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ORIGINAL RESEARCH

Ixekizumab Citrate-Free Formulation: Results from Two Clinical Trials

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ABSTRACT

Introduction: Subcutaneous (SC) injection is a common route of drug administration; however, injection site pain (ISP) might create a negative patient experience. We evaluated ISP, bioequivalence, and overall safety of the citrate-free (CF) formulation of ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin-17A.

Methods: Two phase 1, single-blind studies were conducted in healthy participants. The crossover study A (NCT03848403) evaluated pain intensity on injection as measured by visual analog scale of pain (VAS) scores. Subjects (N = 70) were randomized 1:1:1 at the beginning to three possible treatment sequences and received a 1 mL SC injection of the three formulations sequentially in the abdomen on days 1, 8, and 15, respectively. A mixed-effects repeated measures analysis model was used to analyze VAS score by time post-injection. Study B (NCT04259346) evaluated the bioequivalence of a single 80 mg dose of CF formulation compared to the original commercial formulation. Subjects (N = 245) were randomized 1:1 to either commercial or CF formulation and received a single SC injection into the abdomen, arm, or thigh.

Results: Primary endpoint was achieved in both studies. In study A, least-squares mean (LSM) difference of VAS scores immediately post injection between commercial (n = 61) and CF formulation (n = 63) was − 21.7 ($p < 0.0001$), indicating a lower degree of pain associated with CF formulation. In study B, bioequivalence of the CF formulation was established as 90% CIs for the ratio of geometric LSM $AUC_{0-tlast}$, $AUC_{0-\infty}$, and C_{max} between treatments were contained within the prespecified limits of 0.8 and 1.25. Except for less ISP in the CF formulation, overall safety profile was comparable.

Conclusion: Ixekizumab CF formulation proved to be bioequivalent, was associated with less ISP, and had no other notable differences in

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the safety profile compared to the original commercial formulation.
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Keywords: Ixekizumab; Injection site pain; Bioequivalence; Citrate-free

Key Summary Points
Injection site pain (ISP) is a common adverse event for subcutaneously administered medications and may create a negative patient experience
Citrate is an excipient previously identified to contribute to pain perception
Two test formulations of citrate-free ixekizumab were developed, and one formulation was selected to proceed in the bioequivalence study with the original commercial formulation
Citrate-free formulation of ixekizumab proved to be bioequivalent, was associated with less ISP, and had no other notable differences in the safety profile compared to the original commercial formulation

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.20377029.

INTRODUCTION

Subcutaneous (SC) injection is a common route of drug administration for biologic products given its potential for high bioavailability and rapid onset of action. However, pain at the injection site may create a negative patient experience, limit patient adherence to treatment, and even lead to treatment discontinuation [1]. Factors such as needle sizes, volume injected, injection site location, viscosity, and the buffers used in the formulation have been reported as possible causes of pain upon administration of a SC injection [2–5], whereas speed of injection does not appear to influence pain sensation [6, 7].

Ixekizumab, a high-affinity monoclonal antibody that selectively targets interleukin (IL)-17A, is administered via subcutaneous injection [8, 9]. Injection site reactions (ISRs) are among the most common treatment-emergent adverse events (TEAEs) with an incidence rate per 100 patient-years between 15 and 20 during the first year of ixekizumab administration [9]. Among the ISRs, injection site pain (ISP) and erythema occur most frequently [9] and can be bothersome for some patients. Exploratory studies were conducted and showed that the citrate buffer and the sodium chloride tonicity agent were the main cause of ISP in the original commercial formulation.

Two test formulations of citrate-free (CF) ixekizumab were assessed in the clinical program to address pain associated with injection. On the basis of the relative bioavailability results of the test formulations, one formulation was selected for the pivotal bioequivalence study. The active ingredient in the CF formulation remains ixekizumab 80 mg/ml but differs from the original commercial formulation in that there is no citrate buffer, an excipient previously identified to contribute to pain perception [2–4]. In addition, the tonicity agent was changed from sodium chloride to sucrose (Supplementary Table 1). Here, we report the results of two phase 1 studies that assessed ISP, bioequivalence, and safety of the original commercial formulation versus the CF formulation.

