

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761103Orig1s000

MEDICAL and STATISTICAL REVIEW(S)

Division Memo

Date	May 10, 2019
From	Statistics: Ginto Pottackal, PhD Peiling Yang, PhD Clinical: Suzette Peng, MD Division Director: Sally Seymour, MD Associate Director for Rheumatology and designated signatory: Nikolay Nikolov, MD
Subject	Division Memo: Division of Pulmonary Allergy and Rheumatology Products (DPARP)
BLA #	351(k) BLA 761103
Applicant	Pfizer
Date of Submission	July 25, 2018
BsUFA Goal Date	July 25, 2019
Proprietary Name (proposed)/ Nonproprietary names	RUXIENCE (proposed)/PF-05280586 ¹ (rituximab-pvvr)
Dosage Form(s)/Strength(s)	Injection: 100 mg/10 mL (10 mg/ml) and 500 mg/50 mL (10 mg/ml) solution in single-dose vials
Route of Administration	Intravenous (IV)
Applicant Proposed Indication(s)/Population(s)	<ul style="list-style-type: none"> • Non-Hodgkin’s Lymphoma (NHL) • Chronic Lymphocytic Leukemia (CLL) • Granulomatosis with polyangiitis (GPA) • Microscopic Polyangiitis (MPA)
Applicant Proposed Dosing Regimen(s)	<p>NHL: 375 mg/m² (schedules vary) CLL: 375 mg/m² in the first cycle and 500 mg/m² in Cycles 2-6, in combination with FC, administered every 28 days Component of Zevalin (ibritumomab tiuxetan) Therapeutic regimen: 250 mg/m²</p> <p>GPA and MPA: induction treatment in combination with glucocorticoids, 375 mg/m² once weekly for 4 weeks; maintenance treatment in combination with glucocorticoids, two 500 mg doses separated by two weeks followed by a 500 mg dose every 6 months</p>
Recommendation on Regulatory Action	<i>Approval from DPARP perspective</i>

¹ In this document, we generally refer to Pfizer’s proposed product by the Applicant descriptor “PF-05280586” which was the name used to refer to this product during development. Subsequently, the nonproprietary name for this proposed product, “rituximab-pvvr,” and the proposed proprietary name “Ruxience” have been conditionally accepted.”

1. Introduction

Pfizer (also referred to as “applicant” in this memo) has submitted a biologic license application (BLA) under section 351(k) of the Public Health Service Act (PHS Act) for PF-05280586 as a proposed biosimilar to US-licensed RITUXAN (rituximab). US-licensed Rituxan was originally licensed in the US in November 1997 and non-US-licensed rituximab is marketed in the European Union and is referred to as EU-approved MabThera. In the original submission, the applicant sought licensure of PF-05280586 for the following indications for which US-licensed Rituxan is approved and which are not subject to regulatory exclusivity²:

- Non-Hodgkin’s Lymphoma (NHL)
- Chronic Lymphocytic Leukemia (CLL)
- Rheumatoid arthritis (RA)
- Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

During the review, the applicant amended the indications for which they are seeking licensure (SDN 43). The requested indications are the following:

- Non-Hodgkin’s Lymphoma (NHL)
- Chronic Lymphocytic Leukemia (CLL)
- Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)

The Division of Hematology Products (DHP) is the lead division for this application; please refer to the Cross-Discipline Team Leader Review for the complete assessment regarding licensure of PF-05280586 as a proposed biosimilar to US-licensed Rituxan including data pertinent to the oncology indications. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is the collaborating division for this application and is responsible for the review of the clinical data and information related to the rheumatologic indications.³

2. Background

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was signed into law on March 23, 2010. The BPCI Act created an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to or interchangeable with an FDA-licensed biological reference product.

The biosimilar licensure pathway under section 351(k) of the PHS Act requires (a) that the proposed biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and (b) that there are no clinically meaningful differences between the proposed biosimilar and reference products in terms of safety, purity,

² US-licensed RITUXAN is also approved for pemphigus vulgaris, but this indication is currently protected under orphan drug exclusivity.

³ While this review contains discussion of data and information the applicant submitted from studies conducted in a patient population with rheumatoid arthritis, the statements in this review are not intended to constitute a formal determination regarding licensure of the proposed product for rheumatoid arthritis because the applicant is not seeking licensure for rheumatoid arthritis.

and potency. Both parts of the statutory definition need to be met to demonstrate biosimilarity, but the foundation of the data demonstrating biosimilarity is extensive structural and functional characterization to support a demonstration that the products are highly similar.

The applicant submitted the following to support licensure of PF-05280586:

- A comprehensive analytical characterization of PF-05280586, US-licensed Rituxan, and EU-approved MabThera. These included comparative characterization of physicochemical attributes and comparative functional assessments.
- Nonclinical studies including a single-dose IV tolerability TK study and a 4-week repeat-dose IV toxicity/TK study in adult, sexually mature cynomolgus monkeys to compare the effects of PF-05280586 to those of EU-approved MabThera.
- A comparative clinical PK study (B3281001) in subjects with active RA on background methotrexate (MTX). The study evaluated 3 treatment arms (PF-05280586, US-licensed Rituxan, and EU-approved MabThera) at the dose of 1000 mg infusion on Days 1 and 15. An extension study (B3281004) evaluated the safety of additional treatment including in those subjects who transitioned from US-licensed Rituxan or EU-approved MabThera to PF-05280586.
- A comparative clinical study (B3281006) evaluating comparative efficacy, safety, and immunogenicity of PF-05280586 and EU-approved MabThera in subjects with low tumor burden follicular lymphoma.
- A scientific justification for extrapolation of data and information submitted in the application to support licensure of PF-05280586 for each of the additional indications for which Pfizer is seeking licensure and for which US-licensed Rituxan has been previously licensed.

This Division memo will address the studies conducted in the RA population as well as the justification for extrapolation of data and information submitted in the application to support licensure of PF-05280586 as a biosimilar to US-licensed Rituxan for rheumatologic indications GPA and MPA. In this memo, the proposed biosimilar is referred to as PF-05280586. US-licensed Rituxan is also referred to as rituximab-US, and EU-approved MabThera is referred to as rituximab-EU.

