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ORIGINAL ARTICLE

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A comparative study of PF-06438179/GP1111 (an infliximab biosimilar) and reference infliximab in patients with moderate to severe active rheumatoid arthritis: A subgroup analysis

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Abstract

Aim: PF-06438179/GP1111 (PF-SZ-IFX) is a biosimilar of reference infliximab (Remicade®). This analysis compared the efficacy of PF-SZ-IFX and reference infliximab sourced from the European Union (IFX-EU) in patient subgroups from a randomized, comparative study of PF-SZ-IFX versus IFX-EU.

Methods: Patients with rheumatoid arthritis were randomized 1:1 to PF-SZ-IFX (n = 324) or IFX-EU (n = 326); study drug (3 mg/kg) was administered intravenously at weeks 0, 2, and 6, then every 8 weeks thereafter. Subgroup analyses of efficacy endpoints such as American College of Rheumatology criteria for ≥20% clinical improvement (ACR20), change in high-sensitivity C-reactive protein (hs-CRP), and change in Disease Activity Score in 28 joints, four components based on hs-CRP (DAS28-CRP) at weeks 14 and 30 were performed by age, gender, race, region, immunogenicity status, and treatment history.

Results: Overall, ACR20 response rates as well as changes in DAS28-CRP and hs-CRP at week 14 were similar between PF-SZ-IFX and IFX-EU within the subgroups of age, gender, race, region, treatment history, and immunogenicity status. Results to week 30 support overall similarity in efficacy between the two treatment arms in all subgroups.

Conclusion: Overall, PF-SZ-IFX and IFX-EU were similar in efficacy within the analyzed subgroups of age, gender, race, region, treatment history, and immunogenicity status. The efficacy results from these subgroup analyses were aligned with the previously described results for the overall population up to week 30.

KEYWORDS

arthritis – rheumatoid, biosimilar pharmaceuticals, infliximab, Japan, Latin America

Clinical Trial registration: ClinicalTrials.gov (NCT02222493) and EU Clinical Trials Register (EudraCT number: 2013-004148-49).

1 | INTRODUCTION

Biosimilars are biologic drugs that are highly similar to licensed (ie reference or originator) biologic products, without any clinically meaningful differences in efficacy, safety, and purity.[1,2] The introduction of biosimilars has been associated with cost savings and improved patient access to biologic therapies.[3] The infliximab biosimilar PF-06438179/GP1111 (PF-SZ-IFX) has been approved by several regulatory agencies, such as the US Food and Drug Administration (IXIFI™ [infliximab-qbtx]: Pfizer Inc, New York, NY, USA), the European Medicines Agency (Zessly®: Sandoz GmbH, Kundl, Austria), the Pharmaceuticals and Medical Devices Agency (Infliximab BS for IV Infusion 100 mg [Pfizer]; Pfizer Japan Inc, Tokyo, Japan), and the Brazilian Health Surveillance Agency (Agência Nacional de Vigilância Sanitária, ANVISA; Xilfya®: Wyeth Industria Farmaceutica LTDA, São Paulo, Brazil) for all eligible indications of the reference product (Remicade®; Janssen Biotech, Horsham, PA, USA, and Janssen Biologics BV, Leiden, The Netherlands) in each region.[4-7]

PF-SZ-IFX has the same primary amino acid sequence as the reference infliximab product sourced from the European Union (IFX-EU).[8] A phase I pharmacokinetic (PK) similarity trial conducted in healthy subjects demonstrated PK similarity of PF-SZ-IFX to IFX-EU. Both products displayed comparable safety and immunogenicity profiles.[9] A phase III randomized, double-blind study in patients with moderate to severe active rheumatoid arthritis (RA) confirmed the similarity of PF-SZ-IFX to IFX-EU.[10] The primary efficacy endpoint of American College of Rheumatology (ACR) criteria for ≥20% clinical improvement (ACR20) at week 14 was met, with the 95% and 90% confidence intervals (CIs) for the treatment difference between groups entirely contained within the prespecified equivalence margins, respectively.[10] In addition, PF-SZ-IFX and IFX-EU demonstrated similar safety and immunogenicity profiles up to week 30.[10] Here we report results of the efficacy of PF-SZ-IFX compared with IFX-EU in various subgroups at weeks 14 and 30.

2 | METHODS

The study methodology has been described in detail in previous publications[10,11] and is briefly summarized here.