METHODS

Study Design

Two phase 1, randomized, single-blind studies were conducted. For both studies, healthy participants aged 18–75 with body mass index of 18.0–32.0 kg/m^2 were included if, in the

investigator's opinion, participating in the study would not place the person at risk following a review of the participants medical history, vital signs, ECG, and clinical laboratory tests. Female participants of child-bearing potential must have tested negative for pregnancy prior to initiation of study. Key exclusion criteria were current enrolment in a clinical study involving an investigational product or participation within the last 30 days; have previously received ixekizumab or have ever been administered other IL-17 antagonists; have known allergies to ixekizumab; have a significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrine, or hematologic disorder that in the investigator's opinion poses an unacceptable risk to the subject.

Study A (I1F-MC-RHCS, ClinicalTrials.gov identifier NCT03848403) was a single-dose, subject-blind, three-period, three-formulation crossover study in healthy participants to determine the reduction in ISP for two test CF formulations compared to the original commercial formulation of ixekizumab. Participants were randomized 1:1:1 to one of three formulation sequences. Subjects received a single 1 mL SC injection administered by medical professional using a prefilled syringe of 80 mg ixekizumab commercial formulation, 80 mg ixekizumab CF formulation 1, or 80 mg ixekizumab CF formulation 2 on days 1, 8, and 15, respectively (Supplemental Fig. 1a). The three-period crossover design allowed each subject to act as their own control in comparing the effects of ixekizumab administered using the original commercial formulation to CF formulation 1 and CF formulation 2. All injections were administered in the abdomen for consistency.

CF formulation 1 ("CF formulation") was selected as the optimal formulation to proceed on the basis of relative bioavailability results (ClinicalTrials.gov identifier NCT03848416, supplemental appendix). Study B (I1F-MC-RHCU, ClinicalTrials.gov identifier NCT04259346) was a two-arm, subject-blind, parallel-design study in healthy participants to demonstrate bioequivalence between commercial formulation and CF formulation. Participants were stratified into one of three weight categories (low, less than 70.0 kg; medium, 70.0–80.0 kg; high, more than 80.0 kg). Within the three weight categories, participants were randomized 1:1 to either 80 mg ixekizumab commercial formulation or 80 mg ixekizumab CF formulation (Supplemental Fig. 1b). Subjects in each group were sub-randomized 1:1:1 to injection site (arm, thigh, or abdomen). Participants received a single 80 mg SC dose administered by a medical professional using the autoinjector according to the randomization plan, and they returned as outpatients for pharmacokinetic sampling out to day 85.

All participants were required to give informed consent for participation in the study prior to any study-specific procedures. The protocols were approved by ethical review boards and were conducted according to International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Objectives

The primary objective of study A was to evaluate pain intensity on injection of ixekizumab with different formulations, as measured by visual analog scale of pain (VAS pain) scale, a well-validated tool to assess pain [10]. VAS was presented as a 100-mm line anchored by verbal descriptors such as "no pain" and "worst possible pain." The participant was asked to rate any ISP on the line at prespecified time points following ixekizumab administration.

The primary objective of study B was to evaluate the bioequivalence of a single 80 mg subcutaneous dose of ixekizumab CF formulation compared to the commercial formulation. Secondary and exploratory objectives include evaluation of the safety, tolerability, and immunogenicity of CF formulation compared to the commercial formulation.

Statistical Analyses

VAS pain scores were summarized using standard descriptive statistics. Pain severity was categorized by VAS pain score as mild pain (30 or less), moderate pain (more than 30 and at most 70), and severe pain (more than 70). The number and

percentage of the subjects in each pain severity category were summarized by formulation and time point. A mixed-effects repeated measures analysis model (MMRM) was used to analyze the continuous ISP VAS score by each time post-injection (0, 10, 20, 30, and 60 min). For measures at each time post-injection, the model included formulation, period (day 1, day 8, or day 15), formulation sequence, and formulation by formulation sequence as fixed effects. The covariance structure of the model was unstructured. The Kenward–Roger method was used to estimate the denominator degrees of freedom. Treatment least-squares means (LSM) were estimated within the framework of the MMRM using type III sums of squares. Differences in LSM between each formulation [and associated p values and 95% confidence intervals (CI)] were used for statistical inference.

