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ORIGINAL RESEARCH ARTICLE

A Randomized, Double-Blind, Efficacy and Safety Study of PF-05280586 (a Rituximab Biosimilar) Compared with Rituximab Reference Product (MabThera®) in Subjects with Previously Untreated CD20-Positive, Low-Tumor-Burden Follicular Lymphoma (LTB-FL)

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Abstract

Background Biosimilars are highly similar to the licensed biologic ("reference product"), with no clinically meaningful differences in safety, purity, or potency between the two products.

Objective This comparative 52-week clinical study evaluated the efficacy, safety, immunogenicity, pharmacokinetics (PK), and pharmacodynamics (PD) of PF-05280586 (Ruxience™ [a rituximab biosimilar]) versus rituximab reference product sourced from the EU (MabThera®; rituximab-EU).

Patients and Methods Subjects with CD20-positive, low-tumor-burden follicular lymphoma (LTB-FL) and an Eastern Cooperative Oncology Group performance status 0–1 were randomized (1:1) to PF-05280586 or rituximab-EU (375 mg/m^2 intravenously [once weekly for 4 weeks at days 1, 8, 15, and 22]), stratified using the Follicular Lymphoma International Prognostic Index 2 classification. The primary endpoint was overall response rate (ORR) at week 26 (percentage of subjects achieving complete response [CR] or partial response [PR]). Therapeutic equivalence was concluded if the two-sided 95% confidence interval (CI) for the difference in ORR between groups was within the prespecified margin (± 16%). Secondary endpoints included progression-free survival (PFS), CR rate, safety, immunogenicity, PK, and PD.

Results A total of 394 subjects were randomized: PF-05280586 ($n = 196$) or rituximab-EU ($n = 198$). ORR at week 26 was 75.5% (PF-05280586) versus 70.7% (rituximab-EU), for a difference of 4.66%; 95% CI (−4.16 to 13.47), which was entirely within the prespecified equivalence margin. Rates of CR were 29.3% (PF-05280586) versus 31.0% (rituximab-EU). Estimated 1-year PFS rates were 78.2% (95% CI 70.2–84.2) and 83.0% (95% CI 75.0–88.6) for PF-05280586 and rituximab-EU, respectively. Safety, immunogenicity, and mean serum concentrations were similar between groups.

Conclusions The efficacy, safety, immunogenicity, PK, and PD of PF-05280586 and rituximab-EU were similar up to week 52 in subjects with previously untreated CD20-positive LTB-FL.

Clinical Trial Registration ClinicalTrials.gov, NCT02213263 and EudraCT (2014-000132-41).

Key Points

PF-05280586 (Ruxience™ [a rituximab biosimilar]) and rituximab reference product sourced from the EU (MabThera®; rituximab-EU) (both as monotherapy) demonstrated similar efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics in this comparative clinical study conducted in a suitably sensitive population.

These results are consistent with the similarity between PF-05280586 and reference rituximab shown in earlier studies.

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Enhanced Digital Features To view a plain language summary for this article, go to https://doi.org/10.6084/m9.figshare.10282727.

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1 Introduction

Biosimilars are highly similar to the licensed biologic ("reference product") such that there are no clinically meaningful differences in safety, purity, or potency [1]. The definitions of biosimilarity differ between the European Union (EU) and the United States (US); however, the underlying principles are aligned [1, 2]. The development and pathway to regulatory approval of biosimilars involves a stepwise approach of analytical, comparative physicochemical, and in vitro biological evaluation, and nonclinical and clinical studies (conducted in a suitably sensitive study population), comprising the "totality of the evidence" [1]. Biosimilars are expected to offer cost savings and improve access to biologic medicines [3, 4]. This may lead to improved management of a number of conditions, including hematologic malignancies and autoimmune diseases [4].

Rituximab (Rituxan®; MabThera®) has an important role in the treatment armamentarium for malignant hematology and autoimmune diseases [5, 6]. However, access to rituximab is limited by factors such as availability, reimbursement, and insurance coverage. Moreover, patent portfolios for rituximab have expired or are nearing the end of term, which, in turn, has prompted the development of biosimilars [3].

Rituximab biosimilars are approved by the European Medicines Agency (EMA) [7] and the US Food and Drug Administration (FDA) [8]. PF-05280586 (Ruxience™) was recently approved by the FDA for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), and granulomatosis with polyangiitis and microscopic polyangiitis [9]. PF-05280586 has the same primary amino acid sequence as rituximab reference products sourced from the US (rituximab-US; Rituxan®) and the EU (rituximab-EU; MabThera®) [10]. Moreover, comparative studies have shown similar structural, functional, and animal toxicity profiles of PF-05280586, rituximab-US, and rituximab-EU [10]. Pharmacokinetic (PK) bioequivalence between PF-05280586, rituximab-US, and rituximab-EU has been demonstrated in subjects with rheumatoid arthritis [11]. This study also demonstrated similar CD19-positive B-cell depletion, safety, and immunogenicity between all treatment groups. An extension phase of this study showed acceptable safety, tolerability, and immunogenicity [12].

