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Prescribing decisions should be made based on the approved package insert.

GENERIC DRUG NAME AND/OR COMPOUND NUMBER: PF-05280586

PROTOCOL NO.: B3281006

PROTOCOL TITLE: A Phase 3, Randomized, Double-Blind Study of PF-05280586 Versus Rituximab for the First-Line Treatment of Patients With CD20-Positive, Low Tumor Burden, Follicular Lymphoma

Study Center(s): A total of 160 centers took part in the study: 1 each in Austria, Peru, and Puerto Rico, 2 each in Belarus, Croatia, Georgia, South Africa, Thailand, and Poland, 3 each in Belgium, Switzerland, United Kingdom, and Lebanon, 4 each in France, Greece, Mexico, Portugal, and Romania, 5 each in India, and Ukraine, 7 each in Germany, and the Republic of Korea, 8 each in Brazil, and Turkey, 10 each in the Russian Federation, and Spain, 13 in Italy, 19 in Japan, and 21 in the United States.

Study Initiation Date and Primary Completion or Final Completion Dates:

Study Initiation Date: First subject first visit: 30 September 2014

Final Completion Date: Last subject last visit: 19 April 2018

Phase of Development:

Phase 3

Study Objective(s):

Primary Objective

- To compare the efficacy of PF-05280586 to rituximab-EU when administered as a first-line treatment to subjects with CD20-positive, low tumor burden follicular lymphoma (LTB FL).

Secondary Objectives

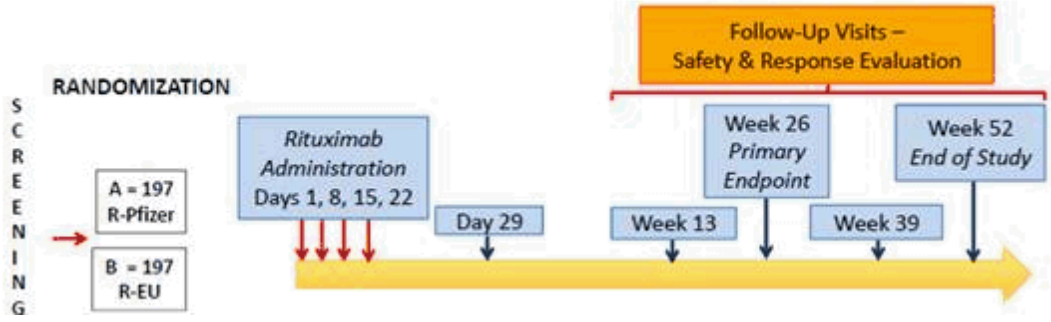
- To evaluate the safety of PF-05280586 and rituximab-EU
- To evaluate the population pharmacokinetics (PK) of PF-05280586 and rituximab-EU
- To evaluate the immunogenicity of PF-05280586 and rituximab-EU
- To characterize CD19-positive B-cell depletion and recovery in subjects receiving PF-05280586 and rituximab-EU.

METHODS

Study Design: This was a double-blind, randomized, comparative clinical trial evaluating the efficacy, safety, PK and immunogenicity of PF-05280586 versus rituximab-EU in subjects with CD20 positive, LTB FL in the first-line treatment setting. Subjects were

randomized in a 1:1 ratio to receive PF-05280586 or rituximab-EU. Randomization was stratified by low, medium, and high risk subjects using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2). During the study, subjects received 4 weekly doses of PF-05280586 or rituximab-EU administered via intravenous infusion. The dose of PF-05280586 or rituximab-EU was 375 mg/m^2 of body surface area (BSA). The maximum dose that could be infused in 1 day was 1125 mg.

Figure 1. Study Schematic



Abbreviations: EU=European Union; R-EU=rituximab-EU; R-Pfizer=rituximab-Pfizer (PF-05280586)

Number of Subjects (Planned and Analyzed): The primary hypothesis to be tested in this study was that the difference between the overall response rate (ORR) of PF-05280586 versus that of rituximab-EU was within a pre-specified equivalence margin of -16% to 16% (-14.9% to 14.9% for Japan). A sample size of approximately 394 subjects (approximately 197 per treatment arm) provided approximately 93% power for achieving equivalence under the specified margin with 2.5% type I error rate assuming an ORR of 77% in both treatment arms. Overall 394 subjects were enrolled globally (196 subjects in the PF-05280586 group and 198 subjects in the rituximab-EU group).

Diagnosis and Main Criteria for Inclusion and Exclusion: Male or female subjects aged 18 years or older with histologically confirmed, Grade 1-3a, CD20-positive FL (containing no elements of diffuse large B-cell lymphoma) were eligible for the study. Documentation of Ann Arbor Staging (II, III, or IV), an Eastern Cooperative Oncology Group status of 0 to 1, and at least 1 measureable disease lesion identifiable by imaging was also required for study eligibility. An eligible subject with LTB FL was defined as serum lactate dehydrogenase ≤1.5 upper limit of normal (ULN), β2-microglobulin ≤1.5 × ULN, largest nodal or extra-nodal mass <7 cm in diameter, no more than 3 nodal sites with a diameter >3 cm, no clinically significant serous effusions detectible on chest radiography, spleen enlargement ≤16 cm by computed tomography scan, no complications such as organ compression or impairment, and no B symptoms (ie, fever >38°C for 3 consecutive days; recurrent, drenching night sweats; unintentional weight loss exceeding 10% body weight in 6 months).

Study Treatment: Blinded rituximab (PF-05280586 or rituximab-EU) was administered at a dose of 375 mg/m^2 at Visits 2, 3, 4, and 5 (Days 1, 8, 15, and 22). The BSA for the subject was calculated using a standard formula and the subject's weight and height. The weight and height at Screening could have been used to calculate the BSA for all doses unless the subject had a clinically significant change in weight from Screening at a dosing visit, in which case the dose could be adjusted if there had been a change of more than 10%. The maximum dose

of rituximab that could be infused in 1 day was 1125 mg. Infusion instructions were followed as per the product labeling; study treatment was administered according to the local product labeling if it differed from the following instructions:

- Day 1 infusion: Infusion was initiated at a rate of 50 mg/hour. After 30 minutes and in the absence of infusion toxicity, infusion rate was increased by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

- Day 8, 15, and 22 infusions: Infusion was initiated at a rate of 100 mg/hour. After 30 minutes and in the absence of infusion toxicity, the infusion rate was increased by 100 mg/hour increments at 30 minute intervals, to a maximum of 400 mg/hour.

- Subjects were closely monitored for the onset of cytokine release syndrome. Subjects who developed evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia had immediate interruption of the infusion. In all subjects, the infusion was not to be restarted until complete resolution of all symptoms, and normalization of laboratory values. At this time, the infusion could be initially resumed at not more than one half the previous rate. If the same severe adverse reactions occurred for a second time, the decision to stop the treatment was seriously considered on a case by case basis.

- Mild to moderate infusion related reactions (IRRs) usually respond to a reduction in the rate of infusion. The infusion rate could have been increased upon improvement of symptoms.

- The subject was observed post-infusion if necessary based on the investigator's medical judgment.

Efficacy Evaluations: The primary efficacy endpoint was ORR at Week 26 of PF-05280586 versus rituximab-EU based on central review which included radiographic assessment and review of clinical data (B-cell depletion and bone marrow biopsy results). As per current guidelines for staging and response assessment of lymphoma, the ORR was defined purely for the purpose of this study as the proportion of subjects who achieved either complete response (CR) or partial response (PR). This updated terminology has been used throughout and is based on the Lugano Classification, the most current response assessment guidelines for malignant lymphoma.

Secondary efficacy evaluations included:

- Time to treatment failure (TTF) defined as the time from date of randomization to progression of disease (PD) based on central review, death due to any cause, or permanent discontinuation from treatment, or discontinuation from study for any reason, whichever came first.