For continuous data, summary statistics included the arithmetic mean, arithmetic standard deviation, median, minimum, maximum, and number of observations. For categorical data, frequency count and percentages were presented.

Pharmacokinetics Analyses

A number of participants' clinical research unit visits were impacted as a result of COVID-19 restrictions, or for other reasons. Only participants who had all PK samples collected up to day 85 or participants who had one missing PK sample after day 15 were included from the primary PK statistical analysis.

Pharmacokinetic parameters were evaluated to determine the bioequivalence of CF formulation compared to the original commercial formulation. The log-transformed C_{max}, $AUC_{0-\infty}$, and $AUC_{0-tlast}$ were evaluated in a linear mixed-effects model with fixed effects for formulation and a random effect for subject. The treatment differences were back-transformed to present the ratios of geometric LS means and the corresponding 90% CIs. Bioequivalence was concluded if the 90% CI was completely contained within the prespecified interval (0.80, 1.25). The t_{max} was analyzed using a Wilcoxon rank sum test. Estimates of the median difference based on the observed means, 90% CI, and p values from the Wilcoxon rank sum test were calculated.

Safety Analyses

All subjects who received at least one dose of study drug, whether they completed all protocol requirements or not, were included in the safety assessments. All protocol deviations that occurred were considered for their severity and impact. Safety and tolerability were assessed by clinical laboratory tests, vital sign measurements, recording of adverse events (AEs), physical examination, medical assessments, and anti-drug antibodies. All AEs were listed. Treatment-emergent AEs were summarized by formulation and severity. The frequency (the number of AEs, the number of subjects experiencing an AE, and the percentage of subjects experiencing an AE) of treatment-emergent AEs was summarized by formulation, using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 preferred term.

RESULTS

Baseline Characteristics

Demographics at baseline for both studies are listed in Table 1. Baseline characteristics were similar overall between groups and between studies.

Primary Objectives

The primary endpoint was achieved in both studies. In study A, LSM pain VAS score (0–100 mm) for the CF formulation at the time of injection was 3.5 mm versus 25.2 mm for the original commercial formulation, with LSM difference of -21.7 ($p < 0.0001$) (Fig. 1). Ten minutes after the injection, the difference in LSM VAS score was -4.5 ($p < 0.0001$). In study B, bioequivalence was demonstrated between CF formulation and the original commercial formulation. The 90% confidence intervals for the ratio of geometric least-squares

Table 1 Baseline demographics

Study A		Study B	
Parameter	**Overall (*N* = 70)**	**IXE80 original commercial (*N* = 126)**	**IXE80 CF (*N* = 119)**
Age, years (mean, SD)	44.5 (13.5)	42.9 (12.8)	46.8 (13.5)
Gender (*n*, %)			
Male	33 (47.1)	59 (46.8)	59 (49.6)
Female	37 (52.9)	67 (53.2)	60 (50.4)
Weight, kg (mean, SD)	74.9 (12.8)	76.2 (12.3)	76.3 (12.9)
BMI, kg/m^2 (mean, SD)	25.9 (3.2)	26.7 (2.9)	26.8 (3.2)
Race (*n*, %)			
American Indian/Alaska Native	2 (2.9)	0	0
Asian	6 (8.6)	0	1 (0.8)
Black	20 (28.6)	32 (25.4)	19 (16.0)
White	41 (58.6)	93 (73.8)	98 (82.4)
Multiple	1 (1.4)	1 (0.8)	1 (0.8)

Includes all enrolled participants
BMI body mass index, *CF* citrate-free, *IXE* ixekizumab, *SD* standard deviation

mean $AUC_{0-tlast}$, $AUC_{0-\infty}$, and C_{max} between treatments were entirely contained within the prespecified limits of 0.8 and 1.25 (Table 2). Between-subject pharmacokinetic variability estimates were moderate and consistent between the commercial formulation and CF formulation. Geometric least-squares mean of C_{max} was 9.66 µg/mL and 9.97 µg/mL for the commercial formulation and CF formulation, respectively. Geometric least-squares mean of AUC was 207 µg/day/mL and 219 µg/day/mL for the commercial and CF formulations,