Relevant Regulatory History

Interactions with the FDA regarding the clinical development of PF-05280586 as a proposed biosimilar to US-licensed Rituxan began in March 2011. The applicant performed 3 clinical studies as part of the clinical development program for PF-05280586. Studies B3281001 and B3281004 were performed in subjects with RA, and study B3281006 was a comparative clinical study conducted in subjects with CD20-positive low-tumor burden follicular lymphoma (LTB-FL). Table 1 summarizes the key Agency interactions, particularly in regards to the design and evaluation of the clinical studies B3281001 and B3281004.

Table 1. Key Regulatory Interactions for Clinical Development of PF-05280586

Meeting Date	Type of Meeting	FDA Recommendations and Major Discussion Topics
March 21, 2011	Pre-IND	<ul style="list-style-type: none"> • Pfizer proposed both a PK similarity study as well as a comparative clinical study (CCS) in RA • Based on plan to use EU-approved MabThera in CCS, Agency recommended a 3-arm PK study in subjects with RA • The Agency did not agree with a non-inferiority study design for the CCS. • The Agency also advised Pfizer to select endpoints that would be sufficiently sensitive to rule out clinically meaningful differences . • Discussion of data and information to support extrapolation
November 3, 2011	General Advice	<ul style="list-style-type: none"> • Pfizer submitted CCS study protocol in RA for review • Agency reiterated need for 3-arm PK study since the CCS study will be evaluating EU-approved MabThera and proposed Pfizer product • Agency made several recommendations for the PK study and CCS in subjects with RA
October 10, 2012	Type B Pre-IND	<ul style="list-style-type: none"> • Discussion of content for BPD3 meeting • Brief discussion of study B3281001 (PK study in RA) and protocol for B3281004 (extension study in RA) • Discussion of clinical study in oncology population
September 5, 2014	BPD3	<ul style="list-style-type: none"> • Pfizer submitted data from study B3281001 • Agency expressed concern that the ACR response rates of the PF-05280568 treatment arms were numerically lower compared to the ACR response in the other two arms in study B3281001. The differences in ACR response rates were more evident than in DAS28-CRP results. Given these findings, the Agency recommended that Pfizer explore potential causes and why the difference was more evident with ACR response rates. • Pfizer suggested that a possible reason for the difference was due to an imbalance in the baseline characteristics in the study arms. Subjects had more severe disease in the US-licensed Rituxan arm. • Agency suggested that Pfizer perform further analyses to understand these differences: <ul style="list-style-type: none"> ○ Propensity score analysis on DAS28 and ACR response to mitigate the effect of imbalances at baseline on the response ○ Cumulative responder analysis to evaluate the impact of differences in gating ○ Confidence intervals and point estimates to describe the treatment effect • Analytical and PK similarity data appeared to support use of EU-approved MabThera as sole comparator in subsequent comparator study B3281006
May 16, 2017	Pfizer's response to BPD2 Preliminary Comments	<ul style="list-style-type: none"> • Agency had reminded Pfizer of the numerically lower ACR response in the PF-05280586 arm in study B3281001 and stated that Pfizer needed to provide justification as to why these differences would not preclude a demonstration of no clinically meaningful difference. • Pfizer acknowledged the comment and confirmed justification would be provided in the 351(k) submission.
April 6, 2018	BPD4	<ul style="list-style-type: none"> • Agency again reiterated the comments regarding the lower ACR response rates of the PF-05280586 arm. Agency advised Pfizer that the requested additional analyses should be included in the BLA submission. • Agency advised Pfizer to provide some specific analyses of efficacy endpoints at the end of Course 1 in study B3281004.

3. CMC/Product Quality

The product quality, analytical similarity, microbiology, and immunogenicity data submitted in this application were reviewed by the Office of Biotechnology Products (OBP), OPQ, CDER. Several reviewers from OBP/DBRR, OPF/DMA, and OPF/DIA contributed to the Quality Review Team.

The following is adapted from the product quality team review.

PF-05280586 is a chimeric monoclonal IgG1 antibody and has been developed as a proposed biosimilar to US-licensed Rituxan. PF-05280586 binds to CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes and malignant B cells. Upon binding to CD20, it mediates B-cell lysis via possible mechanisms of complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), signaling induced cell death (apoptosis), and antibody dependent cellular phagocytosis (ADCP).

The product quality review team noted that the applicant performed a comparative analytical assessment using a sufficient number of PF-05280586 drug substance and drug product lots, US-licensed Rituxan drug product lots, and EU-approved MabThera drug product lots. The product quality attributes evaluated covered biological activities, primary and higher order structure, post-translational modifications, glycosylation profile, product size and charge variants, protein concentration, and the stability profile of the product. The attributes were each assigned to scientifically justified risk categories, and the attribute similarity data package was generated and evaluated using appropriate analytical and statistical methods. The OPQ review of manufacturing determined that the methodologies and processes used for drug substance and drug product manufacturing as well as for release and stability testing were sufficient to assure a consistent and safe product.

Details of the technical assessments for OBP drug substance and drug product quality and immunogenicity assay, DMA microbial drug substance and drug product, DIA facility, OBP labeling, and OBP analytical similarity are available as separate documents in the Panorama informatics platform.

The product quality review team concluded that the comparative analytical assessment supports the following:

- The proposed biological product, PF-05280586, is highly similar to US-licensed Rituxan notwithstanding minor differences in clinically inactive components.
- The analytical component of the scientific bridge has been established to justify the relevance of data generated using the EU-approved MabThera to support the demonstration of biosimilarity of PF-05280586 to US-licensed Rituxan.
- The applicant provided adequate data and information to support that the strength(s) proposed for PF-05280586, 100 mg/10 mL (10 mg/ml) and 500 mg/50 mL (10 mg/ml), meet the statutory “same strength” requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act.

Thus, based on data submitted, the product quality review team recommends approval of PF-05280586.

4. Assessment of Clinical Pharmacology

Clinical Pharmacology Reviewer: Shalini Wickramaratne Senarath Yapa, Ph.D.

Clinical Pharmacology Team Leader: Anshu Marathe, Ph.D., and Salaheldin Hamed, Ph.D.

