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ORIGINAL ARTICLE

Extension Study of PF-05280586, a Potential Rituximab Biosimilar, Versus Rituximab in Subjects With Active Rheumatoid Arthritis

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Objective. **This extension study provided continued treatment to subjects with active rheumatoid arthritis who had participated for ≥16 weeks in a pharmacokinetic similarity study of PF-05280586 (potential rituximab biosimilar). Objectives were to evaluate overall pharmacokinetics, pharmacodynamics, immunogenicity, safety, and tolerability of PF-05280586 after transition from rituximab reference products to PF-05280586, and follow-up of biomarker and efficacy assessments.**

Methods. **Subjects were offered ≤3 additional courses of treatment of PF-05280586, with or without a single transition from rituximab in Europe (rituximab-EU; MabThera) or the US (rituximab-US; Rituxan) to PF-05280586. Each course comprised 2 intravenous infusions (1,000 mg on days 1 and 15, separated by 24 weeks [± 8 weeks]).**

Results. **Of 220 subjects in the parent study, 185 were randomized and included in this study. There were no notable differences in drug concentrations between groups or across courses, with little variation in depletion of CD19+ B cells between groups, and no apparent relationship between infusion-related reactions and antidrug antibodies with or without single transition from rituximab reference products to PF-05280586. Long-term safety and tolerability of PF-05280586 was acceptable in all groups for up to 96 weeks, with a low incidence of treatment-emergent adverse events independent of single drug transition. The percentage of subjects with a low disease activity score and disease activity score remission was similar across groups for all time points, and responses were sustained until end of study.**

Conclusion. **This study demonstrated acceptable safety, tolerability, and immunogenicity, with or without single transition from rituximab reference products to PF-05280586, without increased immunogenicity on single transition.**

INTRODUCTION

Rituximab is a genetically engineered chimeric mouse/human monoclonal immunoglobulin G1κ antibody directed against the CD20 antigen of B cells and is licensed under the trade names of MabThera (Hoffman-La Roche) in Europe (rituximab-EU) (1) and Rituxan (Genentech) in the US (rituximab-US) (2). In combination with methotrexate, rituximab-EU and -US are approved for the treatment of rheumatoid arthritis (RA), among other diseases (1,2).

Biologics are products of genetically engineered living cells and cannot be identical to one another (3). With the expiration of the exclusivity of licensed or approved biologic drugs, recent years have seen the approval of biosimilar products that provide increased access to high-quality established biologic therapies (4,5). While there is an expiration to the patent protection of the primary sequence of biologics, the cell lines remain proprietary, and to develop the same biologic is not possible since a different cell line must be used to produce a biologic product that is "highly

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Significance & Innovations

- This is the first disclosure of the results of the clinical extension study of PF-05280586 (a proposed biosimilar) versus rituximab reference products sourced in the European Union (MabThera, Hoffman-LaRoche) and the US (Rituxan, Genentech) in subjects with active rheumatoid arthritis who had participated in a PF-05280586 pharmacokinetic equivalence study.
- The results provide evidence of comparability of pharmacokinetics, pharmacodynamics, immunogenicity, and safety of PF-05280586, with or without single transition from rituximab reference products, and show no increased immunogenicity on single transition to PF-05280586.

similar" to the approved reference biologic (4,5). The regulatory agencies provide clear guidelines that define the evidence needed to establish similarity between the reference biologic and a biosimilar (4,5).

PF-05280586 is under development as a potential biosimilar of rituximab, with an identical primary amino acid sequence to rituximab; it was demonstrated to be highly similar based on comparison of physicochemical critical attributes, and nonclinical and in vitro functional characteristics (6). In a randomized 3-way pharmacokinetic (PK) similarity study in subjects with active RA, PK equivalence was demonstrated between PF-05280586 and rituximab-EU, PF-05280586 and rituximab-US, and rituximab-EU and rituximab-US. This study also demonstrated comparable CD19+ B cell depletion, pharmacodynamic (PD) responses, safety, and immunogenicity profiles for all treatments (7).

This extension study was designed to provide continued access up to an additional 3 courses of treatment with PF-05280586, with or without a single transition (either at course 1 or course 2) from rituximab-EU or rituximab-US to PF-05280586 in subjects with active RA who fulfilled entry criteria. This article reports the PK, PD, immunogenicity, safety, and clinical data of the extension study, which include blinded randomization with or without single transition from rituximab reference products to PF-05280586, for this cohort of subjects with active RA. Since the study was not designed for a formal statistical analysis of PK, PD, immunogenicity, safety, and efficacy end points, the data are presented with descriptive statistics.

SUBJECTS AND METHODS

Study design. This study was an extension offered to subjects with active RA who had participated in the randomized, parallel-group, 3-arm clinical PK study for at least 16 weeks, up to 2 months after completion of the parent study and who had not received intervening treatment with investigational agents or other biologics (including rituximab-EU or rituximab-US). The parent study included subjects with active RA who were randomized (1:1:1) to receive PF-05280586, rituximab-EU, or rituximab-US, each administered as 2 intravenous (IV) 1,000-mg doses on study days 1 and 15, and has been previously published (7).