- Progression-free survival (PFS) defined as the time from date of randomization to first PD (based on central review) or death due to any cause in the absence of documented PD.

- Complete response at Week 26 defined as per the revised response criteria for malignant lymphoma (based on central review).

- Duration of response (DOR) defined as the time from date of the first documentation of overall response (CR or PR) to the first documentation of PD (central review) or to death due to any cause in the absence of documented PD.

- Overall survival (OS) defined as the time from date of randomization to death due to any cause.

Immunogenicity, Pharmacokinetic and Pharmacodynamic Evaluations

Serum samples for detection of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were collected within 4 hours prior to dose administration on Day 1 and Day 15. Additional samples for detection of ADA and NAb were collected at Weeks 5 (Day 29), 13, 26, 39, and 52. Human serum ADA samples were analyzed using 2 validated, semi-quantitative electrochemiluminescent ADA assay methods. Human serum samples testing positive for the presence of ADA were required to be analyzed for the presence or absence of neutralizing anti-rituximab antibody and neutralizing anti-PF-05280586 antibody using 2 semi-quantitative NAb cell-based assays. Both assays used a tiered approach using screening, confirmation and titer/quantitation. The cross-reactivity sample analysis was done for those study samples that tested positive in the assay for the administered study drug using the alternate assay with titration and confirmatory analysis. For the immunogenicity data, the percentage of subjects with positive ADA and NAb was summarized for each treatment and by visit. For subjects with positive ADA, the magnitude (titer), of ADA response was also described. In addition, possible associations of ADA response with clinical data on the PK, and safety were examined.

On days where study drug was administered (Days 1, 8, 15, and 22), serum samples for measurement of drug concentrations were collected prior to dose administration (within 4 hours of the start of dosing). On Days 1 and 22, additional drug concentration samples were collected within 15 minutes prior to the end of infusion. Additionally, drug concentration samples were collected at Weeks 5 (Day 29), 13, 26, 39 and 52. Rituximab samples were assayed using a validated, sensitive and specific enzyme-linked immunosorbent assay. The serum specimens were stored at approximately -70°C until assay. The serum concentration-time data were summarized using descriptive statistics by treatment.

The pharmacodynamics of PF-05280586 and rituximab-EU was evaluated using circulating CD19-positive B-cell counts (surrogate marker for CD20+ B-cells). Rituximab is known to deplete B-cells, which can result in a decrease in circulating levels of immunoglobulin (Ig)M and IgG. Blood samples for assessment of circulating CD19 positive B-cell counts, and IgM and IgG were collected at Day 1 (Visit 2), Treatment Visits (Visits 3, 4, and 5: Study Days 8, 15, and 22), Follow-up Visits (Visits 6, 7, 8, and 9: Weeks 5, 13, 26, and 39), and the End of Study/Early Termination Visit (Visit 10, Week 52). Blood samples were assayed for CD19+ B-cell counts by laser scanning cytometry. Summary statistics by treatment and visit were provided for the biomarkers including CD19 positive B-cell counts, IgM and IgG.

Safety Evaluations: Safety was characterized by type, incidence, severity, timing, seriousness, and relationship to study treatment of adverse events (AEs), including neutropenia, infections, IRRs, and other clinical outcomes associated with immunogenicity (hereafter referred to as immune-based adverse effects; events relating to Standardized Medical Dictionary for Regulatory Activities Queries of Anaphylaxis and Hypersensitivity reactions, and events meeting Sampson's criteria), and laboratory abnormalities.

Statistical Methods:

The primary efficacy analysis for equivalence was performed after all randomized subjects had the opportunity to complete their Week 26 visit and the assessment of overall response. Analyses were performed with the Intent-to-Treat (ITT) Population defined as all subjects who were randomized. The same analysis based on the Per Protocol (PP) Population, defined as all randomized subjects who received at least 1 dose of study treatment (PF-05280586 or rituximab-EU) as planned, had adequate disease assessment at baseline as confirmed by central review, and had no important protocol deviations that would impact the efficacy assessments significantly, was performed as a sensitivity analysis. Descriptive statistics (frequency and percentage) for CR, PR, and ORR were presented by treatment group and visit. The 95% confidence interval (CI) of these response rates within each group, and the 95% CI of the difference in the response rates between the 2 treatment groups was constructed.

The estimated difference in response rate between PF-05280586 and rituximab-EU was computed (based on the stratified Mantel-Haenszel method) and the asymptotic 95% CI of the difference, as proposed by Miettinen and Nurminen (published in 1985) was constructed. The FLIPI2 categorization (low, medium, and high) was considered as the stratification factor in the Mantel-Haenszel (for the estimated treatment difference) and Miettinen and Nurminen (for the 95% CI) methods.

Progression-free survival was defined as the time from date of randomization to first PD or death due to any cause in the absence of documented PD and was censored as summarized in Table 1:

Table 1. Handling of Missing Assessments and Censoring Rules for PFS Analysis

Situation	Date of Progression or Censoring	Outcome
No baseline or no adequate baseline assessment, and no death	Date of Randomization	Censored
No post-baseline or no adequate post-baseline assessment, and no death	Date of Randomization	Censored
No death or disease progression	Date of last adequate assessment	Censored
Discontinued from study	Date of last adequate assessment	Censored
Disease progression or death	Date of death or first adequate assessment for progression, whichever was earlier	Progressed (event)

The censoring mechanisms for TTF and DOR were similar to those described for PFS above with the exception that for TTF permanent discontinuation from treatment or discontinuation from study was considered as treatment failure, and for DOR when a subject had missing

response assessment(s) but remained as a CR or PR responder at the time of data analysis, the endpoint was censored at the time of the last adequate assessment where CR or PR was declared.

A log-rank test stratified by FLIPI2 risk was used to compare the treatment groups with respect to the secondary endpoints of PFS, OR, TTF and DOR at a 2-sided alpha level of 0.05. Secondary endpoints were also summarized using the Kaplan-Meier method. The Kaplan-Meier 1-year estimates and the 2-sided 95% CI of the rates using the Greenwood's formula were reported. In addition, a Cox model stratified by FLIPI2 was used to estimate the hazard ratio and its 95% CI for the treatment effect.

The primary efficacy endpoint (ORR at Week 26) was also analyzed within subgroups of interest, to evaluate consistency of results relative to overall results.

The analysis for DOR was based on central review assessment and the Response Evaluable Population, defined as all subjects in the ITT Population who received at least 1 dose of study drug, had adequate disease assessment at baseline, and at least 1 post-baseline response assessment.

The safety analyses (including ADA and NAb analyses) were carried out using the Safety Population, defined as all subjects who received at least 1 dose of study drug.

Safety data were described using descriptive statistics. Frequency and percentage of subjects within each treatment group, risk difference, p-value, and 95% CI of risk difference were provided for Tier-1 AEs (pre-specified events considered of potentially clinical importance) and Tier-2 AEs (those events that occurred in at least 6 subjects in either treatment group and were not Tier-1). Individual signs and symptoms of IRRs were documented on the electronic case report form in addition to the preferred term (PT) of "infusion related reaction" for the purpose of comparing the overall percentage of subjects by treatment arm. The reporting of these events and timing of events in relation to the infusion were determined by the investigator. All IRRs, potential allergic and anaphylactic reactions based on Sampson criteria were summarized overall, by treatment group and by ADA status.

RESULTS

Subject Disposition and Demography:

A summary of subject disposition is provided in Table 2. There were 394 subjects assigned to the double-blind treatment; 196 subjects in the PF-05280586 group and 198 subjects in the rituximab-EU group. Of these, 393 subjects were actively treated including 196 treated subjects in the PF-05280586 group and 197 treated subjects in the rituximab-EU group. There was 1 subject who was assigned to the rituximab-EU group who withdrew from the study prior to receiving treatment. Of the 393 subjects actively treated, 390 subjects had completed protocol-specified therapy. They received 4 doses of study treatment given on Days 1, 8, 15, and 22 (194 [99.0%] subjects in the PF-05280586 group and 196 [99.0%] subjects in the rituximab-EU group).