The clinical pharmacology review focused on clinical study B3281001 (the PK similarity study in rheumatoid arthritis [RA]) in addition to the PK and immunogenicity data from study B3281006 (the comparative clinical study in subjects with low tumor burden follicular lymphoma [LTB-FL]). See Section 5 below for a description of the clinical development program for PF-05280586.

PK similarity was demonstrated between PF-05280586 and US-licensed Rituxan in study B3281001 based on results showing the 90% confidence interval (CI) for the geometric mean ratios (GMR) of PF-05280586 to US-licensed Rituxan, PF-05820586 to EU-approved MabThera, and EU-approved MabThera to US-licensed Rituxan for $AUC_{0-\infty}$, AUC_{0-t} , and AUC_{0-2wk} were all within the PK similarity acceptance criteria of 80 to 125%. Table 2 presents the pairwise comparisons between the PK parameters of the three products. Study B3281001 also established the PK element of the scientific bridge between PF-05280586, US-licensed Rituxan, and EU-approved MabThera, thereby, supporting the relevance of data from EU-approved MabThera in the comparative clinical study B3281006. In study B3281006, the PK assessments did show comparable serum concentrations between PF-05280586 and EU-approved MabThera at the end of study (Week 52).

Table 2. Summary of Statistical Comparisons of PK Parameters for PF-05280586, US-licensed Rituxan, and EU-approved MabThera (Study B3281001)

Comparison	PK Parameter	GMR (90% CI)
PF-05280586 vs. US-licensed Rituxan	AUC _{0-∞}	100.45 (89.20, 113.11)
	AUC _{0-t}	101.33 (90.82, 113.04)
	AUC _{0-2wk}	105.56 (96.64, 115.30)
	C _{max}	106.62 (97.65, 116.41)
PF-05280586 vs. EU-approved MabThera	AUC _{0-∞}	104.19 (92.75, 117.06)
	AUC _{0-t}	103.36 (92.81, 115.12)
	AUC _{0-2wk}	103.74 (95.10, 113.15)
	C _{max}	105.67 (96.91, 115.21)
EU-approved MabThera vs. US-licensed Rituxan	AUC _{0-∞}	96.40 (85.57, 108.60)
	AUC _{0-t}	98.03 (87.83, 109.40)
	AUC _{0-2wk}	101.76 (93.13, 111.18)
	C _{max}	100.90 (92.38, 110.20)

Results based on ANOVA model with treatment as a fixed effect

Source: Protocol B3281001 Clinical Study Report. Table 17. Dated August 30, 2016; page 75. Primary Clinical Pharmacology Review by Dr. Shalini Wickramaratne Senarath Yapa. Table 1, page 6.

In the assessment of immunogenicity, serum samples from patients treated with PF-05280586 were tested using the PF-05280586 specific anti-drug antibodies (ADA) and neutralizing antibody (NAb) assay, and serum samples from patients treated with US-licensed Rituxan or EU-approved MabThera were tested using the EU-approved MabThera specific ADA and NAb assays. As ADA rates could not be directly compared between results from two different assays, as originally tested, the applicant re-tested samples from Study B3281006 (LTBFL) using a single ADA assay specific for PF-05280586. In Study B3281006, the overall incidence of immunogenicity at Week 52 was comparable between PF-05280586 and EU-approved MabThera (21.5% and 20.4% ADA+ subjects, respectively). ADA seemed to have an impact on the PK of PF-05280586 and EU-approved MabThera, as there were lower serum concentrations in ADA+ subjects compared to that in ADA- subjects. However, of those subjects who were ADA+, there was no difference in PK between treatment arms. Lastly, the review team noted that ADA did not appear to have an impact on efficacy and safety in patients with CD20+ LTB-FL.

Of note, samples from Study B3281001 were no longer available for retesting. However, the immunogenicity data provided from the LTB-FL Study B3281006 were considered sufficient for making an assessment about whether any meaningful differences in terms of immunogenicity exist between PF-05280586 and EU-approved MabThera. The immunogenicity results from Study B3281001 were not considered necessary and, therefore, not retesting Study B3281001 samples using the ADA assay specific for PF-05280586 was acceptable.

See the primary review by Dr. Wickramartne Senarath Yapa for details regarding the clinical pharmacology assessment.

The Office of Clinical Pharmacology concluded that PK similarity has been demonstrated between PF-05280586 and US-licensed Rituxan, and the PK component of the scientific bridge has been established to scientifically justify the relevance of data generated using the EU-approved MabThera to support the demonstration of biosimilarity of PF-05280586 to US-licensed Rituxan. The PK and immunogenicity results support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan.

5. Assessment of Clinical Safety, Efficacy, and Immunogenicity in RA

Primary Statistical Reviewer: Ginto Pottackal, PhD
Statistical Team Leader: Peiling Yang, PhD

Primary Clinical Reviewer: Suzette Peng, MD
Clinical Team Leader: Nikolay Nikolov, MD

Overview of the Clinical Program in RA

The applicant performed 3 clinical studies as part of the clinical program of PF-05280586. Studies B3281001 and B3281004 were performed in subjects with RA, and study B3281006 was conducted in subjects with CD20-positive LTB-FL. Study B3281006 was a comparative clinical study to evaluate efficacy, safety, and immunogenicity in LTB-FL. The clinical studies in RA were “not designed to allow formal statistical efficacy assessment.” Rather, the primary objective of B3281001 was to demonstrate the PK similarity of PF-05280586, rituximab-EU, and rituximab-US, and the primary objective of B3281004 was to provide continued treatment access to patients with active RA and to evaluate the overall safety, tolerability, and immunogenicity of PF-05280586 after a single transition from either US-licensed Rituxan or EU-approved MabThera.

This portion of the Division memo is a review of these secondary objectives of safety, efficacy, and immunogenicity in the RA studies. Table 3 presents the studies performed in subjects with RA and their objectives. The study designs are summarized in the section below.