Subjects with previously untreated CD20-positive, low-tumor-burden follicular lymphoma (LTB-FL) were considered the most appropriate patient population to demonstrate the clinical similarity of PF-05280586 and rituximab-EU (both in the first-line setting), and this selection was supported by regulatory authorities, since it represents a population suitably sensitive for distinguishing any potential clinically meaningful differences. Moreover, similarity in clinical efficacy between a rituximab biosimilar and the reference product can best be assessed using rituximab monotherapy in this setting [5, 6], without confounding factors that could potentially arise from treatment in other indications requiring rituximab in combination with chemotherapy.

This comparative clinical study evaluated the efficacy, safety, immunogenicity, PK, and pharmacodynamics (PD) of PF-05280586 compared with rituximab-EU in subjects with previously untreated CD20-positive LTB-FL. We report data at study completion (April 19, 2018), when the last randomized subject had completed 52 weeks of follow-up.

2 Methods

2.1 Study Population

Eligibility criteria were similar to those used in published randomized studies of rituximab monotherapy in subjects with LTB-FL [13, 14]. Adults (aged ≥ 18 years) with LTB-FL without lymphoma-related B symptoms (i.e., fever > 38 °C for 3 consecutive days; recurring, drenching night sweats; unintentional weight loss exceeding 10% of body weight in 6 months) were included. Subjects had an Eastern Cooperative Oncology Group performance status of 0–1. LTB was assessed using the *Groupe d'Etude des Lymphomes Folliculaires* criteria [15], and CD20-positive FL was confirmed retrospectively by central pathology review (Online Resource 1, see the electronic supplementary material [ESM]).

Subjects were excluded from the study if they met any of the following criteria: ineligible for rituximab monotherapy, evidence of high-grade or diffuse large B-cell lymphoma, previous history of T-cell lymphoma, ≥ 5000/mm^3 circulating lymphoma cells, or prior treatment with rituximab or other systemic therapy for B-cell NHL. Subjects with severe, acute, or chronic active conditions were also excluded from the study (Online Resource 2, see the ESM).

2.2 Study Design and Treatments

This was a randomized, double-blind, comparative clinical study in subjects with CD20-positive LTB-FL receiving first-line treatment, and was conducted at 160 centers in 29 countries (Online Resource 3, see the ESM).

2.3 Randomization and Masking

Subjects were randomized (1:1) to PF-05280586 or rituximab-EU (375 mg/m^2 intravenously [once weekly for 4 weeks at days 1, 8, 15, and 22]) and followed through to week 52 (Fig. 1). Subjects were stratified (low, medium, and high risk) at randomization using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2) classification

[16]. Randomization was conducted using a web-based automated-response system.

Concomitant medications were permitted, including prescription and nonprescription drugs, nondrug therapy, and dietary supplements and herbal preparations to treat adverse events (AEs) or comorbid conditions. Concomitant administration of any other experimental drug or chemotherapy, anticancer hormonal therapy, radiotherapy, or immunotherapy was not permitted during study participation. Additional doses of rituximab after the initial four weekly doses were also not permitted.

2.4 Primary Study Objective and Endpoint Assessments

The primary objective of the study was to compare the efficacy of PF-05280586 and rituximab-EU. The primary endpoint was overall response rate (ORR) at week 26, defined as the percentage of subjects achieving complete response (CR) or partial response (PR), based on central review, according to the revised response criteria for malignant lymphoma [17].

2.5 Secondary Objectives and Endpoint Assessments

Secondary endpoints included progression-free survival (PFS), CR rate at week 26, time to treatment failure (TTF), duration of response (DOR), overall survival (OS), safety, immunogenicity (including events related to Standardised MedDRA Queries of anaphylaxis and hypersensitivity reactions, and events meeting programmatically identified Sampson's criteria) [18], PK, and PD. Safety endpoints included type, incidence, severity, timing, seriousness and relatedness of AEs, and laboratory abnormalities. AEs were graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). AEs of special interest were identified based on the established safety profile of rituximab.

Immunogenicity endpoints were the percentage of subjects who were positive for antidrug antibodies (ADAs) and neutralizing antibodies (NAbs), using a tiered approach of screening, confirmation, and titer determination. Two semiquantitative electrochemiluminescent ADA assay methods were fully validated at QPS, LLC (Newark, Delaware, USA). Serum ADA samples were analyzed for the presence or absence of anti-PF-05280586 or anti-rituximab antibodies using a validated drug-specific assay with a tiered approach using screening, confirmation, and titer quantitation. Cross-reactivity analysis was conducted for samples that tested positive in the assay for the administered study drug using the alternate assay, with titration and confirmatory analysis.

Two semiquantitative NAb cell-based assay methods were fully validated at QPS, LLC. NAb serum samples that were ADA-positive were analyzed for the presence or absence of neutralizing anti-rituximab antibody and neutralizing anti–PF-05280586 antibody using the validated drug-specific assay with a tiered approach using screening, confirmation, and titer quantitation. Cross-reactivity analysis was conducted for samples that tested positive in the assay for the administered study drug using the alternate assay with titration and confirmatory analysis.

For subjects who tested positive for ADA, the titer, time of onset, and duration of ADA response were recorded.