In total, 340 subjects had completed Week 52 (End of Study) of the study (170 [86.7%] subjects in the PF-05280586 group and 170 [85.9%] subjects in the rituximab-EU group). In

total, 54 (13.7%) subjects had discontinued from the study. The ITT Population (394 [100.0%] subjects) was used for the efficacy analysis, and the Safety Population (393 [99.7%] subjects) was used for the analyses of AEs (393 [99.7%] subjects) and laboratory data (392 [99.5%] subjects), including ADA and NAb analyses. The PP Population (342 [86.8%] subjects) was used for sensitivity analyses of the primary and secondary efficacy endpoints. The modified ITT Population (393 [99.7%] subjects) was used for the biomarker analyses. The Response Evaluable Population (388 [98.5%] subjects) was used for the analysis of DOR. The PK Population (393 [99.7%] subjects), defined as subjects who were treated with PF-05280586 or rituximab-EU and provided at least 1 post-dose drug concentration measurement, was used for analysis of the PK endpoints. The percentage of subjects in each population was comparable between treatment groups.

Table 2. Subject Evaluation Groups

	rituximab-EU	PF-05280586	Total
Number (%) of subjects			
Screened			627
Assigned to study treatments	198	196	394
Treated	197	196	393
Completed treatment	196 (99.0)	194 (99.0)	390 (99.0)
Discontinued treatment	1 (0.5)	2 (1.0)	3 (0.8)
Completed study	170 (85.9)	170 (86.7)	340 (86.3)
Discontinued study	28 (14.1)	26 (13.3)	54 (13.7)
Analyzed for efficacy			
ITT	198 (100.0)	196 (100.0)	394 (100.0)
mITT[a]	197 (99.5)	196 (100.0)	393 (99.7)
PP	176 (88.9)	166 (84.7)	342 (86.8)
Response Evaluable Population	196 (99.0)	192 (98.0)	388 (98.5)
Analyzed for safety[b]			
Safety analysis	197 (99.5)	196 (100.0)	393 (99.7)
Adverse events	197 (99.5)	196 (100.0)	393 (99.7)
Laboratory data	197 (99.5)	195 (99.5)	392 (99.5)
Analyzed for PK			
PK analysis	197 (99.5)	196 (100.0)	393 (99.7)

Abbreviations: ADA=anti-drug antibody; EU=European Union; ITT=Intent-to-Treat; mITT=modified Intent-to-Treat; NAb=neutralizing antibody; PK=pharmacokinetic; PP=per protocol.
a. Included biomarker analyses.
b. Analyzed for safety included ADA and NAb.

A summary of demographic characteristics for the ITT Population is presented in Table 3. Demographic and baseline characteristics were comparable between the 2 treatment groups. The majority of the treated subjects were female (216) and white (304 [77.2%]). The mean age of all subjects was 58.5 years (range 21 to 93 years).

Table 3. Demographic Characteristics - ITT Population

	rituximab-EU	PF-05280586	Total
Number (%) of subjects	198	196	394
Gender			
Male	92 (46.5)	86 (43.9)	178
Female	106 (53.5)	110 (56.1)	216
Age (years)			
<18	0	0	0
18-44	29 (14.6)	27 (13.8)	56 (14.2)
45-64	101 (51.0)	102 (52.0)	203 (51.5)
≥65	68 (34.3)	67 (34.2)	135 (34.3)
Mean (SD)	58.3 (12.8)	58.7 (12.1)	58.5 (12.4)
Median	60.0	59.0	60.0
Range	21-93	25-85	21-93
Race			
White	146 (73.7)	158 (80.6)	304 (77.2)
Black	0	1 (0.5)	1 (0.3)
Asian	44 (22.2)	30 (15.3)	74 (18.8)
Other	8 (4.0)	7 (3.6)	15 (3.8)
Ethnicity			
Hispanic/Latino	26 (13.1)	31 (15.8)	57 (14.5)
Not Hispanic/Latino	172 (86.9)	165 (84.2)	337 (85.5)
Weight (kg)			
N	198 (100.0)	196 (100.0)	394 (100.0)
Mean (SD)	73.2 (18.0)	73.7 (15.6)	73.5 (16.8)
Median	72.0	73.9	73.0
Range	42.2-156.0	37.6-130.0	37.6-156.0
Height (cm)			
N	195 (98.5)	194 (99.0)	389 (98.7)
Mean (SD)	166.1 (9.3)	166.0 (10.5)	166.0 (9.9)
Median	165.0	165.0	165.0
Range	146.4-190.0	137.0-195.0	137.0-195.0
Body mass index (kg/m^2)			
N	195 (98.5)	194 (99.0)	389 (98.7)
Mean (SD)	26.3 (5.2)	26.7 (4.8)	26.5 (5.0)
Median	25.9	26.0	26.0
Range	16.0-54.7	16.1-47.6	16.0-54.7

Abbreviations: EU=European Union; ITT=Intent-to-Treat; N=number of subjects; SD=standard deviation.
Body mass index was defined as weight/(height*.01)**2

Efficacy, Pharmacokinetic, Pharmacodynamic and Immunogenicity Results:

Primary Efficacy Endpoint: The ORR was equivalent between the 2 treatment groups with 148 (75.5%) subjects in the PF-05280586 group, and 140 (70.7%) subjects in the rituximab-EU group achieving CR or PR at Week 26 based on central review.

The analysis of ORR showed an estimated difference of 4.66% (PF-05280586 minus rituximab-EU), with a 95% CI of (-4.16%, 13.47%), which fell entirely within the -16.0% to 16.0% pre-specified equivalence margin agreed to by the Food and Drug Administration (FDA) and European Medicines Agency (EMA), and also within the -14.9% to 14.9% margin agreed to by the Pharmaceuticals and Medical Devices Agency (PMDA) (Table 4).

Table 4. Summary of Overall Response Rate (ORR) at Week 26 - Central Review Assessment - ITT Population

	rituximab-EU (N=198)	PF-05280586 (N=196)	Difference (PF-05280586 minus rituximab-EU)
Overall Response Rate, n (%)	140 (70.7)	148 (75.5)	4.66
(95% CI)	(63.8, 76.9)	(68.9, 81.4)	(-4.16, 13.47)

ORR was defined as the proportion of subjects who achieved either CR or PR at the specified time point.
The stratified Miettinen and Nurminen method was used to obtain the asymptotic 95% CI of the estimated difference (PF-05280586 minus rituximab-EU).
The stratified Mantel-Haenszel method was used to obtain the estimated difference between treatment groups. The FLIPI2 categorization was considered as the stratification factor.
Abbreviations: CI=confidence interval; CR=complete response; EU=European Union; FLIPI2=Follicular Lymphoma International Prognostic Index 2; ITT=Intent-to-Treat; n=number of subjects with observation; N=total number of subjects in the analysis population; ORR=overall response rate; PR=partial response.

Secondary Efficacy Endpoints

Time to Treatment Failure (TTF): A total of 142 (72.4%) ITT subjects in the PF-05280586 and 150 (75.8%) subjects in the rituximab-EU treatment groups were censored (Table 5). The main reason for censorship was 'study completion without treatment failure' for subjects in the PF-05280586 treatment group (139 [97.9%] subjects and 149 [99.3%] subjects in the PF-05280586 and rituximab-EU treatment groups, respectively).

Using a Cox Proportional Hazards model with FLIPI2 categorization (low, medium, and high) as strata, the hazard ratio for TTF for PF-05280586 versus rituximab-EU was 1.163, with a 95% CI of (0.786, 1.720). The stratified log-rank test resulted in a 2-sided p-value of 0.450.