This extension study was conducted at 48 centers in 10 countries in compliance with the provisions of the Declaration of Helsinki and in accordance with international standards of good clinical practice. All subjects provided informed consent prior to undergoing any screening procedures. The final protocol, amendments, and informed consent documentation were reviewed and approved by an institutional review board or independent ethics committee at each of the participating investigational sites. The study was supported by Pfizer and registered at ClinicalTrials.gov (NCT01643928).

Study population. This study was conducted in subjects with active RA who received background therapy with methotrexate, and had an inadequate response to at least 1 tumor necrosis factor antagonist therapy when they entered the parent study. In addition to the criteria related to their participation in the parent study, subjects were excluded from the extension study if they required treatment with prohibited concomitant medications during the study, including live attenuated vaccines, cytotoxic drugs, prednisone >10 mg/day or equivalent, disease-modifying antirheumatic drugs (other than stable dose of methotrexate up to 25 mg weekly), plasma exchange therapy, or immunoglobulin. Subjects were also excluded from the study if they had a severe reaction to rituximab reference products or PF-05280586, or a serious adverse event (SAE) that was deemed to be related to the study drug in the parent study. Subjects with an absolute neutrophil count $\leq$1,500 cells/mm^3 or immunoglobulin G levels <300 mg/dl were also excluded from the study.

Treatments. All subjects were offered up to 3 courses of study treatment. Each course was divided into 2 IV infusions of 1,000 mg of study treatment administered on days 1 and 15, and separated from the next course by 24 weeks ($\pm$ 8 weeks). The first course of this extension study randomized subjects as follows: those who received rituximab-EU in the parent study were blindly randomized (1:1) to either continue on rituximab-EU (E-E) or receive PF-05280586 (E-P), and subjects who received rituximab-US were blindly randomized (1:1) to either continue rituximab-US (U-U) or receive PF-05280586 (U-P). All subjects who continued after the end of course 1 received PF-05280586 for courses 2 and 3 in this study (E-EPP and E-PPP, or U-UPP and U-PPP, respectively). Subjects who received PF-05280586 in the parent study continued blind randomization to receive PF-05280586 for courses 1, 2, and 3 (P-P, P-PP, P-PPP, respectively) (Figure 1). Study treatments were administered in accordance with health authority–approved product labels for RA.

Objectives. This study was designed to provide continued treatment access to subjects with active RA who had participated for at least 16 weeks in the parent study. In addition, the objectives of this study were to evaluate the overall PK, PD, immunogenicity, safety, and tolerability of

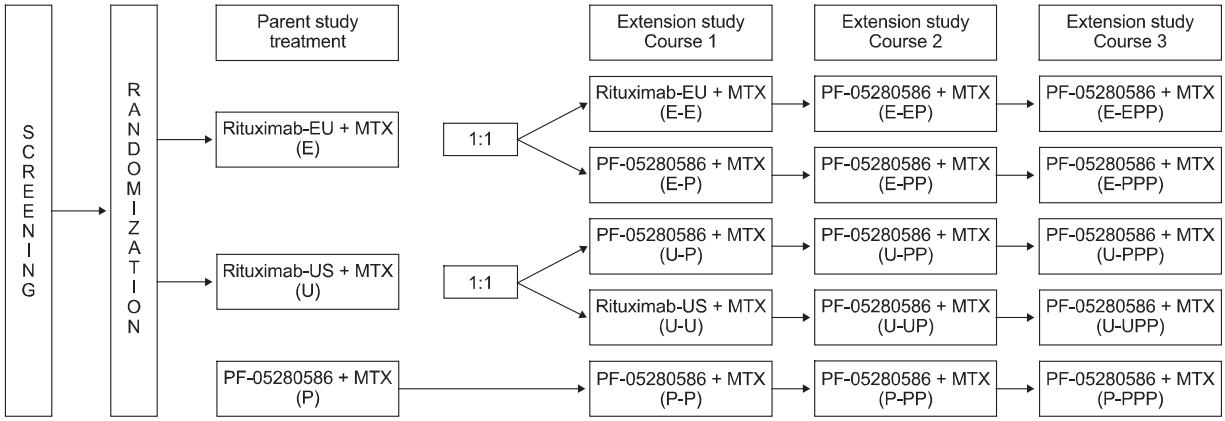


Figure 1. Study design. E-E, E-EP, E-EPP = subjects who were randomized to the rituximab-Europe (EU) cohort in the parent study and then randomized in this study to receive the rituximab-EU reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3; E-P, E-PP, E-PPP = subjects who were randomized to the rituximab-EU cohort in the parent study and then randomized in this study to receive the PF-05280586 investigational product during courses 1, 2 and 3; U-P, U-PP, U-PPP = subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive the PF-05280586 investigational product during courses 1, 2 and 3; U-U, U-UP, U-UPP = subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive the US reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3; P-P, P-PP, P-PPP = subjects who were randomized to PF-05280586 in the parent study and continued receiving the PF-05280586 investigational product in this study during courses 1, 2 and 3; MTX = methotrexate.

PF-05280586 after transition from a rituximab reference product to PF-05280586, and to continue follow-up of biomarker and efficacy end points of interest in the parent study.