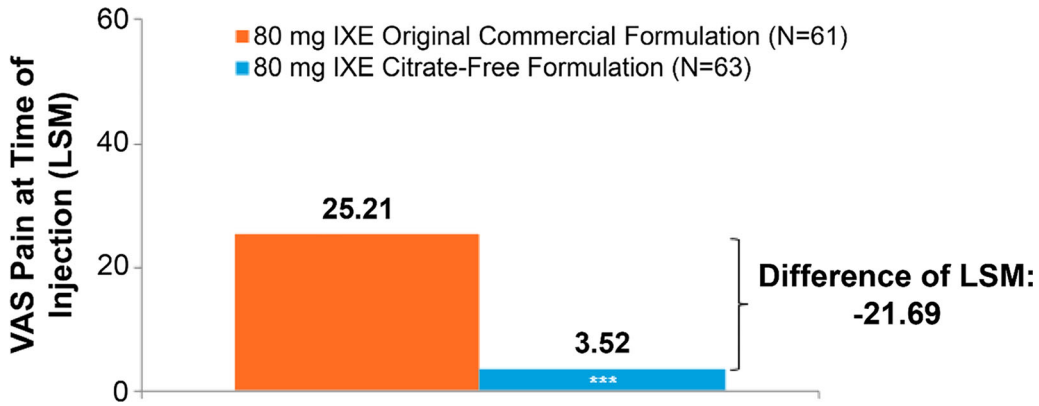

Fig. 1 VAS injection-site pain score at the time of injection in study A. Significantly less pain was reported with the citrate-free formulation than with the original commercial formulation at the time of injection (***$p < 0.0001$). Pain categories were defined as no pain, VAS pain score = 0; mild pain, VAS pain score > 0 and ≤ 30; moderate pain, VAS pain score > 30 and ≤ 70; severe pain, VAS pain score > 70. *LSM* least-squares means, *N* number of subjects, *VAS* visual analog scale

Table 2 Statistical summary of definitive bioequivalence data in study B

Parameter (units)	IXE80 CF (N = 110)	IXE80 original commercial (N = 112)	Ratio of geometric LSM (CF/commercial)	90% CI (lower, upper)
$AUC_{0-tlast}$ (μg day/mL)	219	207	1.06	(0.990, 1.13)
$AUC_{0-\infty}$ (μg day/mL)	227	213	1.07	(0.995, 1.14)
C_{max} (μg/mL)	9.97	9.66	1.03	(0.960, 1.11)

$AUC_{0-\infty}$ area under the concentration versus time curve from time zero to infinity, *$AUC_{0-tlast}$* area under the concentration versus time curve from time zero to time *t*, where *t* is the last time point with a measurable concentration, *CF* citrate-free formulation, *CI* confidence interval, *C_{max}* maximum observed drug concentration, *IXE* ixekizumab, *LS* least square means, *N* number of observations

Table 3 Statistical summary of t_{max} definitive bioequivalence data in study B

Parameter (units)	IXE80 CF (N = 110)	IXE80 original commercial (N = 112)	Median of differences (test − commercial)	90% CI (lower, upper)	*P* value
t_{max} (day)	4.04	4.99	0	(− 0.02, 0.03)	0.7592

CF citrate-free formulation, *CI* confidence interval, *IXE* ixekizumab, *N* number of observations, *t_{max}* time of maximum observed drug concentration