Table 5. Kaplan-Meier Estimates, Time to Treatment Failure (TTF) - Central Review Assessment - ITT Population

	rituximab-EU (N=198)	PF-05280586 (N=196)
Number with event, n (%)[a]	48 (24.2)	54 (27.6)
Number censored, n (%)	150 (75.8)	142 (72.4)
Reason for censorship, n (%)[b]		
Ongoing at data cutoff	0	0
No baseline assessment (or not adequate), no treatment failure	0	0
No post-baseline assessment (or not adequate), no treatment failure	1 (<1.0)	3 (2.1)
Study completion without treatment failure	149 (99.3)	139 (97.9)
Probability (%) of being event-free at 1 year[c] (95% CI)[d]	75.3 (67.6, 81.5)	71.5 (63.7, 77.9)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[e]		
25%	12.1 (11.7, 12.6)	11.8 (11.2, 12.3)
50%	18.9 (12.6, 18.9)	- (12.3, -)
75%	18.9 (- , -)	-
Versus rituximab-EU		
Hazard ratio[f]		1.163
95% CI of hazard ratio		0.786 - 1.720
P-value[g]		0.450

Abbreviations: CI=confidence interval; EU=European Union; FLIPI2=Follicular Lymphoma International Prognostic Index 2; HR=hazard ratio; ITT=Intent-to-Treat; n=number of subjects meeting specified criteria; N=total number of subjects.

a. Time to event was based on the first event to occur (possible events: progression, death, early treatment discontinuation, early study discontinuation).
b. Percentage was calculated based on the number of censored subjects.
c. Estimated from the Kaplan-Meier method.
d. Calculated based on Greenwood method.
e. Kaplan-Meier method used and 2-sided 95% CI calculated based on the Brookmeyer and Crowley method.
f. Hazard ratio and its CIs were estimated from Cox Proportional Hazards model stratified by FLIPI2 risk categorization.
g. 2-sided p-value from the log-rank test stratified by FLIPI2 risk categorization.

Progression-Free Survival (PFS): The percentage of subjects in the ITT Population who had disease progression or died, were censored, or were estimated to be event-free at 1 year was comparable between the 2 treatment groups (Table 6). There were 37 (18.9%) subjects in the PF-05280586 treatment group and 28 (14.1%) subjects in the rituximab-EU treatment group who had an event. A total of 159 (81.1%) subjects in the PF-05280586 treatment group and 170 (85.9%) subjects in the rituximab-EU group were censored.

Using a Cox Proportional Hazards model with FLIPI2 categorization (low, medium, and high) as strata, the hazard ratio when comparing PF-05280586 and rituximab-EU was 1.393,

with a 95% CI of (0.847, 2.291). The stratified log-rank test resulted in a 2-sided p-value of 0.189.

Table 6. Kaplan-Meier Estimates, Progression-Free Survival (PFS) - Central Review Assessment - ITT Population

	Rituximab-EU (N=198)	PF-05280586 (N=196)
Number with event, n (%)	28 (14.1)	37 (18.9)
Type of event, n (%)[a]		
Progression	27 (96.4)	36 (97.3)
Death without progression	1 (3.6)	1 (2.7)
Number censored, n (%)	170 (85.9)	159 (81.1)
Reason for censorship[b]		
No baseline assessment (or not adequate), no death	1 (<1.0)	0
No post-baseline assessment (or not adequate), no death	2 (1.2)	6 (3.8)
Early study discontinuation without progression/death	17 (10.0)	14 (8.8)
Study completion without progression/death	150 (88.2)	139 (87.4)
Probability (%) of being event-free at 1 year[c] (95% CI)[d]	83.0 (75.0, 88.6)	78.2 (70.2, 84.2)
Kaplan-Meier estimates of time to event (months)		
Quartiles (95% CI)[e]		
25%	12.6 (12.1, 18.9)	12.1 (11.8, -)
50%	18.9 (12.6, 18.9)	-
75%	18.9 (- , -)	-
Versus rituximab-EU		
Hazard ratio[f]		1.393
95% CI of hazard ratio		0.847 - 2.291
P-value[g]		0.189

Abbreviations: CI=confidence interval; EU=European Union; FLIPI2=Follicular Lymphoma International Prognostic Index 2; ITT=Intent-to-Treat; n=number of subjects meeting specified criteria; N=total number of subjects.

a. Percentage was calculated based on the number of subjects with event.
b. Percentage was calculated based on the number of censored subjects.
c. Estimated from the Kaplan-Meier method.
d. Calculated based on Greenwood method.
e. Kaplan-Meier method used and 2-sided 95% CI calculated based on the Brookmeyer and Crowley method.
f. Hazard ratio and its CIs were estimated from Cox Proportional Hazards model stratified by FLIPI2 risk categorization.
g. 2-sided p-value from the log-rank test stratified by FLIPI2 risk categorization.

Complete Response (CR) at Week 26: The percentage of all subjects who achieved CR at Week 26 was comparable between the 2 treatment groups. The proportion of subjects in the ITT Population achieving a CR at Week 26 based on central review was 51 (26.0%) subjects in the PF-05280586 group and 57 (28.8%) subjects in the rituximab-EU group, with

97 (49.5%) subjects in the PF-05280586 group and 83 (41.9%) subjects in the rituximab-EU group achieving a PR at Week 26. The analysis of CR derived from central review assessments showed a difference of -2.80% (PF-05280586 minus rituximab-EU), with a 95% CI of (-11.60%, 6.03%) and a difference of 7.46% (-2.41%, 17.18%) for subjects having achieved a PR (Table 7).

Table 7. Summary of Complete Response (CR) and Partial Response (PR) at Week 26 - Central Review Assessment - ITT Population

	Rituximab-EU (N=198)	PF-05280586 (N=196)	Difference (PF-05280586 minus Rituximab-EU)
Complete Response			
n (%)	57 (28.8)	51 (26.0)	-2.80
(95% CI)	(22.6, 35.6)	(20.0, 32.8)	(-11.60, 6.03)
Partial Response			
n (%)	83 (41.9)	97 (49.5)	7.46
(95% CI)	(35.0, 49.1)	(42.3, 56.7)	(-2.41, 17.18)

The stratified Miettinen and Nurminen method was used to obtain the asymptotic 95% CI of the estimated difference (PF-05280586 minus rituximab-EU).
The stratified Mantel-Haenszel method was used to obtain the estimated difference between treatment groups. The FLIPI2 categorization was considered as the stratification factor.
Abbreviations: CI=confidence interval; EU=European Union; FLIPI2=Follicular Lymphoma International Prognostic Index 2; ITT=Intent-to-Treat; n=number of subjects with observation; N=total number of subjects in the analysis population.

Duration of Response (DOR): Using a Cox Proportional Hazards model with FLIPI2 categorization (low, medium, and high) as strata, the hazard ratio between PF-05280586 and rituximab-EU was 1.492, with a 95% CI of (0.823, 2.704). The stratified log-rank test resulted in a 2-sided p-value of 0.185 (Table 8).