PK endpoints were peak and trough drug concentrations. PD was evaluated using circulating CD19-positive B-cell counts as a marker for CD20-positive B-cells.

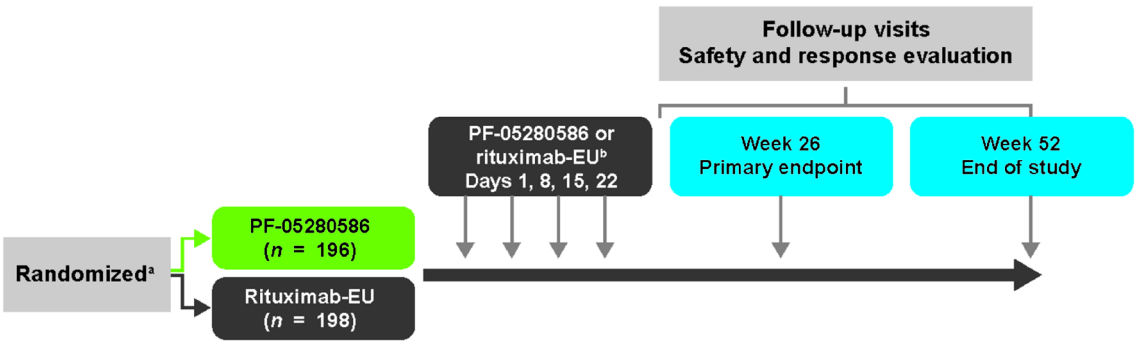

Fig. 1 Study design. [a]Subjects were stratified at randomization (1:1) using the FLIPI2 classification and had an ECOG performance status of 0–1. [b]PF-05280586 or rituximab-EU (375 mg/m^2 intravenously [once weekly for 4 weeks at days 1, 8, 15, and 22]). *ECOG* Eastern Cooperative Oncology Group, *FLIPI2* Follicular Lymphoma International Prognostic Index 2, *rituximab-EU* rituximab reference product from the European Union

2.6 Statistical Methods

A study published by Ardeshna and colleagues is the only randomized trial in subjects with asymptomatic FL that compared rituximab monotherapy with watchful waiting (WW), using the Cheson response criteria [13]. In the study by Ardeshna and colleagues, the response rate to rituximab therapy (weekly for 4 weeks) was estimated to be 77%, and 6% in the WW arm at month 7 [13]. The difference (rituximab − WW) was estimated to be 71% with the 95% confidence interval (CI) of 60–79%. Based on these results, a margin of − 16 to 16% would preserve at least 73% efficacy based on the lower bound of the 95% CI in the ORR difference (rituximab − WW).

The primary efficacy endpoint (ORR) was defined as the percentage of subjects achieving CR or PR at week 26. Assuming a week 26 ORR of 77% in both treatment groups (the stated equivalence margin), a sample size of 394 subjects (197 per treatment arm) was estimated to provide approximately 93% power to demonstrate equivalence with a 2.5% type 1 error rate.

The stratified Miettinen and Nurminen method was used to obtain the 95% CI for the estimated difference between PF-05280586 and rituximab-EU [19]. The stratified Mantel–Haenszel method was used to obtain the corresponding estimated treatment group difference (point estimate). Subjects were stratified by the FLIPI2 classification (low, medium, and high). Subjects with a missing week 26 response were imputed as nonresponders in the primary analysis.

Equivalence was concluded if the two-sided 95% CI for the ORR difference between treatment groups at week 26 was within the equivalence margin of ± 16%. An additional analysis was conducted to test equivalence of the ORR difference using a margin of ± 14.9% in order to meet regulatory requirements.

The intent-to-treat (ITT) population (defined as all subjects who were randomized) was considered primary for the analysis of efficacy endpoints. The per-protocol (PP) population (defined as all subjects who received at least one dose of study treatment to which they were assigned and who had measurable disease at baseline and no important protocol deviations) was used to assess the sensitivity of the ITT efficacy results. The response-evaluable population (defined as all subjects in the ITT population who received at least one dose of study treatment and who had adequate disease assessment at baseline and at least one post-baseline response assessment) was used for the analysis of DOR.

A stratified log-rank test (stratified by FLIPI2) was used to compare PFS, TTF, DOR, and OS between treatment groups. These endpoints were also summarized using Kaplan–Meier plots. A Cox model with FLIPI2 categorization as strata was used to estimate the hazard ratio (HR) and its 95% CI for the treatment effect. CR was analyzed using the same methods as for the analysis of ORR.

The safety population (defined as all subjects who received at least one dose of study treatment) was used for the safety analyses, including AEs, concomitant medication, laboratory tests, vital signs, ADA, and NAb incidence and titers. The serum concentration–time data were summarized using descriptive statistics by treatment (PK population). PD biomarkers were summarized by treatment and study visit (modified ITT population).

3 Results

Overall, 394 subjects were randomized to PF-05280586 ($n = 196$) or rituximab-EU ($n = 198$) and comprised the ITT population. In total, 393 subjects received at least one dose of study drug and were included in the safety population (196 subjects in the PF-05280586 group and 197 in the rituximab-EU group) (Fig. 2).