2.1 | Study population

Adults (aged ≥ 18 years) with a diagnosis of RA ≥4 months, based on the 2010 ACR/European League Against Rheumatism criteria and ACR classes I–III functional status, based on the 1991 revised criteria, were eligible.[12,13] Moderate to severe active RA was defined as ≥6 swollen joints and ≥6 tender joints, at screening and baseline, and high-sensitivity C-reactive protein (hs-CRP) ≥10 mg/L at screening. Patients received oral or parenteral methotrexate (MTX; 10-25 mg/week) for 12 or more weeks and oral folic/folinic acid (≥5 mg/week) for 21 days or longer before the first dose of the study drug. Patients intolerant to 10-25 mg/week MTX received a dose as low as 7.5 mg/week. A lower MTX dose of 6.0 mg/week was allowed in geographic regions where specified by local guidance or standard of care.

Patients were excluded from the study if they were treated with infliximab or lymphocyte-depleting therapies; however, patients were allowed ≤2 doses of a non-depleting, non-infliximab biologic if discontinued ≥12 weeks or 5 half-lives before receiving the first dose of the study drug. Other main exclusion criteria were: clinically significant laboratory abnormalities at screening including inadequate bone marrow, liver, renal, and immune system function; current infection or infection requiring hospitalization or parenteral antimicrobial therapy, judged clinically significant by the investigator within 6 months prior to the first dose of the study drug; evidence or history of heart failure or malignancy within the previous 5 years; positivity for human immunodeficiency virus, or hepatitis B or C virus; and evidence of untreated or inadequately treated latent or active tuberculosis.

2.2 | Study design and treatments

This was a randomized, double-blind, multinational study in patients with moderate to severe active RA in 174 centers in 28 countries. The initial treatment period was 30 weeks (treatment period 1). At the start of treatment period 1, patients were randomized 1:1 to PF-SZ-IFX or IFX-EU. Randomization was stratified by geographic region: North America and Western Europe, Japan, Republic of Korea, Latin America, and Rest of the World. Intravenous infusions of 3 mg/kg PF-SZ-IFX or IFX-EU were administered at weeks 0, 2, and 6, and then every 8 weeks thereafter.

All patients continued on stable background dosages of oral or parenteral MTX (10-25 mg/week) and folic/folinic acid supplementation throughout the study. One-time dose escalation to 5 mg/kg (with PF-SZ-IFX or IFX-EU) was permitted starting at or after week 14 in patients who failed to achieve ≥20% improvement from baseline in both tender (68) and swollen (66) joint counts. Treatment period 1 was followed by two 24-week treatment periods, in which patients who were initially treated with IFX-EU switched to PF-SZ-IFX at week 30 (treatment period 2) or week 54 (treatment period 3), and patients who were initially treated with PF-SZ-IFX continued PF-SZ-IFX treatment (Figure 1).

This study was conducted in compliance with the provisions of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines, and it was reviewed and approved by an institutional review board or independent ethics committee(s) at each of the participating

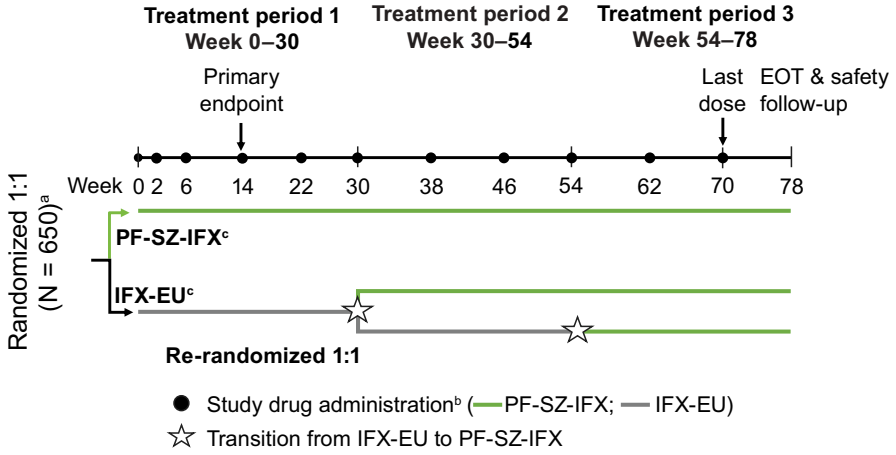

FIGURE 1 Study design.[10] [a]A sample size of approximately 614 patients was planned for enrollment. One patient in the PF-SZ-IFX treatment arm was randomized twice; data were not collected for this patient's second randomization. [b]Intravenous PF-SZ-IFX or IFX-EU (3 mg/kg) in combination with MTX were administered at weeks 0, 2, and 6, and then every 8 weeks thereafter. Dose escalation to 5 mg/kg (with PF-SZ-IFX or IFX-EU) was permitted starting at or after week 14 in patients with an inadequate clinical response. [c]Treatment group evaluation. EOT, end of treatment; IFX-EU, reference infliximab sourced from the European Union; MTX, methotrexate; PF-SZ-IFX, PF-06438179/GP1111. Adapted from Cohen et al. *Arthritis Res Ther* 2018;20:155. ©The Author(s). Reprinted with permission (https://creativecommons.org/licenses/by/4.0)