Table 8. Kaplan-Meier Estimates, Duration of Response (DOR) - Central Review Assessment - Response Evaluable Population

	rituximab-EU (N=196)	PF-05280586 (N=192)
Number of subjects with response (CR or PR), n (%)	166 (84.7)	165 (85.9)
Number with event, n (%)	19 (11.4)	28 (17.0)
Type of event[a]		
Progression	18 (94.7)	28 (100)
Death without progression	1 (5.3)	0
Number censored, n (%)	147 (88.6)	137 (83.0)
Reason for censorship[b]		
Ongoing at data cutoff	0	0
Early study discontinuation without progression/death	11 (7.5)	10 (7.3)
Study completion without progression/death	136 (92.5)	127 (92.7)
Response duration (months)[c]		
Quartiles (95% CI)[d]		
25%	10.4 (9.2, 15.4)	9.3 (9.1, 9.8)
50%	15.4 (10.4, 15.4)	- (9.6, -)
75%	15.4 (- , -)	-
Versus rituximab-EU		
Hazard ratio[e]		1.492
95% CI of hazard ratio		0.823 - 2.704
P-value[f]		0.185

Abbreviations: CI=confidence interval; CR=complete response; DOR=duration of response; EU=European Union; FLIPI2=Follicular Lymphoma International Prognostic Index 2; HR=hazard ratio; n=number of subjects meeting specified criteria; N=total number of subjects; PD=progressive disease; PR=partial response.

a. Percentage was calculated based on the number of subjects with event.
b. Percentage was calculated based on the number of censored subjects.
c. The DOR was defined as the time from date of the first documentation of objective tumor response (CR or PR) to the first documentation of PD or to death due to any cause in the absence of documented PD.
d. Kaplan-Meier method used and 2-sided 95% CI calculated based on the Brookmeyer and Crowley method.
e. Hazard ratio and its CIs were estimated from Cox Proportional Hazards model stratified by FLIPI2 risk categorization.
f. 2-sided p-value from the log-rank test stratified by FLIPI2 risk categorization.

Overall Survival (OS): In the ITT Population, there was 1 (<1.0%) subject who died in each treatment group. The cause of death for both subjects was disease progression. As there were very few deaths during the reporting period the Kaplan-Meier estimates of OS by treatment group for subjects in the ITT Population these data are of limited value and were not interpreted.

Pharmacokinetics: A summary of serum concentrations of PF-05280586 and rituximab-EU by visit is provided for subjects in the PK Population in Table 9. On days where study drug was administered (Days 1, 8, 15, and 22), serum samples for measurement of drug concentrations were collected prior to dose administration (within 4 hours of the start of dosing). On Days 1 and 22, additional drug concentration samples were collected within 15 minutes prior to the end of infusion. Additionally, drug concentration samples were collected at Weeks 5 (Day 29), 13, 26, 39, and 52 (hours not specified).

In general, data indicated similar rituximab serum concentrations at each visit between the 2 treatment groups. The highest (peak) serum concentration (mean [SD]) was observed at Day 22, within 15 minutes prior to the end of the infusion, and were comparable between the 2 treatment groups.

At visits following completion of study treatment, serum concentrations decreased steadily from Week 5 to Week 52 (End of Study; Table 9) and were comparable between the 2 treatment groups.

Table 9. Summary Statistics for Serum Drug Concentrations by Visit, All Subjects - PK Population

Visit	Planned Time Post-Dose	N	NALQ	Mean	SD	%CV	Geometric Mean	Median	Min	Max
Treatment Group: rituximab-EU										
Day 1	0	195	4	756.73	9256.505	1223	0.01	0.00	0.0	128000.0
Day 1	3h 30m	137	133	200618.76	71560.981	36	119755.43	198000.00	0.0	467000.0
Day 8	0	197	197	67011.83	21536.811	32	62311.74	68800.00	3610.0	165000.0
Day 15	0	195	195	117438.46	37652.513	32	109706.91	120000.00	14500.0	218000.0
Day 22	0	193	193	159424.35	53665.005	34	149878.23	156000.00	41400.0	389000.0
Day 22	2h 30m	132	132	351173.48	107275.604	31	334848.88	340000.00	89900.0	757000.0
Week 5	Hours NS	194	193	198907.73	62110.162	31	173747.94	202000.00	0.0	375000.0
Week 13	Hours NS	192	190	33496.71	21601.456	64	20996.36	31200.00	0.0	126000.0
Week 26	Hours NS	185	170	3115.96	3675.020	118	710.05	1740.00	0.0	18600.0
Week 39	Hours NS	170	104	496.05	1208.771	244	6.98	166.50	0.0	12500.0
Week 52a	Hours NS	188	48	1780.23	11727.062	659	0.16	0.00	0.0	108000.0
Treatment Group: PF-05280586										
Day 1	0	192	4	3104.84	25782.027	830	0.01	0.00	0.0	243000.0
Day 1	3h 30m	138	128	185994.13	78045.677	42	55560.74	198000.00	0.0	481000.0
Day 8	0	194	194	70761.03	19656.723	28	66669.15	71800.00	1540.0	138000.0
Day 15	0	193	193	123894.30	38216.182	31	119026.91	122000.00	33300.0	410000.0
Day 22	0	194	194	164903.61	41894.323	25	158294.91	168500.00	37800.0	289000.0
Day 22	2h 30m	138	138	354592.03	96770.732	27	337708.05	359000.00	36200.0	762000.0
Week 5	Hours NS	193	193	206477.20	55455.820	27	197858.84	209000.00	65800.0	335000.0
Week 13	Hours NS	188	187	36887.58	22731.513	62	26154.60	35600.00	0.0	134000.0
Week 26	Hours NS	181	172	3868.45	5345.666	138	1266.97	2360.00	0.0	46500.0
Week 39	Hours NS	171	112	526.70	902.298	171	12.06	227.00	0.0	6010.0
Week 52a	Hours NS	177	48	703.62	4743.707	674	0.18	0.00	0.0	59900.0

Table 9. Summary Statistics for Serum Drug Concentrations by Visit, All Subjects - PK Population

Visit	Planned Time Post-Dose	N	NALQ	Mean	SD	%CV	Geometric Mean	Median	Min	Max

Summary statistics were not presented if NALQ=0.
Summary statistics were calculated by setting concentration values below the lower limit of quantification (<100 ng/mL) to zero.
'Hours not specified' was displayed for visits that did not have planned time for serum PK sampling.
Only samples collected at the scheduled times were included in the above table.
Trough drug concentrations were collected on Days 1, 8, 15, and 22 (within 4 hours prior to the start of dosing). Samples were also collected within 15 minutes prior to the end of the infusion on Days 1 and 22. Additionally, drug concentration samples were collected at Weeks 5 (Day 29), 13, 26, 39, and 52.
Abbreviations: %CV=percent coefficient of variation; EU=European Union; h=hour; m=minute; max=maximum; min=minimum; N=number of observations (non-missing concentrations [ng/mL]); NALQ=number of observations above lower limit of quantification; NS=not specified; PK=pharmacokinetic; SD=standard deviation.
a. End of Treatment/End of Study

Pharmacodynamics: At baseline, the serum CD19-positive B-cell counts results ranged from 0.6 to 2313.1 cells/µL across the 2 treatment groups. The median baseline CD19-positive B-cell count was 119.9 cells/µL in the PF-05280586 group and 114.2 cells/µL in the rituximab-EU group. A decrease from baseline in mean serum CD19-positive B-cell counts was observed at all subsequent time points through Week 26, and was comparable between both treatment groups. The median percentage reduction from baseline at Week 2 was >99% for subjects in both the PF-05280586 and rituximab-EU groups. CD19-positive B-cells showed recovery at Week 39 in both treatment groups, the increase in cell count continued through End of Study (Week 52).

Mean (SD) serum IgG concentrations were comparable between the 2 treatment groups at baseline (10.43 [3.137] G/L in the PF-05280586 group and 10.73 [2.642] G/L in the rituximab-EU group). A small decrease from baseline in median serum IgG concentrations was observed at all subsequent time points, and was comparable between both treatment groups. The greatest median percentage change from baseline was observed at Week 4 in both treatment groups (median percent change of -4.31% for subjects in the PF-05280586 group and -5.54% in the rituximab-EU group).

Mean (SD) serum IgM concentrations were comparable between the 2 treatment groups at baseline (1.06 [1.381] G/L in the PF-05280586 group and 0.99 [0.646] G/L in the rituximab-EU group). In general, mean serum IgM concentrations decreased throughout the duration of the study and were comparable between the 2 treatment groups. The greatest median percentage change from baseline was observed at Week 52 (End of Study; median percent change of 24.00% for subjects in the PF-05280586 group and -21.00% in the rituximab-EU group).