3.1 Baseline Characteristics and Subject Disposition

Demographic characteristics were similar between treatment groups. Subjects had a median age of 60.0 years, and 216 out of 394 (54.8%) were female. The randomization stratification factor was similar between treatment groups. According to FLIPI2, 112 subjects (28.4%) had low, 260 (66.0%) had medium, and 22 (5.6%) had high risk. Overall, 106 subjects (26.9%) had Ann Arbor stage II, 174 (44.2%) had stage III, and 114 (28.9%) had stage IV disease (Table 1).

3.2 Efficacy

3.2.1 Primary Endpoint

The ORR at week 26 (the primary efficacy endpoint, ITT) demonstrated therapeutic equivalence between PF-05280586 and rituximab-EU. In the ITT population, the ORR at week 26 was 75.5% (PF-05280586) versus 70.7% (rituximab-EU) and was identical to the results reported at the primary completion date. For the difference in ORR of 4.66%, the corresponding 95% CI (− 4.16 to 13.47) was entirely contained within the prespecified equivalence margins of ± 16% and ± 14.9% (Table 2). The ORR derived from central review assessments in the PP population was consistent with the corresponding results for the ITT population. The sensitivity analysis using the PP population supported the conclusion of the primary endpoint analysis.

Based on observed data at week 26, the analysis of ORR within both treatment groups (PF-05280586 and rituximab-EU) was consistent with the primary analysis. Furthermore, at week 26 (based on updates to the central review assessment as of the final database lock on May 18, 2018), 51 out of 174

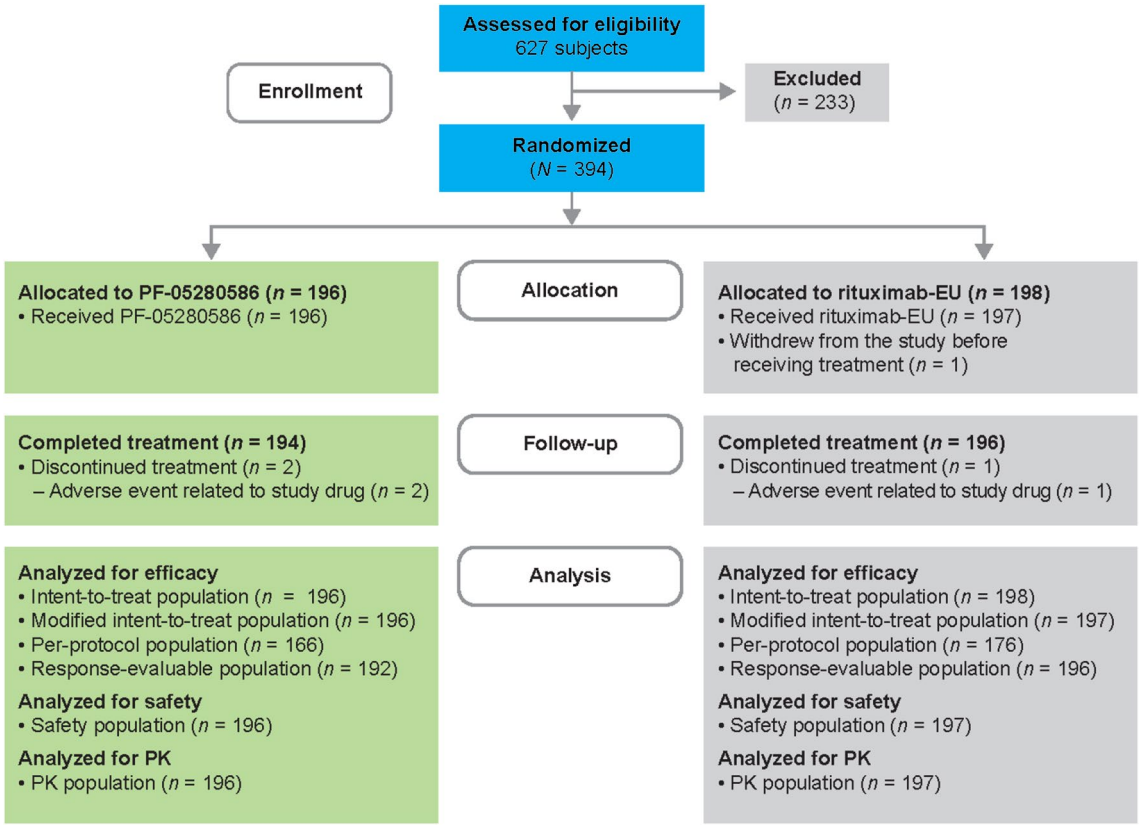

Fig. 2 Subject disposition. *n* number of subjects, *N* total number of subjects randomized, *PK* pharmacokinetic, *rituximab-EU* rituximab reference product from the European Union

subjects (29.3%) versus 57 out of 184 subjects (31.0%) had CR in the PF-05280586 and rituximab-EU groups, respectively, and 97 out of 174 subjects (55.7%) in the PF-05280586 group and 83 out of 184 subjects (45.1%) in the rituximab-EU group had PR. A total of 20 out of 174 subjects (11.5%) versus 36 out of 184 subjects (19.6%) had stable disease in the PF-05280586 and rituximab-EU groups, respectively, and six out of 174 subjects (3.4%) and eight out of 184 subjects (4.3%) had progressive disease (PF-05280586 vs rituximab-EU, respectively) (Online Resource 4, see the ESM).