investigational sites. All patients provided informed consent before undergoing any screening procedures. The study was supported by Pfizer Inc and is registered at ClinicalTrials.gov (NCT02222493) and EU Clinical Trials Register (EudraCT number: 2013-004148-49).

2.3 | Efficacy analyses for subgroups

The primary efficacy endpoint was ACR20 at week 14. Among other secondary efficacy endpoints were ACR20 at week 30, and changes in Disease Activity Score in 28 joints, 4 components based on hs-CRP (DAS28-CRP) and hs-CRP at weeks 14 and 30. Subgroup analyses of ACR20, hs-CRP, and DAS28-CRP were performed by age, gender, race, region, immunogenicity status (anti-drug antibody [ADA]-positive or ADA-negative, and neutralizing antibody [NAb]-positive or NAb-negative), and treatment history (MTX dose and duration and corticosteroid use). For ACR20 response rate, CIs of the treatment differences were calculated using the Wald method (ie normal approximation). Analysis of covariance was used for treatment comparisons of DAS28-CRP and hs-CRP, adjusting for baseline values.

The intent-to-treat population, defined as all patients who were randomized to receive study treatment, was used as the primary analysis population and for the subgroup analysis. For the subgroup analysis, statistical analysis was conducted using observed data without imputation to missing data. Point estimates and two-sided 95% CIs of the differences between the two treatment arms were presented for each parameter. No inference on equivalence was made for any of the subgroups.

3 | RESULTS

3.1 | Patient demographics

There were no notable differences in patient demographics or disease characteristics between the treatment arms at baseline (Table 1).[10]

3.2 | Efficacy

Week 14 ACR20 response rates were similar between PF-SZ-IFX and IFX-EU within each of the subgroups analyzed, including age, gender, race, region, treatment history, and immunogenicity status (Figure 2). ACR20 response rates at week 14 trended higher for ADA-negative and NAb-negative patients than for ADA-positive and NAb-positive patients (Figure 2). However, ACR20 response rates were similar between the two treatment arms in ADA-positive, ADA-negative, NAb-positive, and NAb-negative subgroups. In the PF-SZ-IFX and IFX-EU treatment arms, respectively, week 14 ACR20 response rates were 51.0% and 49.5% for the ADA-positive patients, 69.1% and 71.2% for ADA-negative patients, 50.0% and 45.7% for the NAb-positive patients, and 67.5% and 70.5% for NAb-negative patients (which included all ADA-negative samples not tested for NAb).

Week 30 ACR20 response rates were similar between PF-SZ-IFX and IFX-EU within the subgroups of age, gender, race, region, treatment history, and immunogenicity status (Figure S1); changes from baseline in DAS28-CRP and hs-CRP at week 14 or at week 30 were also similar between treatments within subgroups (Figures S2 and S3).

TABLE 1 Patient demographics and baseline disease characteristics[10]

	PF-SZ-IFX (n = 324)	IFX-EU (n = 326)
Age, mean (SD), y	52.8 (13.3)	52.8 (12.9)
Gender		
Female	258 (79.4)	264 (81.0)
Male	66 (20.4)	62 (19.0)
Race, n (%)		
White	257 (79.3)	247 (75.8)
Black	5 (1.5)	9 (2.8)
Asian	46 (14.2)	45 (13.8)
Other	15 (4.6)	25 (7.7)
Unspecified	1 (0.3)	0
Region, n (%)		
North America and Western Europe	50 (15.4)	51 (15.6)
Japan	24 (7.4)	23 (7.1)
South Korea	4 (1.2)	5 (1.5)
Latin America	22 (6.8)	22 (6.7)
Rest of the World	224 (69.1)	225 (69.0)
MTX dose, mean (SD), mg/wk	14.2 (4.5)[a]	14.4 (4.5)
Corticosteroid use, n (%)	178 (54.9)	192 (58.9)
Duration of MTX use, n (%)		
<6 mo	52 (16.0)	58 (17.8)
≥6 mo to <1 y	78 (24.1)	83 (25.5)
≥1 y to <3 y	86 (26.5)	93 (28.5)
≥3 y	107 (33.0)	92 (28.2)
Sulfasalazine drug use,[b] n (%)	2 (0.6)	2 (0.6)
Anti-malarial drug use,[b] n (%)	2 (0.6)	5 (1.5)
hs-CRP, mean (SD), mg/L	25.8 (24.3)	25.3 (28.4)
DAS28-CRP, mean (SD)	6.0 (1.0)	6.0 (0.9)

Note: Adapted from Cohen et al. *Arthritis Res Ther* 2018;20:155. ©The Author(s). Reprinted with permission (https://creativecommons.org/licenses/by/4.0/).