Immunogenicity: A summary of ADA incidence by visit and overall is presented in Table 10. For subjects in the Safety Population, there were 14 (7.2%) subjects in the PF-05280586 group and 17 (8.7%) subjects in the rituximab-EU group who had a positive ADA test (titer ≥1.88) prior to initiation of study drug at baseline (Day 1). One (0.5%) subject in the PF 05280586 group and 2 (1.0%) subjects in the rituximab-EU group had a positive ADA test pre-dose on Day 15.

Following initiation of treatment, the percentage of subjects with ADA increased over the duration of the study from Week 5 through Week 52 (End of Study), and was similar between treatments. Overall, there were 43 (22.1%) subjects in the PF-05280586 group and 39 (19.8%) subjects in the rituximab-EU group with at least 1 post-dose sample that tested positive for ADA.

In general, of the samples that tested positive for ADA, the majority tested positive in both ADA assays, indicating that the ADA that developed was against shared epitopes between the study treatments with 40/43 (93.0%) subjects with positive ADA cross-reactivity in the PF-05280586 group, and 30/39 (76.9%) subjects in the rituximab-EU group. A titer booster response (an increase in titer upon repeated treatment) was not observed.

Only positive ADA samples were analyzed for NAb. The ADA negative samples were automatically assigned a negative NAb test result. In this study, all ADA positive samples tested negative for NAb.

Table 10. Summary of Anti-Drug Antibody (ADA) Incidence by Visit and Overall - Safety Population

Visit	Criteria		rituximab-EU (N=197) n/N1 (%)	PF-05280586 (N=196) n/N1 (%)
Day 1 (baseline)	ADA Positive		17/195 (8.7)	14/195 (7.2)
		ADA Cross-Reactivity Positive	10/17 (58.8)	12/14 (85.7)
		ADA Cross-Reactivity Negative	7/17 (41.2)	2/14 (14.3)
	ADA Negative		178/195 (91.3)	181/195 (92.8)
Day 8[a]	ADA Positive		-	0/1
		ADA Cross-Reactivity Positive	-	NA
		ADA Cross-Reactivity Negative	-	NA
	ADA Negative		-	1/1 (100.0)
Day 15	ADA Positive		2/192 (1.0)	1/192 (0.5)
		ADA Cross-Reactivity Positive	0/2	1/1 (100.0)
		ADA Cross-Reactivity Negative	2/2 (100.0)	0/1
	ADA Negative		190/192 (99.0)	191/192 (99.5)
Day 22[b]	ADA Positive		0/1	0/3
		ADA Cross-Reactivity Positive	NA	NA
		ADA Cross-Reactivity Negative	NA	NA
	ADA Negative		1/1 (100.0)	3/3 (100.0)
Week 5	ADA Positive		0/193	0/192
		ADA Cross-Reactivity Positive	NA	NA
		ADA Cross-Reactivity Negative	NA	NA
	ADA Negative		193/193 (100.0)	192/192 (100.0)
Week 13	ADA Positive		1/192 (0.5)	2/189 (1.1)
		ADA Cross-Reactivity Positive	1/1 (100.0)	1/2 (50.0)
		ADA Cross-Reactivity Negative	0/1	1/2 (50.0)
	ADA Negative		191/192 (99.5)	187/189 (98.9)
Week 26	ADA Positive		12/191 (6.3)	10/184 (5.4)
		ADA Cross-Reactivity Positive	8/12 (66.7)	9/10 (90.0)
		ADA Cross-Reactivity Negative	4/12 (33.3)	1/10 (10.0)
	ADA Negative		179/191 (93.7)	174/184 (94.6)
Week 39	ADA Positive		25/175 (14.3)	23/174 (13.2)
		ADA Cross-Reactivity Positive	22/25 (88.5)	22/23 (95.7)
		ADA Cross-Reactivity Negative	3/25 (12.0)	1/23 (4.3)
	ADA Negative		150/175 (85.7)	151/174 (86.8)

Table 10. Summary of Anti-Drug Antibody (ADA) Incidence by Visit and Overall - Safety Population

Visit	Criteria		rituximab-EU (N=197) n/N1 (%)	PF-05280586 (N=196) n/N1 (%)
Week 52	ADA Positive		30/168 (17.9)	35/163 (21.5)
		ADA Cross-Reactivity Positive	25/30 (83.3)	35/35 (100.0)
		ADA Cross-Reactivity Negative	5/30 (16.7)	0/35
	ADA Negative		138/168 (82.1)	128/163 (78.5)
Overall	ADA Positive		39/197 (19.8)	43/195 (22.1)
		ADA Cross-Reactivity Positive	30/39 (76.9)	40/43 (93.0)
		ADA Cross-Reactivity Negative	9/39 (23.1)	3/43 (7.0)
	ADA Negative		158/197 (80.2)	152/195 (77.9)

Serum samples for detection of anti-drug antibodies (ADA) and neutralizing antibodies (NAb) were collected within 4 hours prior to dose administration on Day 1 and Day 15. Additional samples for detection of ADA and NAb were to be collected at Weeks 5 (Day 29), 13, 26, 39, and 52.
Percentages have as their numerator (n) the number of subjects tested at a given visit with a sample that met the specified criteria, and denominator (N1) the number of subjects tested who had an observed result at the specified visit. Only subjects with a positive ADA result were further tested for ADA cross-reactivity and NAb. For the Overall row, percentages have as their numerator (n) the number of subjects tested who had at least 1 post-dose (ie, post Day 1) sample that met the specified criteria, and the denominator (N1) was the number of subjects tested who had at least 1 observed post-dose result.
Only subjects with a positive ADA result were further tested for ADA cross-reactivity and NAb. None of the ADA positive samples were NAb positive at any time during the study and in any treatment group.
Abbreviations: ADA=anti-drug antibody; NA=not applicable; NAb=neutralizing antibody; N=number of subjects in the analysis population.

a. Day 8 was an unplanned visit.

b. Sample collected prior to protocol Amendment 1.

Safety Results:

Treatment-Emergent Serious AEs (SAEs): The number of all-causality, treatment-emergent SAEs is summarized in Table 11. A total of 17 (8.67%) subjects in the PF-05280586 group and 15 (7.61%) subjects in the rituximab-EU group experienced a treatment-emergent SAE.

The most common all-causality treatment-emergent SAEs by system organ class (SOC) were Infections and infestations (4 [2.04%] subjects in the PF-05280586 group and 3 [1.52%] subjects in the rituximab-EU group).

Table 11. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

	rituximab-EU			PF-05280586		
	n (%)	**n1**	**n2**	**n (%)**	**n1**	**n2**
Number (%) of Subjects:						
Evaluable for adverse events	197			196		
With adverse events	15 (7.61)			17 (8.67)		
Cardiac disorders	**2 (1.02)**	**2**	**0**	**1 (0.51)**	**1**	**0**
Angina unstable	1 (0.51)	1	0	0	0	0
Atrial fibrillation	0	0	0	1 (0.51)	1	0
Intracardiac thrombus	1 (0.51)	1	0	0	0	0
Gastrointestinal disorders	**1 (0.51)**	**1**	**0**	**3 (1.53)**	**3**	**0**
Abdominal pain	0	0	0	1 (0.51)	1	0
Ileus	0	0	0	1 (0.51)	1	0
Inguinal hernia	1 (0.51)	1	0	0	0	0
Mesenteric artery stenosis	0	0	0	1 (0.51)	1	0
General disorders and administration site conditions	**2 (1.02)**	**2**	**0**	**2 (1.02)**	**2**	**1**
Disease progression	1 (0.51)	1	0	1 (0.51)	1	0
Non-cardiac chest pain	1 (0.51)	1	0	0	0	0
Pyrexia	0	0	0	1 (0.51)	1	1
Hepatobiliary disorders	**1 (0.51)**	**1**	**0**	**0**	**0**	**0**
Cholelithiasis	1 (0.51)	1	0	0	0	0
Immune system disorders	**1 (0.51)**	**1**	**1**	**0**	**0**	**0**
Serum sickness	1 (0.51)	1	1	0	0	0
Infections and infestations	**3 (1.52)**	**4**	**0**	**4 (2.04)**	**5**	**1**
Appendicitis	0	0	0	1 (0.51)	1	0
Clostridium difficile infection	0	0	0	1 (0.51)	1	1
Diverticulitis	0	0	0	1 (0.51)	1	0
Escherichia sepsis	1 (0.51)	1	0	0	0	0
Hepatitis B	1 (0.51)	1	0	0	0	0
Kidney infection	1 (0.51)	1	0	0	0	0
Peritonitis	0	0	0	1 (0.51)	1	0
Urinary tract infection	0	0	0	1 (0.51)	1	0
Viral sinusitis	1 (0.51)	1	0	0	0	0
Injury, poisoning and procedural complications	**1 (0.51)**	**1**	**1**	**1 (0.51)**	**1**	**0**
Contusion	0	0	0	1 (0.51)	1	0