Pharmacokinetics. Blood samples to determine study drug concentrations were collected prior to dosing on days 1 and 15 $\pm$ 3 days, and then on days 85 $\pm$ 7 and 169 $\pm$ 7 days during each of courses 1, 2, and 3. All samples were analyzed at QPS (Newark, DE) using a validated, single enzyme-linked immunosorbent assay to quantitatively measure total concentrations of PF-05280586, rituximab-EU, and rituximab-US in human serum.

Immunogenicity. Serum samples for the determination of antidrug antibodies (ADA) were collected concurrently with PK samples and tested using 2 validated assays. Serum samples from subjects who received PF-05280586 in the parent study were screened for ADA using the assay specific to PF-05280586, and if confirmed positive, samples were also analyzed using the assay specific for the rituximab reference products to assess cross-reactivity of the ADA. Serum samples from subjects who received rituximab reference products in the parent study were screened for ADA using both assays (PF-05280586 and rituximab reference products) to assess any product-specific ADA and/or cross-reactivity, since these subjects were exposed to the rituximab reference products followed by PF-05280586.

Blood samples that were confirmed positive for ADA were further titered and tested for neutralizing antibodies (nAbs). Samples that were confirmed positive for nAbs were also titered. An electrochemiluminescence immunoassay was used for detection of ADAs, while nAbs were detected using a cell-based assay, in accordance with relevant regulatory guidance (4,5).

Safety. Safety evaluations included clinical assessments, vital signs, 12-lead electrocardiograms, adverse events (AEs), and safety laboratory tests. AEs and laboratory abnormalities were characterized by their type, incidence, severity, timing, seriousness, and relatedness to drug treatment. The severity of AEs was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Efficacy. Although this study was not designed for a formal analysis of efficacy, disease activity was assessed by the percentage of subjects achieving low disease activity score (DAS $\leq$3.2, using the 28-joint count) and DAS remission rate (<2.6) per treatment group over time.

Efficacy parameters were assessed on weeks 1, 6, 13, and 25 of each course, with a follow-up on weeks 24 and 48 after the final day of the last course of treatment. As the time between courses could range from 16 to 32 weeks after the first day of dosing of the previous course of treatment, some subjects entered the next course before week 25 of that course. Here, we report assessments of all courses at weeks 1 and 13, and also at week 25 of course 3.

Statistical analysis. No formal hypothesis or statistical inferences were evaluated in this study. Descriptive statistics were presented for study disposition, demographics, PK, immunogenicity, safety, and efficacy data. The intent-to-treat (ITT) population was defined as all subjects who were randomized to the study treatment, and was primarily used for subject accountability. Subjects' disposition, demographics, and baseline characteristics were summarized based on the ITT population. The modified ITT (mITT) population was defined as all subjects who were randomized and received at least 1 dose of study treatment.

The evaluations for PK, immunogenicity, safety, and efficacy data were conducted on the mITT population.

RESULTS

Subject demographics and disposition. Of the 220 subjects treated in the parent study, 35 did not meet the inclusion criteria for the extension study; therefore, 185 subjects were randomized and included in the ITT population in this study (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at http://onlinelibrary.wiley.com/doi/10.1002/acr.23586/abstract). Of these 185 subjects, 59 received PF-05280586 in the parent study and remained on PF-05280586 in this study, 66 received rituximab-EU in the parent study and were blindly randomized 1:1 to continued rituximab-EU or PF-05280586 in this study, and 60 who received rituximab-US in the parent study were blindly randomized 1:1 to either continued rituximab-US or PF-05280586 in this study (Figure 1). All subjects who continued after the end of course 1 received PF-05280586 for courses 2 and 3 in this study. Six subjects in the P-PPP group, and 1 subject each in the E-EPP and E-PPP groups discontinued treatment. There were no treatment discontinuations in the U-UPP or U-PPP groups. Baseline demographics were similar across treatment groups (Table 1).

Study drug concentrations. During course 1, the geometric mean (coefficient of variation) concentrations of study drug increased from 10.9 ng/ml (232.5%) at week 1 to a maximum of 97,537.6 ng/ml (30.5%) at week 3. This was followed by a slow decline to 594.7 ng/ml (162.6%) at week 25. Similar trends were noted during courses 2 and 3. There were no notable differences in drug concentrations between treatment groups or across treatment courses.

In general, the appearance of ADA resulted in a slight decrease in drug concentrations; however, this observation should be interpreted with caution given the relatively small numbers of subjects who were ADA+. None of the samples that tested positive for ADAs tested positive for neutralizing activity in this study.

Pharmacodynamics. Depletion of CD19+ B cells from treatment in the parent study was seen at the time of

Table 1. Demographic and baseline characteristics by treatment sequence (ITT population)*