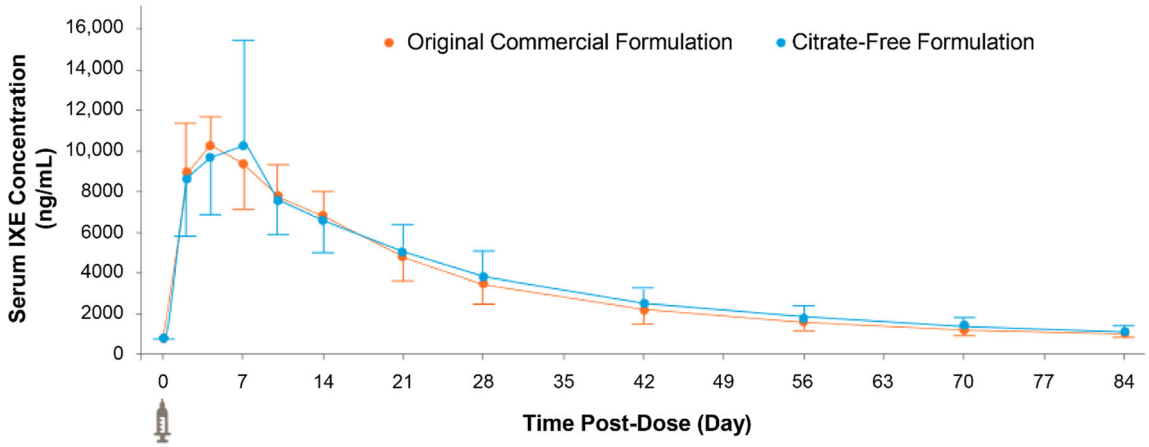

Fig. 2 Mean serum concentrations of citrate-free formulation vs. original commercial formulation to 85 days post-injection in study B. Errors bars represent the standard of deviation. *IXE* ixekizumab

respectively. There was no statistically significant difference in t_{max} between the CF formulation and original commercial formulation (Table 3), and the overall PK profile remained the same (Fig. 2).

Safety

In study B, 35.5% participants (N = 245) reported a total of 135 AEs (Table 4). Most were mild to moderate in severity, and no AEs were serious

Table 4 Summary of treatment-emergent AEs in study B, all causalities

Treatment-emergent AEs	IXE80 original commercial (*N* = 126)	IXE80 CF (*N* = 119)	Total (*N* = 245)
Participants with TEAE (*n*, %)	55 (43.7)	32 (26.9)	87 (35.5)
Any TEAE (*n*)	85	50	135
Mild	83	43	126
Moderate	2	7	9
Severe	0	0	0
SAE (*n*)	0	0	0
Discontinuation due to AE (*n*)	1	1	2

AE adverse event, *CF* citrate-free formulation, *IXE* ixekizumab, *n* number of observations, *SAE* serious adverse event, *TEAE* treatment-emergent adverse event

Table 5 Summary of injection-site reactions in study B: pain, pruritis, erythema

Treatment-emergent AEs	IXE80 commercial (*N* = 126)	IXE80 CF (*N* = 119)
Participants reporting ISRs (*n*, %)	30 (23.8)	11 (9.2)
Number of reported ISRs (*n*)	58	25
Pain severity (*n*, %)		
Mild	5 (8.6)	2 (8.0)
Moderate	8 (13.8)	0
Severe	1 (1.7)	0
Pruritus severity (*n*, %)		
Mild	6 (10.3)	2 (8.0)
Moderate	0	0
Severe	0	0
Erythema severity (*n*, %)		
Noticeable but mild	11 (19.0)	7 (28.0)
Clearly red	4 (6.9)	2 (8.0)
Bright red	7 (12.1)	1 (4.0)
Unknown	1 (1.7)	0

Percentages are based on number of reported ISRs by treatment.
Only the maximum severity of each adverse event is reported
AEs adverse events, *CF* citrate-free formulation, *IXE* ixekizumab, *ISR* injection-site reaction, *n* number of observations

or severe. One participant from each group discontinued because of COVID-19 infection.

More ISRs were reported in subjects who received the original commercial formulation compared with those who received the CF formulation (Table 5). Of participants reporting an ISR, more moderate and severe levels of pain and erythema were observed in participants of