3.2.2 Secondary Endpoints

Based on cumulative data at study completion, estimated 1-year PFS rates were 78.2% (95% CI 70.2–84.2) and 83.0% (95% CI 75.0–88.6) in the PF-05280586 and rituximab-EU groups, respectively. The HR for PFS for PF-05280586 versus rituximab-EU was 1.393 (95% CI 0.847–2.291), $p = 0.189$ (Online Resource 5a, see the ESM). The DOR was similar between the two treatment groups. Using a Cox proportional hazards model with FLIPI2 categorization as strata, the HR for TTF for PF-05280586 versus rituximab-EU was 1.163 (95% CI 0.786–1.720), $p = 0.450$ (Online Resource 5b, see the ESM).

3.3 Safety

The incidence of all-causality treatment-emergent adverse events (TEAEs) was similar in the two treatment groups (79.6% [PF-05280586] vs 73.6% [rituximab-EU]). The most frequently reported TEAEs (≥ 2% of subjects in either group) were infusion-related reactions (IRRs) (25.0% vs 29.9%), pruritus (6.6% vs 11.2%), and headache (8.2% vs 9.6%) (PF-05280586 vs rituximab-EU, respectively) (Table 3). In total, there were 28 out of 196 subjects (14.3%) in the PF-05280586 group and 26 out of 197 subjects (13.2%) in the rituximab-EU group with a TEAE reported at grade 3 or higher. The incidence of serious AEs was similar between groups (8.7% and 7.6% in the PF-05280586 and rituximab-EU groups, respectively). All-causality grade 3 TEAEs were reported in 13.8% (PF-05280586) versus 12.2% (rituximab-EU) of subjects. The most frequently reported grade 3 TEAEs were IRRs (2.0% vs 0.5%) and hypertension (1.0% vs 2.0%) in the PF-05280586 and rituximab-EU groups, respectively.

Treatment-related TEAEs were similar between groups (Online Resource 6, see the ESM). A total of four subjects reported five treatment-related serious AEs. These were grade 3 pyrexia and grade 3 *Clostridium difficile* infection in

Table 1 Baseline subject demographic and clinical characteristics (ITT population)[a]

Baseline characteristics	PF-05280586 $N=196$	Rituximab-EU $N=198$
Demographic		
Gender, *n* (%)		
Female	110 (56.1)	106 (53.5)
Male	86 (43.9)	92 (46.5)
Age, mean (SD), years	58.7 (12.1)	58.3 (12.8)
Body mass index, mean (SD), kg/m^2	26.7 (4.8)	26.3 (5.2)
Race, *n* (%)		
White	158 (80.6)	146 (73.7)
Black	1 (0.5)	0
Asian	30 (15.3)	44 (22.2)
Other	7 (3.6)	8 (4.0)
Ethnicity, *n* (%)		
Hispanic/Latino	31 (15.8)	26 (13.1)
Not Hispanic/Latino	165 (84.2)	172 (86.9)
Clinical characteristics		
Ann Arbor stage, *n* (%)		
I	0	0
II	52 (26.5)	54 (27.3)
III	89 (45.4)	85 (42.9)
IV	55 (28.1)	59 (29.8)
ECOG performance status, *n* (%)[b]		
0	171 (87.2)	169 (85.4)
1	25 (12.8)	28 (14.1)
FLIPI2 risk classification, *n* (%)		
Low	54 (27.6)	58 (29.3)
Medium	133 (67.9)	127 (64.1)
High	9 (4.6)	13 (6.6)

ECOG Eastern Cooperative Oncology Group, *FLIPI2* Follicular Lymphoma International Prognostic Index 2, *ITT* intent-to-treat, *rituximab-EU* rituximab reference product from the European Union, *SD* standard deviation

[a]All subjects who were randomized to treatment

[b]ECOG status not reported for one subject in the rituximab-EU group

the PF-05280586 group, and grade 3 serum sickness, grade 3 IRR, and grade 2 dyspnea in the rituximab-EU group. Overall, 86 subjects (43.9%) in the PF-05280586 group and 94 subjects (47.7%) in the rituximab-EU group reported treatment-related TEAEs, a total of 258 in each treatment group. The most frequently reported treatment-related TEAEs were IRRs (49 subjects [25.0%] in the PF-05280586 group and 59 subjects [29.9%] in the rituximab-EU group) and pruritus (ten subjects [5.1%] in the PF-05280586 group and 18 subjects [9.1%] in the rituximab-EU group).

The incidence of grade 3 treatment-related TEAEs was similar between groups (4.6% [PF-05280586] vs 3.6% [rituximab-EU]). One treatment-related TEAE (grade 4 neutropenia) was reported in one subject in the rituximab-EU group, but was not associated with any signs or symptoms of infection. No subjects in the PF-05280586 group reported grade 4 treatment-related TEAEs. Two deaths occurred during the study (one in each group) due to disease progression, and were deemed not to be treatment-related.