Characteristic	PS: PF-05280586, ES: PPP (n = 59)†	PS: rituximab-EU		PS: rituximab-US		Total (n = 185)
		ES: EPP (n = 33)	ES: PPP (n = 33)‡	ES: UPP (n = 30)	ES: PPP (n = 30)§	
Age, years¶						
No.	59	33	33	30	30	185
Mean ± SD	55.4 ± 1.91	56.3 ± 1.82	56.7 ± 9.35	52.6 ± 3.73	55.8 ± 0.35	55.4 ± 11.51
Range	29–80	30–75	40–74	26–81	34–82	26–82
Sex, no. (%)						
Male	9 (15.3)	3 (9.1)	10 (30.3)	10 (33.3)	5 (16.7)	37 (20.0)
Female	50 (84.7)	30 (90.9)	23 (69.7)	20 (66.7)	25 (83.3)	148 (80.0)
Race, no. (%)						
White	44 (74.6)	23 (69.7)	26 (78.8)	25 (83.3)	21 (70.0)	139 (75.1)
Black	1 (1.7)	3 (9.1)	3 (9.1)	3 (10.0)	2 (6.7)	12 (6.5)
Asian	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.6)
Other	11 (18.6)	7 (21.2)	4 (12.1)	2 (6.7)	7 (23.3)	31 (16.8)
Height, cm						
No.	59	32	32	29	30	182
Mean ± SD	164.90 ± 8.170	165.28 ± 0.623	166.92 ± 10.193	167.09 ± 9.426	164.39 ± 8.226	165.59 ± 9.175
Range	147.4–188.0	145.4–190.5	143.5–188.0	148.6–185.4	150.0–188.0	143.5–190.5
Weight, kg						
No.	59	33	33	30	30	185
Mean ± SD	86.51 ± 20.960	78.10 ± 21.176	86.78 ± 16.585	87.98 ± 23.661	73.74 ± 18.335	83.23 ± 20.841
Range	41.7–127.9	43.5–121.1	54.1–122.5	49.8–133.3	45.0–128.6	41.7–133.3
BMI, kg/m^2						
No.	59	32	32	29	30	182
Mean ± SD	31.81 ± 7.514	28.59 ± 6.833	31.46 ± 5.367	30.68 ± 6.420	27.12 ± 5.487	30.23 ± 6.739
Range	18.0–45.0	15.8–43.1	21.3–41.6	20.7–42.7	17.3–41.0	15.8–45.0

* ITT = intent-to-treat; PS = parent study treatment; ES = extension study treatment; EPP = subjects who were randomized to rituximab-EU (European Union) in the parent study and then randomized in this study to receive the EU reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3; UPP = subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive the US reference product during courses 1, followed by the PF-05280586 investigational product during courses 2 and 3; BMI = body mass index.

† Subjects who were randomized to PF-05280586 investigational product in the parent study and continued receiving PF-05280586 investigational product in this study during courses 1, 2, and 3.

‡ Subjects who were randomized to rituximab-EU in the parent study and then randomized in this study to receive PF-05280586 investigational product during courses 1, 2, and 3.

§ Subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive PF-05280586 investigational product during courses 1, 2, and 3.

¶ Age at randomization.

Table 2. ADA status of subjects who reported an infusion-related reaction*

Treatment group	IRR/AE	Grade	Day*	Course	ADA status†	Action	ADA and IRR for this subject (parent study)
P-P	Rash papular	3	4	1	+ (at course 1/week 1)	Permanently discontinued from study due to IRR	In parent study, treatment-emergent ADA+ at all time points; no IRRs reported
P-PPP	Throat irritation	1	1	1	– (at all time points)	Infusion rate reduced	In parent study, ADA–; 2 grade 2 IRRs on day 1 (both itchy ear/throat that resolved with diphenhydramine)
P-PPP	IRR	1	247	2	+ (at course 3/week 1)	Infusion rate reduced	In parent study, ADA+ at baseline only; no IRRs reported
U-UPP	Hot flush‡	3	1	1	+ (at course 2/week 1)	Infusion rate reduced	In parent study, ADA–; no IRRs reported
	Hot flush	2	15	1	+ (at course 2/week 1)	Infusion rate reduced	In parent study, ADA–; no IRRs reported
E-PPP	IRR	1	219	2	+ (at course 1/week 1)	Infusion rate reduced	In parent study, ADA–; no IRRs reported
U-PPP	Oropharyngeal pain	2	1	1	– (at all time points)	Infusion rate reduced	In parent study, ADA–; reported IRR, throat and abdominal pain, diarrhea on day 1; abdominal pain and diarrhea on day 15
	Ear pain	2	1	1	– (at all time points)	Infusion rate reduced	

* From first dose in this study. ADA = antidrug antibody; IRR = infusion-related reaction; AE = adverse event. See Table 1 for additional definitions.
† Two assays were performed (anti-rituximab Europe assay and anti–PF-05280586 assay). All 4 ADA+ subjects had cross-reacting ADA with similar titers in both assays. Only 1 subject had cross-reacting ADA+ sera in the parent study.
‡ Only the first event was listed as an IRR; the second event was not. The first event led to temporary discontinuation of the infusion, which was subsequently given at a lower rate. For both events, no action was taken and both resolved.

entry in this study, and showed little variation between treatment groups after course 1.

ADA test results. ADA samples were available from 181 subjects who received at least 1 dose of study drug. The incidence of ADA response observed in this study during the combined courses 1–3 was 13.3% with the anti-rituximab antibody assay and 10.0% with the anti–PF-05280586 antibody assay.