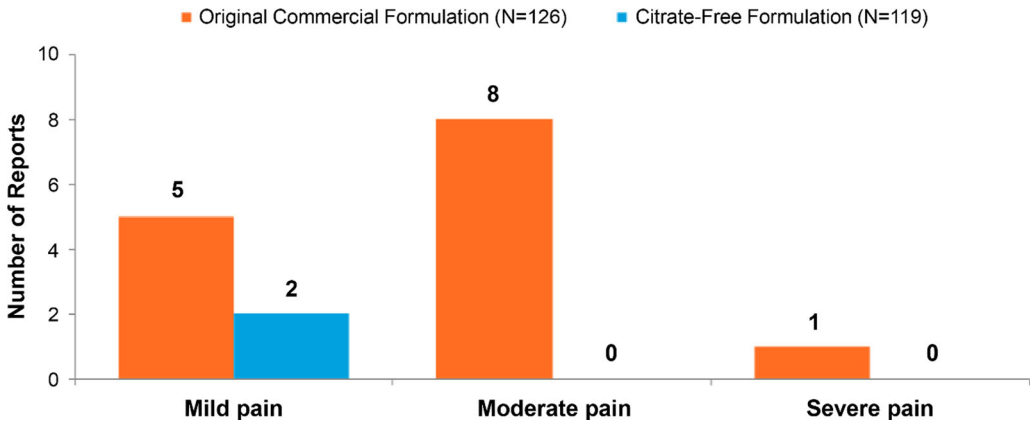

Fig. 3 Number of injection site pain events in study B. For the original commercial formulation, there were eight cases of moderate injection site pain and one case of severe pain. No severe injection site pain was reported for the CF formulation group

the original commercial formulation group compared to the milder levels reported in CF group. Eight cases of moderate ISP and one case of severe pain were reported for the original commercial formulation group. No moderate or severe ISP was reported for the CF formulation group (Fig. 3).

After receiving the commercial formulation, 9.8% of subjects were positive for treatment-emergent anti-drug antibodies (TE-ADA); 3.4% of subjects were TE-ADA positive following the CF formulation.

DISCUSSION

Efficacy and safety of ixekizumab have been demonstrated across its indications from almost 21,000 patient-years of exposure [9]. ISRs were the second most common TEAE of special interest across psoriasis, psoriatic arthritis, and axial spondyloarthritis studies, and ISP is one of the most common ISRs [9]. The CF formulation was developed to improve overall patient experiences. Studies of other compounds have demonstrated that changing the buffer reduced injection site pain, which may have implications for improving patient compliance [11, 12]. In the etanercept reformulation study, the mean VAS pain score for the original formulation was 23.1 mm versus the phosphate-free formulation VAS pain of 19.1 mm [13]. With the original formulation of adalimumab, the mean VAS pain score for pain was 37 mm, with 43% of subjects reporting moderate pain and 12% reporting severe pain. With the citrate-free adalimumab formulation, the VAS was 12 mm and the percentages for moderate and severe pain were 12% and 2%, respectively [14]. A retrospective cohort study evaluating patient adherence and persistence with citrate-free adalimumab found that adherence and persistence are significantly improved with citrate-free adalimumab compared to adalimumab-containing citrate [15].

In our studies, there was a reduction of ISP based on mean VAS pain score from 25.2 mm with the original formulation to 3.5 mm with the CF formulation. Bioequivalence with the commercial formulation was clearly established. When statistical analyses were conducted on the data from the pharmacokinetic population for each injection site separately, the 90% CIs for all comparisons were again completely contained within the confidence limits of 0.80 and 1.25. This result had an added benefit as it suggested that the two formulations were interchangeable at the injection site level.

The safety data showed that there were no reports of moderate or severe pain with the CF formulation. In addition, reports of ISRs were less frequent and less severe following the CF formulation compared to the commercial formulation in study B. With the exception of ISP, the safety profile of ixekizumab across the two formulation was consistent.

Conducting the clinical program in healthy volunteers bears both strengths and limitations. As healthy participant studies, there were fewer confounding factors that could impact the results (e.g., concomitant medications, pain related to disease state). In addition, the recruitment of healthy participants made it possible to collect intensive PK samples over a long period of time (nearly 3 months) after a single dose. Furthermore, the injections were administered by trained professionals, which also decreased potential confounders. For study A, an important strength is the comparative nature of its crossover study design. As all subjects received all three injections, absolute perception of pain by patients may vary but this was diminished by the design of the study. For study B, a key strength was its large sample size. It is important to keep in mind that studies conducted in healthy participants should not be compared with studies conducted with actual patients. Measurements of clinical efficacy were not collected; however, the equivalent pharmacokinetics demonstrated in this study suggest the CF formulation would be equally clinically effective. Moreover, other than the absence of citrate and change in tonicity agent, the CF and original commercial formulations are comparable. The stability and bio-immunological features are the same, and the binding affinity is not expected to be affected in any way. Post-marketing surveillance activities would monitor and evaluate any potential new safety signals.