Abbreviations: DAS28-CRP, Disease Activity Score in 28 joints, 4 components based on high-sensitivity C-reactive protein; hs-CRP, high-sensitivity C-reactive protein; IFX-EU, reference infliximab sourced from the European Union; MTX, methotrexate; PF-SZ-IFX, PF-06438179/GP1111; RF, rheumatoid factor; SD, standard deviation.

[a]Total weekly dose of MTX was 16 mg/wk for one patient (PF-06438179/GP1111) but incorrectly recorded as 32 mg/wk; incorrect dose was the maximum value of the MTX dose range and was used for calculation of mean dose.

[b]Use of sulfasalazine and anti-malarial drugs was allowed only in the original protocol, but not in subsequent protocol amendments.

4 | DISCUSSION

Overall, subgroup analyses suggested that age, gender, race, region, treatment history, and immunogenicity status did not influence similarity of efficacy between the two treatment arms as measured by ACR20 response at week 14. Results to week 30 continued to show that efficacy, as measured by ACR20 response and change from baseline in DAS28-CRP and hs-CRP, was similar overall between PF-SZ-IFX and IFX-EU in all subgroups beyond week 14.

Biologic therapies, including biosimilars, may elicit an immunogenic response, which could potentially impact the pharmacokinetics, efficacy, and safety of the medication.[14] In the previous analysis of the overall population, the safety profiles (including immunogenicity) of PF-SZ-IFX and IFX-EU were shown to be similar, with no clinically meaningful differences observed between arms during treatment periods 1 or 2.[10,11] Moreover, a population PK analysis of data from the same study established that the PK parameters for PF-SZ-IFX and IFX-EU were similar and were significantly influenced by the same covariates (baseline body weight, gender, and ADA titer), but were unaffected by ethnicity, based on consideration of Japanese versus non-Japanese patients.[15] In the current analysis of patient subgroups, ACR20 response rates trended higher and changes from baseline in DAS28-CRP and hs-CRP were greater for ADA-negative and NAb-negative patients than for ADA-positive and NAb-positive patients. However, these measures of efficacy were similar between the two treatment arms in each immunogenicity subgroup over the 30-week treatment period.

One limitation of the current study is that DAS28-CRP and hs-CRP subgroup analyses were created post hoc. Nevertheless, results demonstrate that efficacy, as measured by ACR20 response and change from baseline in DAS28-CRP and hs-CRP, was similar overall between PF-SZ-IFX and IFX-EU in all subgroups examined up to week 30. The efficacy results based on these subgroup analyses were aligned with the previously reported results for the overall population.[10]

DATA-SHARING

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the USA and/or EU, or (2) in programs that have been terminated (ie development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