There were 173 samples with baseline ADA test results available. Of the 27 subjects who were ADA+ at baseline in this study, 19 (70%) were also ADA+ in the parent study, 20 (74%) had cross-reactive ADA with similar titers, and 23 (85%) reverted to ADA– by their last visit. The remaining 4 subjects were ADA+ at their last visit. Of these, 1 subject (randomized to the P-PPP group) had stable titers of treatment-emergent, cross-reactive ADA+ without infusion-related reactions (IRRs) throughout the parent study, and entered this extension study with similar ADA titers, reporting an IRR during course 1 that led to withdrawal from the study. Another subject (E-PPP) had cross-reactive ADA titers of <1.88/2.64 at entry into the extension study and 4.87/4.58 at the follow-up visit, with no IRR. The last 2 subjects had stable titers and no IRR (E-PPP and U-UPP).

Of the 146 subjects who were ADA– at pre-dose, 1 (<1%) had tested positive in the parent study but remained ADA– throughout this study, despite testing positive in the parent study. Additionally, 17 of 146 subjects (12%) became ADA+ during this study, of which 15 of 17 (88%) were ADA– in the parent study. Finally, 5 of 146 subjects (3.4%) remained ADA+ at the last visit and did not report an IRR. In total, 11 of 17 subjects (65%) who were ADA+ had cross-reactive ADAs with similar titers.

Infusion-related reactions. Overall, 6 subjects reported an IRR during the study that was deemed to be related to study treatment (Table 2). Of these, 2 of 6 subjects (33.3%; 1 each in the P-PPP and U-PPP groups) were ADA–. The remaining 4 of 6 subjects (66.7%) were ADA+, of whom 1 subject in the P-P group experienced grade 3 IRR (rash papular) and was ADA+ at the same time point. This subject was permanently discontinued from the study. Two subjects (1 each in the U-UPP and E-PPP groups) were ADA+ after reporting their IRRs and 1 in the P-PPP group was ADA+ before reporting an IRR (Table 2). All IRRs occurred at course 1 or 2, and none were reported at the final drug exposure on course 3. None of the IRRs were serious in nature and all were resolved.

Safety results. Among subjects who received course 1 treatment, 90 of 183 subjects (49.2%) experienced at least 1 treatment-emergent adverse event (TEAE) by the end of course 1. Of those who received treatment courses 1 and 2, 115 of 173 subjects (66.5%) experienced TEAEs by the end of course 2. Among those who received 3 courses of treatment, 119 of 164 subjects (72.6%) experienced TEAEs by the end of course 3 (Table 3). The most frequent TEAEs (occurring in at least 5 subjects) were from the system organ class of infections and infestations (Table 4). The most frequent and common single TEAE was worsening of the subject's RA. TEAEs led to withdrawals from study treatment in 3 of 183 subjects (3.4%) by the end of course 1 (1 subject each in the P-P, E-E, and U-P groups), 3 of 173 (1.8%) by the end of course 2 (1 in the P-PP and 2 in the U-UP groups), and 1 of 164 (0.4%) by the end of course 3 (U-PPP group). There were no dose reductions due to AEs during this study.

By the end of course 3, 46 of 164 subjects (28.0%) reported treatment-related AEs: 12 of 48 (25.0%), 5 of 30 (16.7%), 11 of 30 (36.7%), 11 of 27 (40.7%), and 7 of 29 subjects (24.1%) in the P-PPP, E-EPP, E-PPP, U-UPP, and U-PPP groups, respectively. The most frequent treatment-related AEs across all treatment groups were infections, reported as sinusitis in 7, bronchitis in 6, upper respiratory tract infection in 5, and oral herpes in 3 subjects. In addition, cough was reported in 4 subjects, and decreased white blood cell count and headache in 3 subjects each.

Table 3. Treatment-emergent adverse events (TEAEs; all causalities) by treatment sequence in subjects who received courses 1, 2, and 3 (modified intent-to-treat population)*

Subjects	PS: PF-05280586, ES: PPP (n = 48)†	PS: Rituximab-EU		PS: Rituximab-US		Total (n = 164)
		ES: EPP (n = 30)	ES: PPP (n = 30)‡	ES: UPP (n = 27)	ES: PPP (n = 29)§	
Any TEAE	34 (70.8)	21 (70.0)	23 (76.7)	20 (74.1)	21 (72.4)	119 (72.6)
Serious TEAE	4 (8.3)	1 (3.3)	4 (13.3)	1 (3.7)	1 (3.4)	11 (6.7)
TEAE resulting in withdrawal from study treatment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (0.6)
TEAE resulting in withdrawal from study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (0.6)
Treatment-related TEAE	12 (25.0)	5 (16.7)	11 (36.7)	11 (40.7)	7 (24.1)	46 (28.0)
TEAE grade ≥3	5 (10.4)	2 (6.7)	7 (23.3)	2 (7.4)	3 (10.3)	19 (11.6)

* Values are the number (percentage). PS = parent study treatment; ES = extended study treatment; EU = European Union; EPP = subjects who were randomized to rituximab-EU in the parent study and then randomized in this study to receive the EU reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3; UPP = subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive the US reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3.

† Subjects who were randomized to PF-05280586 investigational product in the parent study and continued receiving PF-05280586 investigational product in this study during courses 1, 2, and 3.

‡ Subjects who were randomized to rituximab-EU in the parent study and then randomized in this study to receive PF-05280586 investigational product during courses 1, 2, and 3.

§ Subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive PF-05280586 investigational product during courses 1, 2, and 3.