CONCLUSION

Ixekizumab CF formulation proved to be bioequivalent, was associated with less ISP, and had no other notable differences in the safety profile compared to the original commercial formulation.

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Compliance with Ethics Guidelines. All participants were required to give informed

consent for participation in the study prior to any study-specific procedures. The protocols were approved by ethical review boards and were conducted according to International Conference on Harmonization Good Clinical Practice guidelines and the Declaration of Helsinki.

Data Availability. Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at http://www.vivli.org. Data are also available on clinicaltrials.gov: NCT03848403, NCT04259346.

REFERENCES

1. Usach I, Martinez R, Festini T, Peris JE. Subcutaneous injection of drugs: literature review of factors influencing pain sensation at the injection site. Adv Ther. 2019;36(11):2986–96.

2. Heise T, Nosek L, Dellweg S, et al. Impact of injection speed and volume on perceived pain during subcutaneous injections into the abdomen and thigh: a single-centre, randomized controlled trial. Diabetes Obes Metab. 2014;16(10):971–6.

3. Laursen T, Hansen B, Fisker S. Pain perception after subcutaneous injections of media containing different buffers. Basic Clin Pharmacol Toxicol. 2006;98(2):218–21.

4. Veys N, Dhondt A, Lameire N. Pain at the injection site of subcutaneously administered erythropoietin: phosphate-buffered epoetin alpha compared to citrate-buffered epoetin alpha and epoetin beta. Clin Nephrol. 1998;49(1):41–4.

5. St Clair-Jones A, Prignano F, Goncalves J, Paul M, Sewerin P. Understanding and minimising injection-site pain following subcutaneous administration of biologics: a narrative review. Rheumatol Ther. 2020;7(4):741–57.

6. Zijlstra E, Jahnke J, Fischer A, Kapitza C, Forst T. Impact of injection speed, volume, and site on pain sensation. J Diabetes Sci Technol. 2018;12(1):163–8.

7. Tangen LF, Lundbom JS, Skarsvåg TI, et al. The influence of injection speed on pain during injection of local anaesthetic. J Plast Surg Hand Surg. 2016;50(1):7–9.

8. Company ELa. Taltz® prescribing information. https://uspl.lilly.com/taltz/taltz.html#section-1. Published 2020. Updated 06/2021. Accessed 16 Sep 2021.

9. Genovese MC, Mysler E, Tomita T, et al. Safety of ixekizumab in adult patients with plaque psoriasis, psoriatic arthritis and axial spondyloarthritis: data from 21 clinical trials. Rheumatology (Oxford). 2020;59(12):3834–44.

10. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14(7):798–804.

11. Gely C, Marín L, Gordillo J, et al. Impact of pain associated with the subcutaneous administration of adalimumab. Gastroenterol Hepatol. 2020;43(1):9–13.

12. Yoshida T, Otaki Y, Katsuyama N, Seki M, Kubota J. New adalimumab formulation associated with less

injection site pain and improved motivation for treatment. Mod Rheumatol. 2019;29(6):949–53.

13. Cohen S, Samad A, Karis E, et al. Decreased injection site pain associated with phosphate-free etanercept formulation in rheumatoid arthritis or psoriatic arthritis patients: a randomized controlled trial. Rheumatol Ther. 2019;6(2):245–54.

14. Nash P, Vanhoof J, Hall S, et al. Randomized crossover comparison of injection site pain with 40 mg/0.4 or 0.8 mL formulations of adalimumab in patients with rheumatoid arthritis. Rheumatol Ther. 2016;3(2):257–70.

15. Bergman M, Patel P, Chen N, Jing Y, Saffore CD. Evaluation of adherence and persistence differences between adalimumab citrate-free and citrate formulations for patients with immune-mediated diseases in the United States. Rheumatol Ther. 2021;8(1):109–18.