TEAEs of special interest were similar between treatment groups. The most frequently reported TEAEs of special interest were IRRs (Online Resource 7, see the ESM). There were no reports of tumor lysis syndrome or progressive multifocal leukoencephalopathy in either treatment group. No clinically significant differences in laboratory values or vital signs were observed between the two treatment groups.

In total, 54 subjects (13.7%) discontinued the study (26 out of 196 subjects [13.3%] in the PF-05280586 group and 28 out of 198 subjects [14.1%] in the rituximab-EU group) (Online Resource 8, see the ESM). No subjects in either treatment group reported an AE that led to a dose reduction. In total, 37 subjects (18.9%) in the PF-05280586 group and 51 (25.9%) in the rituximab-EU group experienced AEs that led to an infusion interruption.

3.4 Immunogenicity

Prior to initiation of study drugs at baseline (day 1), 7.2% of subjects in the PF-05280586 group and 8.7% of subjects in the rituximab-EU group had a positive ADA test (titer ≥ 1.88). The ADA titers were low in these positive pre-dose samples. Prior to dosing on day 15, there was no increase in ADA titers, indicating that a booster response was not observed. The ADA titers reported at week 13 and beyond did not increase and further confirmed the absence of a booster response.

Overall, 22.1% and 19.8% of subjects in the PF-05280586 and rituximab-EU groups, respectively, tested positive for ADA, post-dose. Of the samples that tested positive for ADA, the majority were positive in both ADA assays (anti–PF-05280586 or anti-rituximab antibodies), with 93.0% of subjects with positive ADA cross-reactivity in the PF-05280586 group and 76.9% in the rituximab-EU group (Online Resource 9, see the ESM). No ADA-positive subjects were positive for NAbs. No clinically meaningful differences were observed in immune-related AEs in subjects who were treatment-emergent ADA-positive versus those who were ADA-negative.

The percentage of IRRs in ADA-positive subjects was 25.6% in both treatment groups. Events of anaphylaxis/hypersensitivity (broad and narrow Standardised MedDRA Query) in ADA-positive subjects were similar in both treatment groups (16.3% [PF-05280586] vs 12.8% [rituximab-EU]). Events potentially meeting Sampson's criteria in ADA-positive subjects were also similar (11.6% [PF-05280586] vs 10.3% [rituximab-EU]).

Table 2 Overall response rate at week 26[a] (central review assessment)

Endpoint	PF-05280586	Rituximab-EU	Difference (PF-05280586 minus rituximab-EU)
ITT population			
Number of subjects	196	198	
Overall response rate, *n* (%)[b,c,d]	148 (75.5)	140 (70.7)	4.66
(95% CI)	(68.9–81.4)	(63.8–76.9)	(−4.16 to 13.47)
PP population			
Number of subjects	166	176	
Overall response rate, *n* (%)[b,c,e]	143 (86.1)	138 (78.4)	7.49
(95% CI)	(79.9–91.0)	(71.6–84.2)	(−0.67 to 15.80)

CI confidence interval, *CR* complete response, *ITT* intent-to-treat, *PP* per-protocol, *PR* partial response, *rituximab-EU* rituximab reference product from the European Union

[a]Based on the central review assessments as of the final database lock on May 18, 2018

[b]Subjects missing their week 26 radiology assessments were imputed as nonresponders

[c]Defined as the percentage of subjects achieving CR or PR, based on central review

[d]ITT population

[e]PP population

3.5 Pharmacokinetics

Mean serum concentrations of PF-05280586 and rituximab-EU were similar. The peak mean serum concentrations were observed at day 22, within 15 min before the end of the infusion, and were similar between the two treatment groups. No notable differences were observed in mean serum concentrations between ADA-positive and ADA-negative subjects in either treatment group (Online Resource 10, see the ESM).

3.6 Pharmacodynamics

In both treatment groups, rapid depletion in CD19-positive B-cell counts was observed after initial dosing, with initial recovery by week 39 and a sustained increase until the end of week 52 (Online Resource 11, see the ESM).

4 Discussion

This study demonstrated therapeutic equivalence between PF-05280586 and rituximab-EU at week 26 for the primary efficacy endpoint, ORR, in subjects with previously untreated CD20-positive LTB-FL. The 95% CI for the difference for ORR was entirely contained within the prespecified equivalence margins. Based on the central review assessments as of the final database lock, there were no clinically meaningful or statistically significant differences in CR rate at week 26, PFS, DOR, or TTF, all of which were similar between treatment groups. PF-05280586 and rituximab-EU showed similar safety profiles. The safety profile of PF-05280586 was similar to the established safety profile of rituximab-EU [5, 6]. The immunogenicity, PK, and PD of PF-05280586 and rituximab-EU were similar during the study. Rapid depletion in CD19-positive B-cell counts was observed following initial dosing, with similar results in both treatment groups followed by recovery.