Table 3. Clinical Studies in Patients with Rheumatoid Arthritis (RA)

Study Number	Study Drugs	Study Drug Doses	Subject Population	Number of Subjects Randomized	Objectives
B3281001 Completed	Randomized, double-blind, comparative PK and bridging study	1 course of 2 IV infusions of 1000mg PF-05280586, or rituximab-US given on Days 1 and 15	Patients with active RA eligible for anti-CD20 therapy on background MTX and with inadequate response to ≥ 1 TNF-antagonists	ITT population = 220 subjects PF-05280586 + MTX: n=73 Rituximab-EU + MTX: n=74 Rituximab-US + MTX: n=73	<u>Primary:</u> To evaluate the PK similarity of PF-05280586, rituximab-EU, and rituximab-US <u>Secondary:</u> <ul style="list-style-type: none"> To utilize population PK/PD modeling approaches to integrate PK and PD data for the purpose of detecting potential differences in PK/PD profiles among PF-05280586, rituximab-EU, and rituximab-US To assess additional clinical response endpoints of PF-05280586, rituximab-EU, and rituximab-US To evaluate the overall safety, tolerability, and immunogenicity of PF-05280586, rituximab-EU, and rituximab-US To evaluate health outcomes using HAQ-DI in subjects receiving PF-05280586, rituximab-EU, and rituximab-US
B3281004 Completed	Extension study: PF-05280586 vs. rituximab-EU and rituximab-US	Up to 3 courses (6 doses) of study treatment. Each course: 2 IV infusions of 1000mg/500mL of study treatment, each administered on D1	Patients with RA who had participated in the Study B3281001	ITT Population: Course 1: n=185 rituximab-EU + MTX, rituximab-US + MTX, PF-05280586 + MTX	<ul style="list-style-type: none"> To provide continued access to treatment in patients with RA who participated for at least 16 weeks in B3281001 study To evaluate the overall safety, tolerability, and immunogenicity of PF-05280586 occurring after a single transition from either rituximab-US or rituximab-EU to PF-05280586 To continue follow-up of biomarker and efficacy endpoints of interest in the B3281001 study

		<p>and 15 of a 24 (± 8 week) course</p> <p>Courses were administered ≥ 16 weeks after the initiation of the previous course</p> <p>Last course began no later than 64 weeks from study baseline</p> <p>Study duration: 48-96 weeks</p>		<p>Course 2: n=173 PF-05280586 + MTX</p> <p>Course 3: n=164 PF-05280586 + MTX</p>	
--	--	---	--	---	--

rituximab-US = US-licensed Rituxan; rituximab-EU = EU-approved MabThera
Source: Pfizer Summary of Clinical Efficacy. Table 1. Dated July 3, 2018. Pages 11-13.

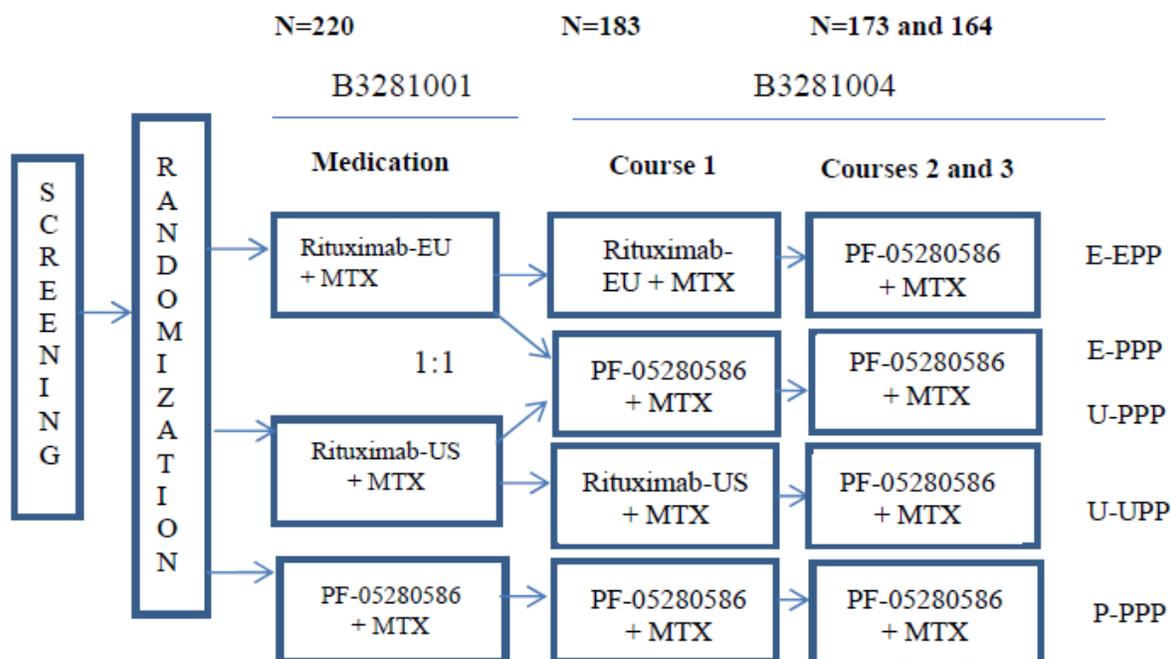
PF-05280586 Clinical Program in RA: Study Design and Endpoints

Study B3281001 was a multinational, randomized, double-blind, controlled study in subjects with active RA on background MTX who have had an inadequate response to ≥ 1 TNF antagonist therapies to evaluate the PK/PD similarity, safety, and clinical response of PF-05280586, EU-approved MabThera, and US-licensed Rituxan. Subjects were randomized 1:1:1 to 1 of the 3 treatment groups. Blinded study drug (PF-05280586, EU-approved MabThera, US-licensed Rituxan) was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. A total of 220 subjects were randomized.

Study B3281004 was an extension study for subjects with active RA who had participated for at least 16 weeks in study B3281001 and had not received intervening treatment with investigational agents or other biologics. Subjects assigned to PF-05280586 in study B3281001 continued to receive PF-05280586. Subjects who were assigned to US-licensed Rituxan and EU-approved MabThera in study B3281001 were blindly randomized 1:1 to either remain on their previously assigned study drug or transition to PF-05280586 for the first treatment course. All subsequent treatments for all subjects were PF-05280586. Subjects were offered up to 3 courses of study treatment. Each course was defined as 2 IV infusions of 1000 mg administered on Days 1 and 15 of a 24-week (± 8 week) period. Courses were administered no sooner than 16 weeks after the initiation of the previous course. Thus, the total length of study participation ranged from 48 to 96 weeks. One hundred eighty-five of the 220 subjects in study B3281001 were enrolled in the extension study.