Table 4. Treatment-emergent adverse events (all causalities) in at least 5 subjects who received courses 1, 2, and 3 (modified intent-to-treat population)*

Events	PS: PF-05280586, ES: PPP (n = 48)†	PS: Rituximab-EU		PS: PF-05280586		Total (n = 164)
		ES: EPP (n = 30)	ES: PPP (n = 30)‡	ES: UPP (n = 27)	ES: PPP (n = 29)§	
Any AE	34 (48.8)	21 (50.1)	23 (52.3)	20 (53.4)	21 (50.2)	119 (50.7)
Blood and lymphatic disorders	3 (4.3)	0 (0.0)	2 (4.5)	1 (2.7)	1 (2.4)	7 (3.0)
Eye disorders	0 (0.0)	1 (2.4)	2 (4.5)	2 (5.3)	0 (0.0)	5 (2.1)
Gastrointestinal disorders	6 (8.6)	6 (14.3)	4 (9.1)	6 (16.0)	4 (9.6)	26 (11.1)
Diarrhea	1 (1.4)	1 (2.4)	1 (2.3)	3 (8.0)	2 (4.8)	8 (3.4)
Nausea	3 (4.3)	0 (0.0)	1 (2.3)	1 (2.7)	2 (4.8)	7 (3.0)
Vomiting	2 (2.9)	1 (2.4)	2 (4.5)	1 (2.7)	1 (2.4)	7 (3.0)
General disorders and administration site conditions	6 (8.6)	6 (14.3)	2 (4.5)	4 (10.7)	2 (4.8)	20 (8.5)
Edema peripheral	1 (1.4)	2 (4.8)	1 (2.3)	3 (8.0)	0 (0.0)	7 (3.0)
Infections and infestations	23 (33.0)	13 (31.0)	12 (27.3)	9 (24.0)	16 (38.2)	73 (31.1)
Bronchitis	5 (7.2)	2 (4.8)	2 (4.5)	3 (8.0)	2 (4.8)	14 (6.0)
Upper respiratory tract infection	2 (2.9)	4 (9.5)	1 (2.3)	4 (10.7)	3 (7.2)	14 (6.0)
Sinusitis	4 (5.7)	2 (4.8)	3 (6.8)	2 (5.3)	2 (4.8)	13 (5.5)
Urinary tract infection	5 (7.2)	1 (2.4)	3 (6.8)	1 (2.7)	2 (4.8)	12 (5.1)
Nasopharyngitis	1 (1.4)	0 (0.0)	1 (2.3)	1 (2.7)	2 (4.8)	5 (2.1)
Injury, poisoning, and procedural complications	6 (8.6)	6 (14.3)	8 (18.2)	4 (10.7)	5 (12.0)	29 (12.3)
Fall	1 (1.4)	3 (7.2)	2 (4.5)	1 (2.7)	0 (0.0)	7 (3.0)
Investigations	4 (5.7)	3 (7.2)	2 (4.5)	3 (8.0)	2 (4.8)	14 (6.0)
Metabolism and nutrition disorders	3 (4.3)	2 (4.8)	4 (9.1)	6 (16.0)	3 (7.2)	18 (7.7)
Musculoskeletal and connective tissue disorders	15 (21.5)	5 (11.9)	9 (20.4)	6 (16.0)	8 (19.1)	43 (18.3)
Arthralgia	1 (1.4)	1 (2.4)	2 (4.5)	2 (5.3)	0 (0.0)	6 (2.6)
Back pain	2 (2.9)	0 (0.0)	2 (4.5)	2 (5.3)	0 (0.0)	6 (2.6)
Rheumatoid arthritis	5 (7.2)	3 (7.2)	3 (6.8)	2 (5.3)	2 (4.8)	15 (6.4)
Neoplasms (benign/malignant/unspecified/cysts/polyps)	2 (2.9)	0 (0.0)	2 (4.5)	2 (5.3)	0 (0.0)	6 (2.6)
Nervous system disorders	4 (5.7)	1 (2.4)	6 (13.6)	4 (10.7)	2 (4.8)	17 (7.2)
Headache	1 (1.4)	0 (0.0)	2 (4.5)	1 (2.7)	1 (2.4)	5 (2.1)
Dizziness	2 (2.9)	1 (2.4)	1 (2.3)	1 (2.7)	1 (2.4)	6 (2.6)