The development of PF-05280586 as a biosimilar to rituximab-EU is supported by a body of analytical, nonclinical, and clinical data that assess comparative similarity between the two products, which comprises the totality of the evidence [10–12, 20]. The analytical assessment supports the conclusion that PF-05280586 is highly similar to rituximab-EU and that the minor differences do not impact the in vitro biological activity of these products, and is unlikely to be clinically relevant [10]. Nonclinical toxicity data support the totality of the evidence that PF-05280586 is similar to rituximab-EU [10]. Results of the in vitro assays demonstrated that PF-05280586, rituximab-US, and rituximab-EU are highly similar in attributes relevant to the known mechanisms of action [10]. In addition, clinical comparability studies showed similar PK profiles of PF-05280586 and the reference rituximab products in subjects with rheumatoid arthritis [11, 12] and in those with LTB-FL. Similar efficacy profiles were also observed for PF-05280586 and rituximab-EU in this comparative clinical study in subjects with LTB-FL. Finally, similar immunogenicity profiles were observed for PF-05280586 and rituximab-EU in the current study, and no new safety concerns were identified. The clinical similarity assessment supports the conclusion that PF-05280586 is similar to rituximab-EU. Based on the totality of the evidence, the FDA granted approval of PF-05280586 for the

Table 3 Treatment-emergent adverse events (all-causality, ≥ 2%) (safety population)

Category	PF-05280586 *N* = 196 *n* (%)	Rituximab-EU *N* = 197 *n* (%)
Subjects with AE	156 (79.6)	145 (73.6)
Injury, poisonings, and procedural complications	61 (31.1)	65 (33.0)
Infusion-related reaction	49 (25.0)	59 (29.9)
Fall	5 (2.6)	2 (1.0)
Gastrointestinal disorders	58 (29.6)	52 (26.4)
Nausea	15 (7.7)	17 (8.6)
Diarrhea	14 (7.1)	12 (6.1)
Abdominal pain upper	9 (4.6)	5 (2.5)
Constipation	8 (4.1)	8 (4.1)
Abdominal pain	8 (4.1)	3 (1.5)
Vomiting	3 (1.5)	7 (3.6)
Dyspepsia	5 (2.6)	2 (1.0)
Infections and infestations	52 (26.5)	63 (32.0)
Upper respiratory tract infection	9 (4.6)	5 (2.5)
Nasopharyngitis	5 (2.6)	9 (4.6)
Urinary tract infection	5 (2.6)	5 (2.5)
Sinusitis	5 (2.6)	2 (1.0)
Influenza	4 (2.0)	6 (3.0)
Pharyngitis	4 (2.0)	4 (2.0)
Bronchitis	3 (1.5)	7 (3.6)
Respiratory, thoracic, and mediastinal disorders	46 (23.5)	56 (28.4)
Throat irritation	14 (7.1)	10 (5.1)
Cough	11 (5.6)	11 (5.6)
Oropharyngeal pain	2 (1.0)	10 (5.1)
Dyspnea	6 (3.1)	9 (4.6)
Oropharyngeal discomfort	4 (2.0)	1 (0.5)
General disorders and administration-site conditions	52 (26.5)	53 (26.9)
Fatigue	12 (6.1)	13 (6.6)
Asthenia	9 (4.6)	13 (6.6)
Pyrexia	12 (6.1)	11 (5.6)
Edema peripheral	2 (1.0)	7 (3.6)
Influenza-like illness	2 (1.0)	4 (2.0)
Skin and subcutaneous tissue disorders	39 (19.9)	47 (23.9)
Pruritus	13 (6.6)	22 (11.2)
Rash	10 (5.1)	8 (4.1)
Erythema	7 (3.6)	2 (1.0)
Urticaria	3 (1.5)	6 (3.0)
Musculoskeletal and connective-tissue disorders	38 (19.4)	42 (21.3)
Back pain	8 (4.1)	10 (5.1)
Myalgia	9 (4.6)	5 (2.5)
Pain in extremity	7 (3.6)	4 (2.0)
Arthralgia	7 (3.6)	6 (3.0)
Nervous system disorders	34 (17.3)	33 (16.8)
Headache	16 (8.2)	19 (9.6)
Dizziness	2 (1.0)	6 (3.0)
Psychiatric disorders	15 (7.7)	17 (8.6)
Insomnia	5 (2.6)	8 (4.1)
Anxiety	6 (3.1)	7 (3.6)
Investigations	15 (7.7)	14 (7.1)
Neutrophil count decreased	5 (2.6)	0
White blood cell count decreased	4 (2.0)	1 (0.5)
Vascular disorders	11 (5.6)	15 (7.6)
Hypertension	5 (2.6)	7 (3.6)
Flushing	1 (0.5)	4 (2.0)
Metabolism and nutrition disorders	13 (6.6)	12 (6.1)
Hyperglycemia	1 (0.5)	4 (2.0)
Cardiac disorders	7 (3.6)	9 (4.6)
Palpitations	5 (2.6)	2 (1.0)

Subjects were only counted once per treatment for each row. Events are displayed by MedDRA (v21.0) system organ class and preferred term

AE adverse event, *n* number of subjects, *N* total number of subjects receiving treatment in each group, *rituximab-EU* rituximab reference product from the European Union

treatment of NHL, CLL, and granulomatosis with polyangiitis and microscopic polyangiitis [9].