Figure 1 shows the study schema of both studies in RA. It also shows the numbers of subjects who received each course of therapy.

Figure 1. Study Schema of Studies B3281001 and B3281004



P=PF-05280586; E=EU-approved MabThera(rituximab-EU); U=US licensed Rituxan (rituximab-US)
Source: Pfizer Summary of Clinical Efficacy. Figure 2. Dated July 3, 2018. Page 18.

Patient Population and Endpoints

Study B3281001

Some of the notable criteria for enrollment included the following:

- Age 18 years or older
- Confirmed diagnosis of RA based on the 2010 ACR/EULAR classification criteria
- Class I, II, or III of the ACR 1991 Revised Criteria for Global Functional Status in RA
- RA serpositivity as documented by rheumatoid factor (RF) and/or anti-cyclic peptide antibodies (anti-CCP) at Screening
- Active disease as defined by the following:
 - ≥ 6 tender/painful joints (of 68 assessed) at Screening and Baseline and
 - ≥ 6 swollen joints (of 66 assessed) at Screening and Baseline and
 - High-sensitivity C-reactive protein (hsCRP) $>$ upper limit of normal (ULN) at Screening and
 - Screening DAS28-CRP (Disease Activity Score in 28 joints – C-reactive protein) >3.2

Subjects must have received methotrexate (MTX, oral or parenteral) for at least 3 months and must have been on stable doses of methotrexate (10-25 mg/week) for at least 4 weeks prior to first dose of study drug. Subjects must also have had an inadequate response to at least 1 TNF antagonist therapy. The investigator determined inadequate response, which was defined as failure to achieve adequate clinical response during therapy or relapse following clinical response to TNF antagonist therapy or adverse events (AE) to TNF antagonist therapy leading to discontinuation. Subjects must have discontinued any biologic therapy and some conventional

disease modifying anti-rheumatic drugs (DMARDs, e.g., leflunomide). Oral corticosteroids at a stable dose of prednisone ≤ 10 mg (or equivalent) were allowed during the study.

For study B3281001, the primary and major secondary endpoints were PK/PD assessments. The primary endpoints were C_{max} and $AUC_{0-\infty}$, whereas the secondary PK parameters included AUC_{0-2wk} and $AUC_{0-\tau}$. Secondary PD endpoints included CD19+ B-cell count and circulating IgM. These PK/PD endpoints are summarized in the Clinical Pharmacology section (Section 4 of this memo) and in the Clinical Pharmacology review by Dr. Wickramaratne Senarath Yapa.

Other secondary endpoints assessed safety and efficacy. Safety endpoints included assessment of AEs (type, incidence, severity, timing, seriousness, and relatedness), laboratory abnormalities, and incidence of anti-drug antibodies (ADA, including neutralizing antibodies [Nab]) and associated safety. Efficacy endpoints included ACR assessments and mean change from baseline in DAS28-CRP, EULAR response, LDAS ≤ 3.2 , DAS remission <2.6 , and HAQ-DI. Descriptions of these endpoints are provided in the Appendix.

Study B3281004

Subjects who had participated in study B3281001 for at least 16 weeks were eligible to proceed to the extension study up to 2 months after completion of study B3281001.

Subjects were discontinued from the extension study if (1) they did not experience response to treatment (decrease in DAS28-CRP ≤ 1.2) compared to the Baseline assessment by the time the second course was being considered in the extension study and (2) in the investigator's opinion, the next course of treatment is not needed within the allowed window of 24 (± 8) weeks.

As described in Table 3, the primary objective of this study was to continue treatment access to subjects who participated in study B3281001. In this extension study, safety, tolerability, and immunogenicity after transition from either US-licensed Rituxan or EU-approved MabThera to PF-05280586 was measured by AEs, laboratory abnormalities, and incidence of ADA. Other assessments included biomarkers (e.g., CD19+ B-cell count, IgG, IgM, RF, anti-CCP, and complement) and efficacy endpoints (e.g., DAS28-CRP, EULAR response, LDAS, DAS-CRP remission, ACR response, HAQ-DI).

Demographics and Disposition

Study B3281001

Two hundred twenty subjects with RA were randomized in study B3281001 and were evenly distributed in each treatment arm, n=73 in the rituximab-US arm, n=74 in the rituximab-EU arm, and n=73 in the PF-05280586 arm. Table 4 presents the disposition of patients who were randomized. The majority of subjects completed the study. A total of 16 subjects discontinued the study with numerically higher number in the PF-05280586 arm, n=5 (6.8%) in the rituximab-US arm, n=3 (4.1%) in the rituximab-EU arm, and n=8 (11.0%) in the PF-05280586 arm. Treatment arms with US-licensed Rituxan and EU-approved MabThera had 1 discontinuation due to an AE, whereas there were 3 subjects who discontinued the study in the PF-05280586 (two of whom withdrew before the Day 15 dose). These will be discussed in the safety review below. A total of 6 subjects did not receive both doses of study drug, and these occurred more

evenly across treatment arms, n=3 (4.1%) in the rituximab-US arm, n=1 (1.4%) in the rituximab-US arm, and 2 (2.7%) in the PF-05280586 arm. One hundred eighty-three subjects rolled over into the extension study, and these subjects will be described below.

Table 4. Study B3281001 Subject Disposition

	Rituximab-US n (%)	Rituximab-EU n (%)	PF-05280586 n (%)
No. of subjects randomized/treated	73 (100)	74 (100)	73 (100)
No. of subjects completed study	62 (84.9)	69 (93.2)	61 (83.6)
Discontinuations	5 (6.8)	3 (4.1)	8 (11.0)
Adverse event	1 (1.4)	1 (1.4)	3 (4.1)
Subject death	0	0	1 (1.4)
Protocol violation	0	0	0
Lost to follow-up	1 (1.4)	0	1 (1.4)
No longer willing to participate in study	2 (2.7)	2 (2.7)	2 (2.7)
Other	1 (1.4)	0	1 (1.4)

Source: Protocol B3281001 Clinical Study Report. Table 6. Dated August 30, 2016; page 64.