Table 11. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related)

	rituximab-EU			PF-05280586		
	n (%)	**n1**	**n2**	**n (%)**	**n1**	**n2**
Infusion related reaction	1 (0.51)	1	1	0	0	0
Musculoskeletal and connective tissue disorders	**2 (1.02)**	**2**	**0**	**1 (0.51)**	**1**	**0**
Intervertebral disc disorder	0	0	0	1 (0.51)	1	0
Polyarthritis	1 (0.51)	1	0	0	0	0
Spinal column stenosis	1 (0.51)	1	0	0	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	**2 (1.02)**	**2**	**0**	**4 (2.04)**	**4**	**0**
Bladder cancer	1 (0.51)	1	0	0	0	0
Colon adenoma	0	0	0	1 (0.51)	1	0
Lung adenocarcinoma stage I	0	0	0	1 (0.51)	1	0
Prostate cancer	0	0	0	1 (0.51)	1	0
Squamous cell carcinoma of lung	1 (0.51)	1	0	0	0	0
Uterine cancer	0	0	0	1 (0.51)	1	0
Nervous system disorders	**0**	**0**	**0**	**2 (1.02)**	**2**	**0**
Paraesthesia	0	0	0	1 (0.51)	1	0
Transient ischaemic attack	0	0	0	1 (0.51)	1	0
Respiratory, thoracic and mediastinal disorders	**2 (1.02)**	**2**	**1**	**0**	**0**	**0**
Dyspnoea	1 (0.51)	1	1	0	0	0
Pulmonary embolism	1 (0.51)	1	0	0	0	0

Except for ‘n1’ and ‘n2’ subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v21.0) coding dictionary applied.
Abbreviations: EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1=number of occurrences of treatment-emergent all causalities adverse events; n2=number of occurrences of treatment-emergent causally related to treatment adverse events.

Non-Serious Treatment-Emergent AEs (TEAEs): The number of all-causality, non-serious TEAEs in >5% of subjects are summarized in Table 12. A total of 93 (47.45%) subjects in the PF-05280586 group and 95 (49.24%) subjects in the rituximab-EU group experienced a non-serious TEAE.

For subjects in the PF-05280586 group, the most common all-causality non-serious TEAEs by SOC group were Injury, poisoning and procedural complications (49 [25.00%] subjects), General disorders and administration site conditions (30 [15.31%] subjects), and Gastrointestinal disorders (25 [12.76%] subjects).

For subjects in the rituximab-EU group, the most common all-causality non-serious TEAEs by SOC were Injury, poisoning and procedural complications (58 [29.44%] subjects), General disorders and administration site conditions (33 [16.75%] subjects), and Respiratory, thoracic and mediastinal disorders (30 [15.23%] subjects).

The most common treatment-related non-serious TEAEs by PT, for subjects in the PF-05280586 group, were infusion related reaction (58 subjects), throat irritation (15 subjects), and pruritus (11 subjects).

For subjects in the rituximab-EU group, the most common treatment-related non-serious TEAEs by PT were infusion related reaction (63 subjects), pruritus (18 subjects), and oropharyngeal pain (12 subjects).

Table 12. Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term in >5% Subjects (All Causalities and Treatment-Related)

Number (%) of subjects with adverse events by:	rituximab-EU			PF-05280586		
System Organ Class **MedDRA Preferred Term**	**n (%)**	**n1**	**n2**	**n (%)**	**n1**	**n2**
Number (%) of Subjects:						
Evaluable for adverse events	197			196		
With adverse events	97 (49.24)			93 (47.45)		
Gastrointestinal disorders	**27 (13.71)**	**37**	**17**	**25 (12.76)**	**35**	**16**
Diarrhoea	12 (6.09)	15	7	14 (7.14)	16	7
Nausea	17 (8.63)	22	10	15 (7.65)	19	9
General disorders and administration site conditions	**33 (16.75)**	**43**	**18**	**30 (15.31)**	**37**	**19**
Asthenia	13 (6.60)	15	8	9 (4.59)	11	5
Fatigue	13 (6.60)	16	9	12 (6.12)	15	6
Pyrexia	11 (5.58)	12	1	11 (5.61)	11	8
Injury, poisoning and procedural complications	**58 (29.44)**	**63**	**63**	**49 (25.00)**	**58**	**58**
Infusion related reaction	58 (29.44)	63	63	49 (25.00)	58	58
Musculoskeletal and connective tissue disorders	**10 (5.08)**	**11**	**1**	**8 (4.08)**	**8**	**1**
Back pain	10 (5.08)	11	1	8 (4.08)	8	1
Nervous system disorders	**19 (9.64)**	**31**	**8**	**16 (8.16)**	**18**	**5**
Headache	19 (9.64)	31	8	16 (8.16)	18	5
Respiratory, thoracic and mediastinal disorders	**30 (15.23)**	**33**	**22**	**24 (12.24)**	**30**	**20**
Cough	11 (5.58)	11	1	11 (5.61)	13	4
Oropharyngeal pain	10 (5.08)	12	12	2 (1.02)	2	1
Throat irritation	10 (5.08)	10	9	14 (7.14)	15	15
Skin and subcutaneous tissue disorders	**28 (14.21)**	**32**	**25**	**22 (11.22)**	**28**	**20**
Pruritus	22 (11.17)	23	18	13 (6.63)	14	11
Rash	8 (4.06)	9	7	10 (5.10)	14	9

Except for 'n1' and 'n2' subjects are only counted once per treatment for each row.
Includes data up to 999 days after last dose of study drug.
MedDRA (v21.0) coding dictionary applied.
Abbreviations: EU=European Union; MedDRA=Medical Dictionary for Regulatory Activities; n=number of subjects in this reporting group affected by any occurrence of this adverse event, all causalities; n1=number of occurrences of treatment-emergent all causalities adverse events; n2=number of occurrences of treatment-emergent causally related to treatment adverse events.

Immune-Based Adverse Effects: A summary of ADA and immune-based adverse effects overall is presented in Table 13.

Overall, the percentage of subjects reporting immune-based adverse effects post-treatment was comparable between treatment groups, and also between ADA positive and ADA negative subjects.

The percentage of treatment-emergent IRR AEs (all causalities) was comparable between the treatment groups with 49 (25.0%) subjects in the PF-05280586 group and 59 (29.9%) subjects in the rituximab-EU group with reported IRRs.

The incidence of treatment-emergent (all causalities) anaphylactic reaction/hypersensitivity AEs was comparable between the treatment groups. Overall, there were 39 (19.9%) subjects in the PF-05280586 group and 48 (24.4%) subjects in the rituximab-EU group with an event meeting the broad and narrow SMQ of Anaphylaxis/Hypersensitivity.