One potential limitation of the current study is that it does not show that PF-05280586 is equivalent in every indication for which rituximab is approved; however, this was not the aim of the study and is not required for the regulatory approval of a biosimilar [1, 2]. In addition, the interpretation of AE data is limited due to the relative size of the current study; indeed, the safety of a biosimilar relies on a finding of biosimilarity and the safety profile of the reference product across the indications for which it is approved. Another potential limitation of the current study is that subjects received four doses of PF-05280586 or rituximab-EU; this is in contrast to eight doses of rituximab in aggressive lymphomas or 16–20 doses of rituximab in indolent lymphomas as induction and maintenance therapy [6, 21].

Treatment options for LTB-FL include WW and rituximab monotherapy [22]. This study was designed based on a randomized clinical trial that compared rituximab monotherapy (weekly dosing for 4 weeks) with WW, using the revised response criteria for malignant lymphoma [13]. After 7 months, the estimated response rate was 77% in the rituximab group versus 6% in the WW group, with an estimated difference of 71% (95% CI 60–79) [13]. In the study

conducted by Ardeshna and colleagues, the rituximab induction group (ORR at month 7: 77%) was closed earlier than the rituximab maintenance group (ORR at month 7: 88%) [13]. However, in the current study, retreatment following progression was not precluded and was consistent with a randomized phase III study comparing two rituximab dosing strategies for LTB-FL [14]. The ORR observed with the rituximab-EU group (76%; observed data at week 26) in the current study was consistent with the ORR observed in the study conducted by Ardeshna and colleagues (77%; observed data at month 7), showing good reproducibility of results across the two trials for the rituximab-EU (control) groups [13]. In addition, the subject eligibility criteria in this study were similar to other randomized studies conducted with rituximab monotherapy in the LTB-FL setting [13, 14].

In contrast to this comparative study of PF-05280586 and rituximab-EU (each as monotherapy), two approved rituximab biosimilars (CT-P10 and L01XC02) were studied in combination with chemotherapy in patients with FL [23, 24]. A second study by Ogura and colleagues of CT-P10 or rituximab as monotherapy was subsequently performed in subjects with previously untreated CD20-positive LTB-FL, in order to demonstrate biosimilarity without the confounding effects of chemotherapy [25]. In this study, patients who had disease control after the induction period progressed to maintenance treatment with CT-P10 or rituximab (every 8 weeks for six cycles) and, if completed, a second year of maintenance treatment of CT-P10 was offered [25]. That design was in contrast to this comparative study of PF-05280586 and rituximab-EU (each administered as monotherapy, in line with current standard of care for LTB-FL) [22]. As such, this reduces the potentially confounding factors that could arise from rituximab in combination with chemotherapy, as observed in other pivotal studies of rituximab biosimilars [23, 24]. The study by Ogura and colleagues was different in design to the current study and may account for the differences in ORR between the two studies [25]. In the study by Ogura and colleagues, as CT-P10 was used as a maintenance regimen, higher ORR (81%) was observed with rituximab-EU, whereas in the current study, PF-05280586 was administered as an induction regimen, without a maintenance phase, with an ORR of 71% with rituximab-EU [25]. Indeed, the differences in ORR between these two studies can also be explained by differences in patient characteristics and statistical variations.

In conclusion, this study demonstrated therapeutic equivalence between PF-05280586 and rituximab-EU for the primary efficacy endpoint, ORR at week 26, and similar safety, immunogenicity, PK, and PD in both groups up to week 52 in subjects with previously untreated CD20-positive LTB-FL.

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Compliance with Ethical Standards

This study was conducted in compliance with the ethical principles originating in, or derived from, the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines, and was reviewed and approved by institutional review boards and/or independent ethics committees. In addition, all local regulatory requirements were followed, particularly those affording greater protection to the safety of trial participants. All subjects provided informed consent before undergoing any screening procedures. The study was sponsored by Pfizer and is registered on ClinicalTrials.gov Identifier (NCT02213263) and EudraCT (2014-000132-41).

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Conflict of interest J.P. Sharman received consulting fees and research funding from Pfizer Inc, Genentech, and TG Therapeutics. A.M. Liberati declares no competing interests. K. Ishizawa received grants from Pfizer and personal fees from Chugai during the conduct of the study, grants and personal fees from Kyowa Kirin, grants from Sanofi and AbbVie, personal fees from MSD, Janssen, Celgene, Eizai, Ono, and Novartis, grants from Otsuka, and grants and personal fees from Takeda outside the submitted work. T. Khan is a full-time employee of, and declares stock holdings or stock options from, Pfizer Inc. A. Alcasid is a full-time employee of Pfizer Inc. J.A. Rosenberg and J. Robbins were employees of, and held stock holdings or stock options from, Pfizer Inc at the time of the study. I. Aurer received research funding and honoraria from Roche and Pfizer Inc, and consultancy fees from Roche.

Availability of Data 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 (i.e., 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.

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