Table 5 describes the baseline demographics. The majority of subjects were female and Caucasian. Demographics of subjects at baseline were similar across treatment arms.

Table 5. Baseline Demographics of Study B3281001 (mITT Population)

	Rituximab-US N=73	Rituximab-EU N=74	PF-05280586 N=73
Age (years)			
Mean (SD)	53.4 (11.9)	54.9 (11.1)	54.9 (11.5)
Median	53.0	55.0	56.0
Min, Max	25, 80	20, 73	28, 82
Sex, n (%)			
Male	19 (26.0)	17 (23.0)	14 (19.2)
Female	54 (74.0)	57 (77.0)	59 (80.8)
Race			
White	58 (79.5)	57 (77.0)	56 (76.7)
Black	5 (6.8)	6 (8.1)	2 (2.7)
Asian	1 (1.4)	0	3 (4.1)
Other	9 (12.3)	11 (14.9)	12 (16.4)
BMI			
Mean (SD)	29.0 (6.7)	29.8 (6.3)	31.5 (8.1)
Median	27.2	29.4	29.9
Min, Max	17.3, 46.6	16.1, 45.3	16.4, 61.7

BMI = Weight(kg)/Height(m)²

Source: Pfizer Summary of Clinical Efficacy. Table 13. Dated July 3, 2018; page 41.

Table 6 presents the baseline disease characteristics. There are some differences across treatment arms. First, the majority of subjects were seropositive (RF+ and anti-CCP+) in all treatment arms, but the number was numerically higher in the rituximab-US arm (n=62 [84.9%]) compared to the other arms (n=58 [78.4%] in the rituximab-EU arm and n=55 [75.3%] in the PF-05280586 arm). Most notably, subjects who received US-licensed Rituxan had more swollen

and tender joints along with a higher mean serum CRP compared to subjects who received the other 2 products. Accordingly, these subjects in the rituximab-US arm had a higher baseline DAS28-CRP compared to the other 2 arms; the mean DAS28-CRP was 6.22 in the rituximab-US arm, compared to 5.79 and 5.69 in the rituximab-EU and PF-05280586 arms, respectively. Thus, it appears that subjects who received US-licensed Rituxan may have had more active disease at baseline compared to subjects who received EU-approved MabThera and PF-05280586. These differences are relevant and warrant caution in the interpretation of the efficacy results from this PK similarity study, as discussed in further detail in this Section.

Table 6. Baseline Disease Characteristics of Study B3281001 (mITT Population)

	Rituximab-US N=73	Rituximab-EU N=74	PF-05280586 N=73
Disease duration since first diagnosis (months), Mean (SD)	125.0 (96.8)	140.6 (98.9)	153.3 (99.3)
RF and anti-CCP, n (%)			
RF+ and anti-CCP+	62 (84.9)	58 (78.4)	55 (75.3)
RF+ and anti-CCP-	7 (9.6)	7 (9.5)	6 (8.2)
RF- and anti-CCP+	3 (4.1)	6 (8.1)	11 (15.1)
RF- and anti-CCP-	1 (1.4)	3 (4.1)	1 (1.4)
Swollen joint count (28), Mean (SD)	14.1 (5.9)	13.0 (6.5)	11.7 (5.4)
Tender/painful joint count (28), Mean (SD)	18.1 (6.5)	14.9 (6.8)	14.6 (6.7)
Swollen joint count (66), Mean (SD)	19.3 (8.7)	17.8 (10.6)	15.6 (8.9)
Tender/painful joint count (68), Mean (SD)	30.4 (15.3)	23.3 (13.23)	22.9 (12.5)
HAQ-DI score, mean (SD)	1.75 (0.62)	1.59 (0.54)	1.65 (0.57)
Serum hsCRP (mg/L)			
Mean (SD)	18.2 (24.8)	14.8 (17.4)	12.7 (15.3)
Min, Max	0.6, 118.0	0.2, 112.0	0.2, 105.0
DAS28-CRP, Mean (SD)	6.22 (0.89)	5.79 (0.95)	5.69 (0.85)
Previous drug treatment for RA, n (%)			
Methotrexate	73 (100)	74 (100)	73 (100)
Steroids	53 (72.6)	47 (63.5)	48 (65.8)
Other	66 (90.4)	69 (93.2)	66 (90.4)

Source: Protocol B3281001 Clinical Study Report. Table 14. Dated August 30, 2016; page 71.

Study B3281004

As noted above, 185 subjects from study B3281001 rolled over into the extension study. These included 58 subjects who received PF-05280586 in study B3281001, 66 subjects who received EU-approved MabThera, and 60 subjects who received US-licensed Rituxan. However, 2 subjects (1 from the PF-05280586 arm, 1 from the rituximab-EU arm) did not receive study treatment. Therefore, 183 subjects ended up receiving Course 1 in study B3281004; 173 subjects received Course 2; and 164 subjects received Course 3.

Table 7 details the disposition of subjects who entered study B3281004. As described in the study design description above, subjects who received EU-approved MabThera or US-licensed Rituxan in study B3281001 were randomized to continue treatment or to receive PF-05280586 for Course 1 of study B3281004. This randomization was even for both treatment arms, leading to approximately 30 subjects who originally received EU-approved MabThera or US-licensed

Rituxan and then transitioned to PF-05280586 for Course 1. For Courses 2 and 3 of study B3281004, all subjects received PF-05280586.

One hundred sixty-subjects completed study B3281004. Discontinuations were low across all treatment arms but were numerically higher in subjects who originally received PF-05280586 (n=11, 18.6%). There did not appear to be more discontinuations in subjects who transitioned from EU-approved MabThera or US-licensed Rituxan to PF-05280586. Discontinuations secondary to AEs will be described briefly below under safety.

