10 or 30 min post-dose on the Draize scale.

DISCUSSION

Results of these two phase 2, randomized crossover studies in patients with RA were consistently in favor of a 40 mg/0.4 mL formulation compared with the 40 mg/0.8 mL formulation of adalimumab with regard to injection site-related pain. The primary endpoint, significantly lower immediate pain after injection for the 40 mg/0.4 mL versus the 40 mg/0.8 mL formulation, was met for both studies. The mean difference on the patient-reported VAS for the pooled data (−2.48 cm) was also clinically relevant, based on assessments of the MCID in other settings.

The MCID has been reported to range between 1.0 and 1.6 cm in settings of acute pain [19–21], and between 0.5 and 1.1 cm in observational studies of chronic pain in patients with RA [22].

Most other patient-reported endpoints were statistically significantly in favor of the 40 mg/0.4 mL formulation immediately after injection in Study 1 and at both time points after injection for Study 2. As observed for the primary and most other endpoints, differences between formulations were of larger magnitude in Study 2 compared with Study 1. The reasons for dissimilar pain ratings for these two identically designed studies are unclear, but they may relate to population differences where the studies were conducted (Belgium and the Czech Republic versus Australia, Canada, and Germany).

The MPQ-SF pain experience scale assesses both sensory and affective dimensions of the pain experience. It should be noted that differences that were observed between formulations were mainly related to sensory aspects of pain. Affective dimension scores were generally low for both formulations and differed significantly between formulations only in Study 2. In patients able to distinguish between the pain of needle entry versus injected solution, pain was most often attributed to the solution with the 40 mg/0.8 mL formulation and to needle entry with the 40 mg/0.4 mL formulation. The effect of volume on the ability to distinguish pain was not tested.

Results of the Draize scale, which was assessed by site staff, suggested that both formulations were similar with regard to the presence and severity of injection site hemorrhage/petechiae, erythema, edema, and pruritus. Notably, scores for each of four scale items were generally low for the 40 mg/0.4 mL and 40 mg/0.8 mL formulations of adalimumab, indicating the generally good tolerability of both formulations. There were no unexpected safety signals with the 40 mg/0.4 mL formulation.

An important strength of these studies was that the populations included patients who might be expected to experience injection site pain: 40 mg/0.8 mL users of adalimumab who had rated their average injection site pain score as ≥ 3 cm on a pain VAS during the month preceding the study, and patients who were biologic-naive. However, results were limited to only one injection of each formulation, administered ew or eow based on each patient's regular adalimumab dosing schedule.

Results of both studies consistently demonstrated lower injection site-related pain with the 40 mg/0.4 mL formulation; however, it is not clear which feature(s) of the 40 mg/0.4 mL formulation (composition, volume, and/or needle size) is most responsible for pain reduction. Citrate-based buffers have been identified by others as a key ingredient in injection site pain [9–11].

CONCLUSION

Results of two phase 2, randomized crossover studies in patients with RA demonstrated that the 40 mg/0.4 mL formulation of adalimumab is associated with less injection site-related pain compared with the currently available formulation. Although this study was conducted in patients with RA, similar outcomes would be expected in other immune-mediated inflammatory diseases for which adalimumab is approved.

ACKNOWLEDGMENTS

Compliance with Ethics Guidelines. Independent ethics committees/institutional review boards reviewed and approved all study-related documents, including study protocols and any amendments, per Good Clinical Practice requirements. All patients provided informed consent before participating in any study-related procedures. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013.

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