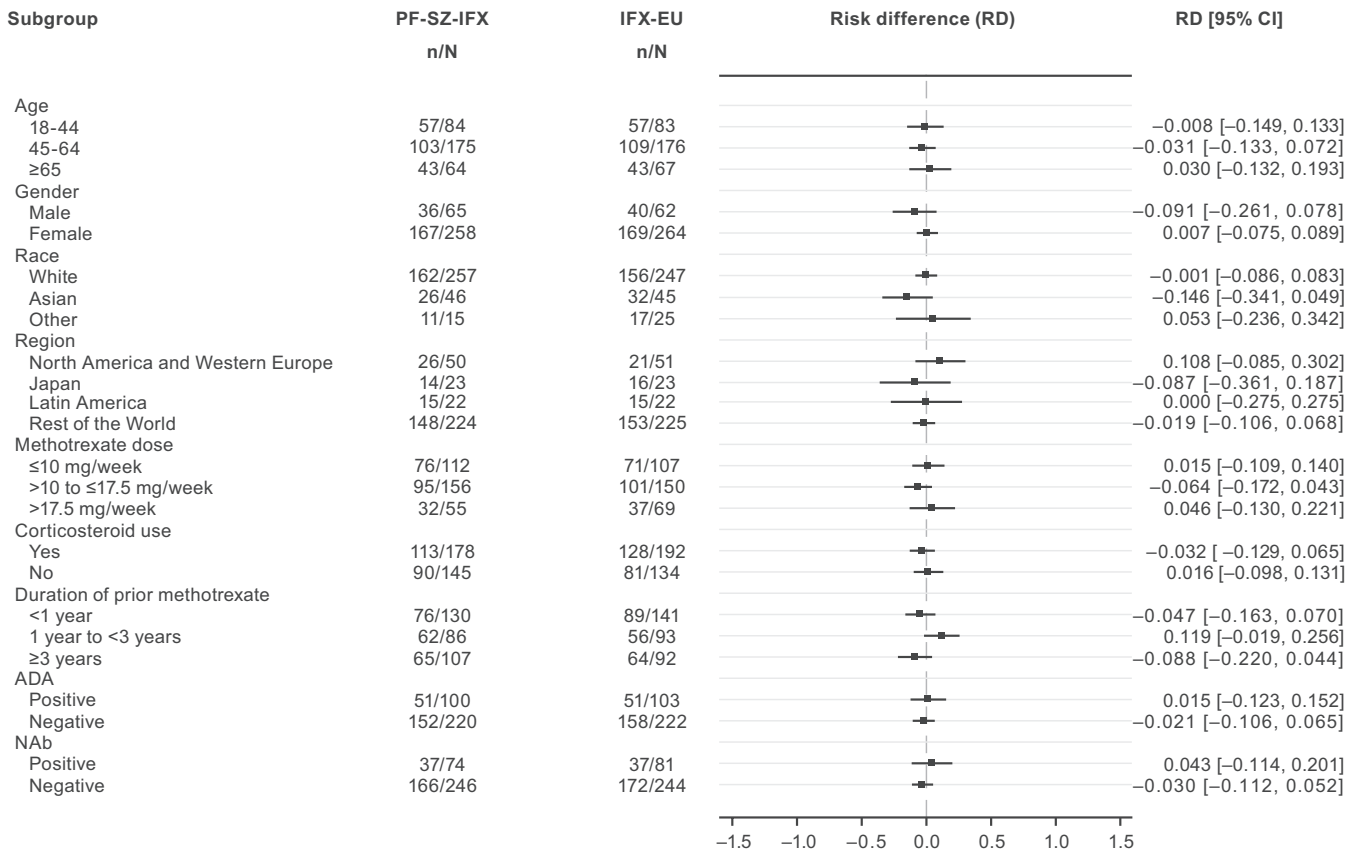

FIGURE 2 Subgroup analysis of ACR20 response at week 14. ACR20, American College of Rheumatology criteria for ≥20% clinical improvement; ADA, anti-drug antibody; CI, confidence interval; IFX-EU, reference infliximab sourced from the European Union; NAb, neutralizing antibody; PF-SZ-IFX, PF-06438179/GP1111

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CONFLICTS OF INTEREST

HK reports grants from Pfizer; grants and personal fees from AbbVie GK, Asahi Kasei Pharma, Astellas Pharma Inc, Chugai Pharmaceutical Co. Ltd., Eisai Co. Ltd., Mitsubishi Tanabe Pharma, and Novartis; and personal fees from Bristol-Myers Squibb, Eli Lilly Japan KK, and Janssen Pharmaceutical KK. EU has no competing interests to disclose. TA reports personal fees for consulting from Chugai Pharmaceutical Co. Ltd., Eli Lilly Japan KK, GlaxoSmithKline KK, Pfizer, and UCB Japan Co. Ltd; grants and personal fees for speakers' bureaus from AbbVie Inc, Astellas Pharma Inc, Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Eli Lilly Japan KK, Mitsubishi Tanabe Pharma Co., Otsuka Pharmaceutical Co. Ltd., Pfizer, Takeda Pharmaceutical Co. Ltd, and UCB Japan Co. Ltd; and grants from Alexion Pharmaceuticals, Inc. CA-M reports personal fees for speakers' bureaus from Pfizer, Lilly, Abbvie, and Roche. KK is an employee of Pfizer. TM, DPL, MIR, and MZ are employees of and own stock or options in Pfizer. SCR has received research grants from Pfizer.

AUTHOR CONTRIBUTIONS

HK, EU, TA, CA-M, and SCR contributed to the acquisition of data; MIR contributed to conception or design of the study; KK, TM, and DPL contributed to design of the post hoc analysis, and MZ contributed to data analysis. All authors participated in the interpretation of the data, contributed to the drafting or revision of the manuscript, read and gave final approval of the submitted manuscript, were involved in the decision to submit the manuscript for publication, and accept accountability for all aspects of the work.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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