Table 7. Subject Disposition in Study B3281004

B3281001 Treatment	PF-05280586	Rituximab-EU		Rituximab-US	
B3281004 Treatment	PPP N=59 n (%)	EPP N=33 n (%)	PPP N=33 n (%)	UPP N=30 n (%)	PPP N=30 n (%)
No. of Subjects Treated	58 (98.3)	32 (97.0)	33 (100)	30 (100)	30 (100)
ITT Population ^a	59 (100)	33 (100)	33 (100)	30 (100)	30 (100)
mITT Population ^b	58 (98.3)	32 (97.0)	33 (100)	30 (100)	30 (100)
mITT Population – Course 1 ^c	58 (98.3)	32 (97.0)	33 (100)	30 (100)	30 (100)
mITT Population – Course 2 ^d	54 (91.5)	30 (90.9)	31 (93.9)	29 (96.7)	29 (96.7)
mITT Population – Course 3 ^e	48 (81.4)	30 (90.9)	30 (90.9)	27 (90.0)	29 (96.7)
No. of Subjects Completed Study	48 (81.4)	30 (90.9)	30 (90.9)	27 (90.0)	28 (93.3)
No. of Subject Discontinuations	11 (18.6)	3 (9.1)	3 (9.1)	3 (10.0)	2 (6.7)
Adverse event	2 (3.4)	1 (3.0)	0	1 (3.3)	2 (6.7)
Subject death	0	0	0	0	0
Protocol violation	0	0	0	0	0
Lost to follow-up	1 (1.7)	1 (3.0)	2 (6.1)	0	0
No longer willing to participate in study	2 (3.4)	0	0	1 (3.3)	0
Pregnancy	0	0	0	1 (3.3)	0
Other	6 (10.2)	1 (3.0)	1 (3.0)	0	0

- ITT population was defined as all patients who were randomized to study treatment.
- mITT population was defined as all patients who were randomized and received at least 1 dose of study treatment.
- mITT population – Course 1 was defined as all patients who were randomized and received the treatment of the first course of study B3281004.
- mITT population – Course 2 was defined as all patients who were randomized and received the treatments of the first 2 courses of study B3281004.
- mITT population – Course 3 was defined as all patients who were randomized and received the treatments of all 3 courses of study B3281004.

E=EU-approved MabThera; U=US-licensed Rituxan; P=PF-05280586. Therefore, the 3 letter combination (i.e., PPP, EPP, UPP) refers to the study drug administered for Course 1, Course 2, and Course 3 of the study. For example, PPP refers to a patient who received PF-05280586 for each of the 3 courses of study.

Source: Pfizer Summary of Clinical Efficacy. Table 13. Dated July 3, 2018; page 41.

As subjects in study B3281004 are those who were enrolled in study B3281001, the demographics and baseline disease characteristics are not further presented in this memo.

Statistical Methodologies

The protocol defined several populations for analysis.

- Intent-to-treat (ITT) population: The ITT population was defined as all subjects who were randomized to the study treatment. This population was primarily used for subject accountability.
- Modified intent-to-treat (mITT) population: The mITT population was defined as all subjects who were randomized and received at least 1 dose of study treatment. The mITT population was used for assessments of safety, tolerability, immunogenicity, PD, and evaluation of measures of clinical response.
- Per Protocol (PP) population: The PP population was defined as all subjects who were randomized, received the full doses of the assigned study treatment, and had no major protocol violations that could impact the PK analysis, such as receiving the second infusion outside of the protocol prespecified window. The PP population was only used for the primary endpoint analysis (PK bioequivalence testing). The determination of which subjects were excluded from the PP population was based on a blinded data review by the Medical Monitor and Clinical Pharmacologist.
- Population PK/PD analysis population: The population PK/PD analysis population was defined as all randomized subjects who received full doses of the assigned study treatment and had at least 1 protocol-specified measurement for drug concentration and the PD response of interest collected after receiving the assigned study treatment, as well as the respective Baseline values.

Study B3281001 was not designed for formal statistical evaluation of efficacy endpoints. The data on selected disease activity measures were collected as secondary endpoints and descriptive statistics were used to analyze the components and total scores for each clinical outcome such as, disease activity score with C-reactive protein (DAS28-CRP) and the proportion of subjects achieving American College of Rheumatology 20%, 50%, and 70% improvement (ACR20, ACR50, ACR70); the proportion of subjects with European League Against Rheumatism (EULAR) response, low disease activity response (DAS28-CRP \leq 3.2), and disease activity score (DAS) remission (DAS28-CRP $<$ 2.6); and the mean change from baseline in HAQ-DI.

Efficacy analyses were conducted based on the modified intent-to-treat (mITT) population. No missing data imputation was implemented for the analysis of DAS28-CRP and non-responder imputation was used for missing values in the analysis of ACR20. Following the recommendation provided by FDA, the applicant conducted several post-hoc analyses to further explore the efficacy across treatment arms. Change from baseline in DAS28-CRP was evaluated by linear mixed-effect model with fixed effect variables of treatment, visit, treatment-by-visit, region, baseline RA duration, baseline RF status, baseline HAQ-DI, baseline patient global assessment of arthritis, baseline physician's global assessment of arthritis, baseline patient global assessment of arthritis pain, baseline DAS28-CRP, baseline tender/painful joint count 28, baseline swollen joint count 28, and baseline CRP (three levels). Toeplitz covariance structure within subject was used in these analyses.

ACR20, ACR50, ACR70 response rates were analyzed using a logistic regression model separately at each visit and with baseline factors including: region, RA duration, CRP (three levels), RF status, tender/painful joint count 68, swollen joint count 66, patient global assessment of arthritis, Physician’s global assessment of arthritis, patient global assessment of arthritis pain, and HAQ-DI. Treatment group difference estimates and 95% corresponding confidence intervals were generated for each visit.

The efficacy endpoint, DAS28 was calculated using a weighted sum of number of tender joints (0-28), number of swollen joints (0-28), C-Reactive Protein (CRP) measurement (mg/L), and Patient Global Assessment of Disease Activity measured on VAS (0 – 100 mm).