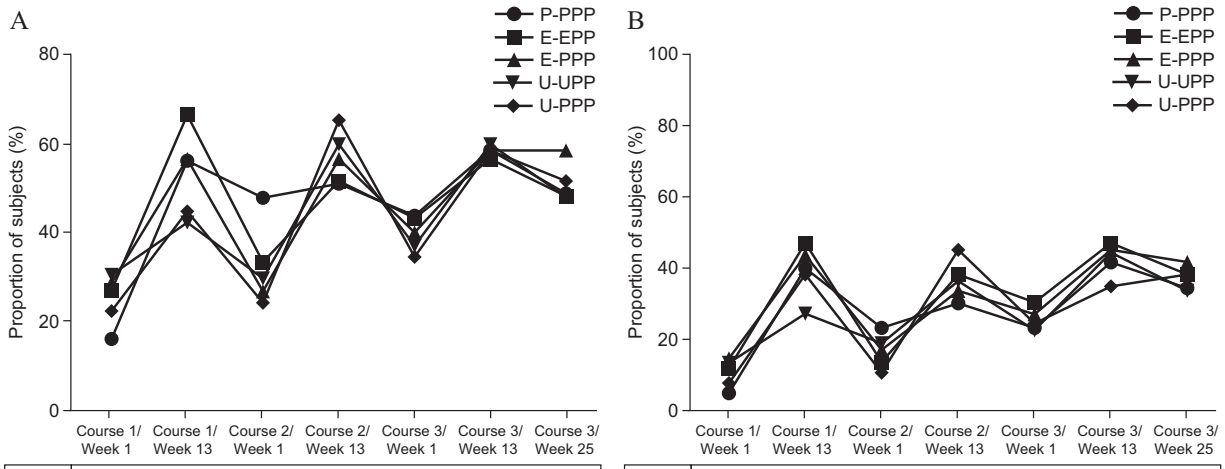
* Values are the number (percentage). PS = parent study treatment; ES = extended study treatment; EU = European Union; EPP = subjects who were randomized to rituximab-EU in the parent study and then randomized in this study to receive the EU reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3; UPP = subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive the US reference product during course 1, followed by the PF-05280586 investigational product during courses 2 and 3.
† Subjects who were randomized to PF-05280586 investigational product in the parent study and continued receiving PF-05280586 investigational product in this study during courses 1, 2 and 3.
‡ Subjects who were randomized to rituximab-EU in the parent study and then randomized in this study to receive PF-05280586 investigational product during courses 1, 2, and 3.
§ Subjects who were randomized to rituximab-US in the parent study and then randomized in this study to receive PF-05280586 investigational product during courses 1, 2, and 3.

SAEs were reported in 11 of 183 subjects (6.0%) during course 1, 14 of 173 (8.1%) by the end of course 2, and in 11 of 164 subjects (6.7%) by the end of course 3. There were no observed clinically meaningful differences in the incidence of SAEs across treatment groups. Pneumonia was the most frequently reported SAE in 3 of 164 subjects (1.8%; 1 of 48 [1.4%] in the P-PPP group and 2 of 30 subjects [4.5%] in the E-PPP group). Three subjects reported 3 SAEs (pericarditis [E-PPP], infectious arthritis [P-PPP], and wound staphylococcal infection [E-PPP]) that were deemed to be treatment related. No cases of progressive multifocal leukoencephalopathy (an event of special interest) were reported during the study.

There were no deaths in this study. There were no observed clinically meaningful changes in laboratory parameters or vital signs, and no observed clinically meaningful differences among the treatment groups.

Efficacy results. *Low DAS rate (≤3.2).* This study reports efficacy measures independent from baseline. The overall low DAS rate in subjects who received course 1 of treatment was 23.3% at week 1. The overall low DAS rate was 53.1% at course 1, week 13. For subjects who received course 1 and course 2 treatments, the overall low DAS rate was 55.7% at course 2, week 13. All groups showed similar low DAS rates after 3 courses of treatment (Figure 2A). The overall low DAS response rate was 50.9% at the end of treatment.

DAS remission rate (<2.6). The overall DAS remission rate was 37.9% at course 1, week 13. For subjects who received both course 1 and course 2 treatments, the overall DAS remission rate was 35.3% at course 2, week 13. For subjects who received 3 courses of treatment, all groups showed similar DAS remission rates over time (Figure 2B). The overall DAS remission rate was 42.1% at week 13, course 3. The overall DAS remission rate was 36.6% at the end of treatment.



n/N							
P-PPP	7/44	27/48	23/48	24/47	21/48	27/46	23/47
E-EPP	7/26	20/30	10/30	15/29	13/30	17/30	14/29
E-PPP	8/28	17/30	8/30	17/30	12/30	17/29	17/29
U-UPP	7/23	11/26	8/27	15/25	10/27	15/25	13/27
U-PPP	6/27	13/29	7/29	19/29	10/29	17/29	15/29

n/N							
P-PPP	2/44	19/48	11/48	14/47	11/48	19/46	16/47
E-EPP	3/26	14/30	4/30	11/29	9/30	14/30	11/29
E-PPP	4/28	13/30	5/30	10/30	8/30	13/29	12/29
U-UPP	3/23	7/26	5/27	9/25	6/27	11/25	9/27
U-PPP	2/27	11/29	3/29	13/29	7/29	10/29	11/29

Figure 2. A, Low Disease Activity Score (DAS; ≤3.2) rate by treatment sequence and visit (modified intent-to-treat population [mITT]); n = proportion of subjects with low DAS (≤3.2) for each treatment sequence and visit. **B,** DAS remission (<2.6) rate by treatment sequence and visit (mITT population); n = proportion of subjects with DAS remission (<2.6) for each treatment sequence and visit. N = total number of subjects receiving treatment in each course/week. See Figure 1 for randomized study group descriptions.

DISCUSSION

As patent protection and data exclusivity for rituximab expire, potential rituximab biosimilars are in development. Indeed, CT-P10, a biosimilar version of rituximab, is approved in South Korea (8) and Europe (9) for the treatment of RA, chronic lymphocytic leukemia (CLL), and non-Hodgkin's lymphoma (NHL). Another rituximab biosimilar, L01XC02, is approved in Europe for the treatment of NHL, CLL, RA, granulomatosis with polyangiitis, and microscopic polyangiitis (also approved under a duplicate marketing authorization for the treatment of NHL, RA, granulomatosis with polyangiitis, and microscopic polyangiitis) (9). The availability of rituximab biosimilars may increase patient access to safe and efficacious medicines (10).