Overall, there were 17 (8.7%) subjects in the PF-05280586 group and 17 (8.6%) subjects in the rituximab-EU group with an event potentially meeting Sampson criteria. Medical review of events utilizing Sampson criteria did not identify any subject meeting the criteria of anaphylaxis as described in the Second Symposium on the Definition of Anaphylaxis.

The percentage of IRRs (as assessed by the investigator), events retrieved utilizing the SMQ of Anaphylaxis/Hypersensitivity (broad and narrow), and events potentially meeting the Sampson Criteria occurring in ADA positive subjects was comparable between the treatment groups:

- In the PF-05280586 group: 11/43 (25.6%) subjects with IRRs, 7/43 (16.3%) subjects with events of Anaphylaxis/Hypersensitivity (broad and narrow), and 5/43 (11.6%) subjects with events potentially meeting the Sampson Criteria.

- In the rituximab-EU group: 10/39 (25.6%) subjects with IRRs, 5/39 (12.8%) subjects with events of Anaphylaxis/Hypersensitivity (broad and narrow), and 4/39 (10.3%) subjects with events potentially meeting the Sampson Criteria.

Table 13. Summary of ADA and Immune-Based Adverse Effects Overall - Safety Population

Overall	Criteria	rituximab-EU (N=197) n/N1 (%)	PF-05280586 (N=196) n/N1 (%)
Total IRR reported		59/197 (29.9)	49/196 (25.0)
Total Sampson's criteria fulfilled		17/197 (8.6)	17/196 (8.7)
Total Anaphylaxis/Hypersensitivity (SMQ)[a]		48/197 (24.4)	39/196 (19.9)
ADA Positive		**39/197 (19.8)**	**43/195 (22.1)**
	IRR reported	10/39 (25.6)	11/43 (25.6)
	Sampson's criteria fulfilled	4/39 (10.3)	5/43 (11.6)
	Anaphylaxis/Hypersensitivity (SMQ)[a]	5/39 (12.8)	7/43 (16.3)
ADA Negative		**158/197 (80.2)**	**152/195 (77.9)**
	IRR reported	46/158 (29.1)	36/152 (23.7)
	Sampson's criteria fulfilled	13/158 (8.2)	12/152 (7.9)
	Anaphylaxis/Hypersensitivity (SMQ)[a]	35/158 (22.2)	22/152 (14.5)

Serum samples for detection of ADA and NAb were to be collected within 4 hours prior to dose administration on Day 1 and Day 15. Additional samples for detection of ADA and NAb were to be collected at Weeks 5 (Day 29), 13, 26, 39 and 52.
Events of interest: IRR adverse events, adverse events which fulfill Sampson's criteria, and adverse events which belong to the Anaphylaxis or Hypersensitivity SMQs.
Events must have occurred during the study to be counted.
The ADA positive subgroup refers to subjects who had a sample positive for ADA.
Abbreviations: ADA= anti-drug antibodies; EU=European Union; IRR=infusion related reaction; MedDRA=Medical Dictionary for Regulatory Activities; n=the corresponding number of those subjects represented in each denominator with at least 1 specified event during the study; n=number of subjects in the analysis population; NAb=neutralizing antibodies; N1=the number of subjects in the analysis population (and within the ADA status subgroup where applicable) for the study; SMQ=Standardized MedDRA Query.
a. Standardized MedDRA Query from the MedDRA dictionary (v20.1).

Discontinuations: The number of TEAEs leading to withdrawal from the study are summarized in Table 14.

There were 2 (1.0%) subjects in the PF-05280586 group who permanently discontinued from the study due to treatment-related AEs.

In total, there were 27 (13.6%) subjects who discontinued from the study in the PF-05280586 group and 23 (11.7%) subjects in the rituximab-EU group. The most frequent reason for discontinuation was progressive disease (14 [7.1%] subjects and 20 [10.1%] subjects in the PF-05280586 and rituximab-EU groups, respectively).

There were 3 (1.5%) subjects in the PF-05280586 group and 1 (0.5%) subject in the rituximab-EU group who permanently discontinued from the study due to TEAEs (infusion related reaction and angioedema, rash maculo-papular, and Non-Hodgkin's lymphoma in the PF-05280586 group; and Grade 2 bladder cancer in the rituximab-EU group).

Table 14. Discontinuations from Study

	rituximab-EU n (%)	PF-05280586 n (%)
Number of subjects	198	196
Completed	170 (85.9)	170 (86.7)
Discontinuations:		
Relation to study drug not defined	27 (13.6)	23 (11.7)
Insufficient clinical response	4 (2.0)	3 (1.5)
Lost to follow-up	0	1 (0.5)
No longer willing to participate in study	3 (1.5)	4 (2.0)
Progressive disease	20 (10.1)	14 (7.1)
Protocol violation	0	1 (0.5)
Related to study drug	0	2 (1.0)
Adverse event, not serious	0	2 (1.0)
Not related to study drug	1 (0.5)	1 (0.5)
Adverse event, not serious	0	1 (0.5)
Adverse event, serious non-fatal	1 (0.5)	0
Total	28 (14.1)	26 (13.3)

Abbreviations: EU=European Union; n=number of subjects in this reporting group.

Deaths: Two subjects, 1 in each treatment group, died during the study due to disease progression (Table 15), which occurred outside the active reporting period (through and including 28 calendar days after the last study visit) and were not considered to be related to treatment.

Table 15. Summary of Deaths

Number of subjects evaluable for adverse events		Rituximab-EU N=197		PF-05280586 N=196	
System organ class	Preferred term	n	n1	n	n1
General disorders and administration site conditions		0	0	1	0
	Disease progression	0	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		1	0	0	0
	Neoplasm progression	1	0	0	0
Total number of fatalities from adverse events[a]		1		1	
Total number of deaths all causes[b]		1		1	

A subject death could be associated with more than 1 treatment if the first onset date of the case fell within multiple treatment group periods.
A fatality could be associated with multiple events.
MedDRA v.21.0J coding dictionary applied.
Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; N=total number of subjects; n=number of adverse events associated with a fatality; n1=number of adverse events associated with a fatality and thought to be associated or related to treatment; SAE=serious adverse event.
Source of Actual treatment Group is Oracle Clinical or Phase I Management System. Source of SAE is Safety Data Warehouse.
a. Total number of deaths in this reporting group thought to be causally related to adverse events.
b. Total number of deaths (all causes) in this reporting group. This includes deaths not related to the trial.

CONCLUSION(S):

- Equivalence between PF-05280586 and rituximab-EU was statistically demonstrated in the ITT Population for the primary efficacy endpoint, ORR. The analysis of ORR at Week 26 derived from central review assessments showed an estimated difference of 4.66% (PF-05280586 minus rituximab-EU), with a 95% CI of (-4.16%, 13.47%), which fell entirely within the -16.0% to 16.0% pre-specified equivalence margin agreed to by the FDA and EMA, and also within the -14.9% to 14.9% margin agreed to by the PMDA.

- There were no clinically meaningful or statistically significant differences in the secondary endpoint results for CR rate at Week 26, PFS, OS, and TTF, which were comparable between the 2 treatment groups, in the ITT Population. There were also no clinically meaningful or statistically significant differences in the secondary endpoint of DOR in the Response Evaluable Population.

- A comparable safety profile was observed between the treatment groups and with the safety information described in the reference product label.

- The observed rate of ADA was comparable between the 2 treatment groups. A titer booster response (an increase in titer upon repeated treatment) was not observed. No ADA positive subjects tested positive for NAb.

- The serum concentrations of PF-05280586 and rituximab-EU groups were comparable.

- No notable differences were observed in mean serum concentrations between ADA positive and ADA negative subjects in either treatment group.

- CD19 positive B-cell depletion and recovery were comparable between the treatment groups and consistent with the reference product label.

- No clinically meaningful differences were observed in terms of potential immunogenicity associated AEs in those who were treatment-emergent ADA positive versus those who were ADA negative.