This study provided continued treatment access to a small cohort of subjects with active RA who had participated in the parent study of a rituximab biosimilar (7). In this extension study, subjects were offered up to 3 additional courses of treatment, with or without a single transition from rituximab reference products to PF-05280586. Although the number of subjects who discontinued treatment in the P-PPP arm was numerically higher than in the other treatment groups, this was not considered clinically relevant. Similar drug concentrations were observed across treatment groups in this study. All treatment groups showed complete and sustained depletion of CD19+ B cells.

The incidence of ADA response observed in this study during the combined courses 1–3 was consistent with the published incidence of ADA: 11% in subjects with RA treated with rituximab in long-term studies (2). There was no apparent time relationship between IRR reports and ADA+ with or without single transition from rituximab reference products to PF-05280586 in this study. In total, 6 subjects experienced an IRR during this study that was deemed to be related to study treatment. However, no consistent trends were observed between IRRs after single transition from rituximab reference products to PF-05280586. Moreover, IRRs occurred at courses 1 or 2, and none were noted at course 3 during the last drug re-challenge.

The long-term safety and tolerability of PF-05280586 was acceptable in all groups up to 96 weeks in this extension study, with a low incidence of TEAEs or discontinuations due to AEs, independent of single transition from rituximab reference products to PF-05280586. The pattern and frequency of SAEs, incidence of IRRs, grade ≥3 TEAEs, and withdrawal of subjects due to AEs were similar across the treatment groups. The percentage of subjects with low DAS and DAS remission were similar across the treatment groups for all time points, and the responses were sustained until the end of the study.

In conclusion, this study demonstrated tolerability and acceptable safety with or without single transition from rituximab reference products to PF-05280586, and did not demonstrate increased immunogenicity on re-challenge or single transition based on either ADA or IRR reports. These data support the continued development of PF-05280586 as a potential biosimilar to rituximab. A randomized comparative clinical study evaluating efficacy, safety, PK, and immunogenicity of PF-05280586 and rituximab-EU monotherapy in treatment-naive subjects with CD20+ low tumor burden follicular lymphoma is ongoing (ClinicalTrials.gov NCT02213263).

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Vázquez-Abad had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study conception and design. Cohen, Burgos-Vargas, Emery, Jin, Cronenberger, Vázquez-Abad.
Acquisition of data. Cohen, Burgos-Vargas, Emery, Jin, Cronenberger, Vázquez-Abad.
Analysis and interpretation of data. Cohen, Burgos-Vargas, Emery, Jin, Cronenberger, Vázquez-Abad.

ROLE OF THE STUDY SPONSOR

Pfizer, Inc. sponsored the study, facilitated its design, was involved in the collection, analysis, and interpretation of the data, and approved the final manuscript prior to submission. Medical writing support was provided by Neel Misra, MSc, of Engage Scientific Solutions and funded by Pfizer, Inc. Patient-level data for this study and for the parent study were provided by Adesh Saxena, an employee of Pfizer, Inc. Publication of this article was not contingent upon approval by Pfizer, Inc.

REFERENCES

1. Hoffmann-La Roche, Ltd. MabThera (rituximab): summary of product characteristics. 2009. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000165/WC500025821.pdf.
2. Genentech, Inc. Rituxan (rituximab) prescribing information. 2013. URL: http://www.gene.com/download/pdf/rituxan_prescribing.pdf.
3. Schneider CK, Vleminckx C, Gravanis I, Ehmann F, Trouvin JH, Weise M, et al. Setting the stage for biosimilar monoclonal antibodies. Nat Biotechnol 2012;30:1179–85.
4. US Food and Drug Administration. Guidance for industry: scientific considerations in demonstrating biosimilarity to a reference product. 2015. URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf.
5. European Medicines Agency. Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. 2015. URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2015/01/WC500180219.pdf.
6. Ryan AM, Sokolowski SA, Ng CK, Shirai N, Collinge M, Shen AC, et al. Comparative nonclinical assessments of the proposed biosimilar PF-05280586 and rituximab (MabThera). Toxicol Pathol 2014;42:1069–81.
7. Cohen S, Emery P, Greenwald M, Yin D, Becker JC, Melia LA, et al. A phase I pharmacokinetics trial comparing PF-05280586 (a potential biosimilar) and rituximab in patients with active rheumatoid arthritis. Br J Clin Pharmacol 2016;82:129–38.
8. Generics and Biosimilars Initiative (GaBI). Biosimilar rituximab approved in South Korea. 2016. URL: http://gabionline.net/Biosimilars/News/Biosimilar-rituximab-approved-in-South-Korea.
9. European Medicines Agency. Human medicines. 2016. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124.
10. Baer II WH, Maini A, Jacobs I. Barriers to the access and use of rituximab in patients with non-Hodgkin's lymphoma and chronic lymphocytic leukemia: a physician survey. Pharmaceuticals (Basel) 2014;7:530–44.