DAS28(CRP) was calculated as:

$$\text{DAS28 (CRP)} = (0.56 * \sqrt{\text{TJC28}}) + (0.28 * \sqrt{\text{SJC28}}) + (0.36 * \ln(\text{CRP} + 1)) + (0.014 * \text{GH}) + 0.96$$

where,

TJC28 = number of tender joints (0-28): tender joint count (TJC)

SJC28 = number of swollen joints (0-28): swollen joint count (SJC)

CRP = C-Reactive Protein (CRP) measurement (mg/L)

GH = Patient Global Assessment of Disease Activity measured on VAS (0–100mm)

ACRX response was calculated as: at least X% improvement from baseline in swollen and tender joint counts and at least a X% improvement from baseline in at least 3 of the following 5 remaining ACR core set measures: subject and physician global assessment using a 100 mm visual analogue scale (VAS), pain assessment using a 100 mm VAS, disability assessment using the health assessment questionnaire disability index (HAQ-DI), and acute phase reactant level (CRP).

The EULAR response criteria derived using DAS28 score defined in Table 8.

Table 8: Definition of EULAR response criteria using the DAS28

Present DAS28	Improvement in DAS28 from baseline		
	> 1.2	> 0.6 and ≤ 1.2	≤ 0.6
≤ 3.2 (low)	good response	moderate response	no response
> 3.2 to ≤ 5.1 (moderate)	moderate response	moderate response	no response
> 5.1 (high)	moderate response	no response	no response

Source: Applicant

PF-05280586 Clinical Program in RA: Efficacy Results and Conclusions

Study B3281001

The study B3281001 was designed to compare the PK and safety (including immunogenicity) of PF-05280586, rituximab-EU and rituximab-US in subjects with active RA. In addition, the following efficacy endpoints were analyzed to evaluate the similarity between the treatment arms.

Change from Baseline in DAS28-CRP at Week 24

The key efficacy endpoint in the study was the change from baseline in DAS28 (CRP), which was analyzed using linear mixed model by adjusting for relevant covariates and the results are given in Table 9. The mean DAS28-CRP decrease from baseline was numerically larger in the rituximab-US treatment group than in the rituximab-EU and PF-05280586 treatment groups. Of note, the rituximab-US group had the highest DAS28-CRP score at baseline. Further, the mean overall change from baseline derived from DAS28-CRP over 25 weeks of the study B3281001 are shown in Figure 2.

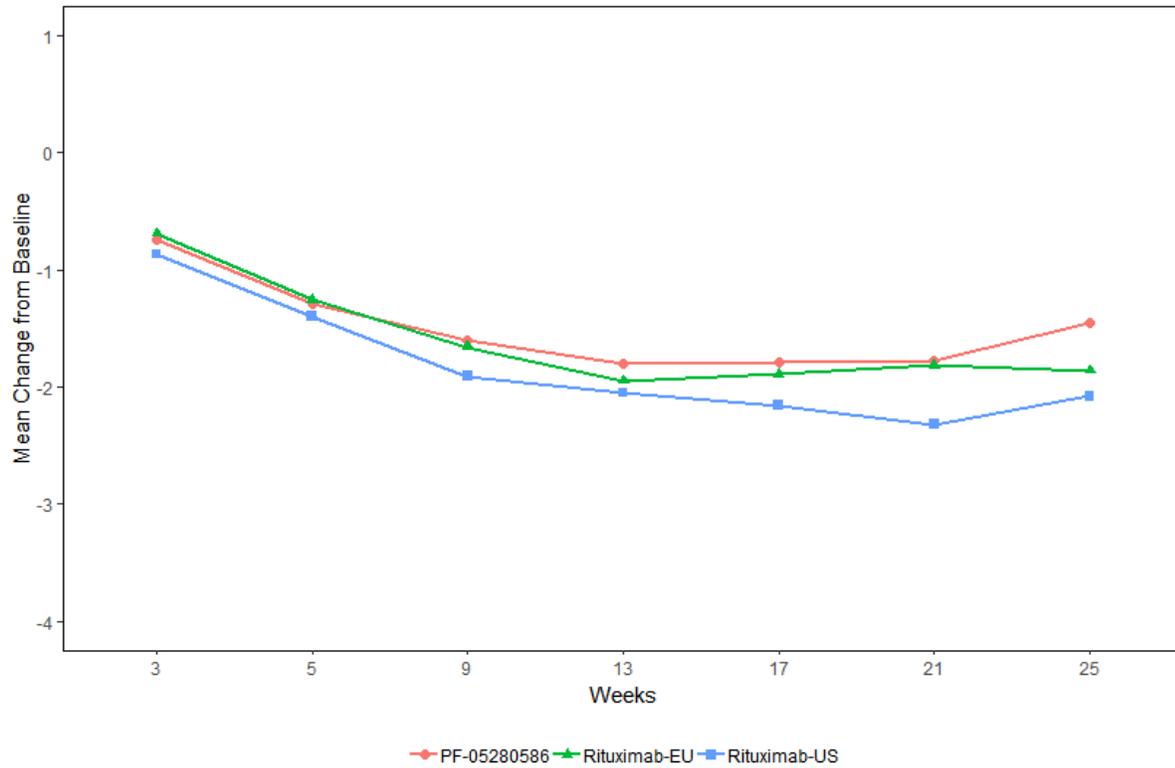
Table 9: Change from Baseline in DAS28-CRP by Treatment Group by Visit - study B3281001

Week	LS Mean Change from baseline			LS Mean change difference (95% CI)	
	PF-05280586	Rituximab-EU	Rituximab-US	PF-05280586 Vs Rituximab-EU	PF-05280586 Vs Rituximab-US
13	-1.7	-1.9	-2.0	0.1 (-0.3, 0.6)	0.2 (-0.2, 0.7)
17	-1.7	-1.8	-2.1	0.1 (-0.3, 0.5)	0.4 (-0.1, 0.8)
21	-1.7	-1.8	-2.3	0.1 (-0.4, 0.5)	0.6 (0.1, 1.0)
25	-1.4	-1.8	-2.1	0.4 (-0.04, 0.9)	0.6 (0.2, 1.0)

Source: FDA Statistical Reviewer

The number of subjects in each treatment group decreased on and after week 17 because they could rollover to the extension study. Fixed effect variables in the linear mixed model included; treatment, visit, treatment-by-visit, region, baseline RA duration, baseline RF status, baseline HAQ-DI, baseline patient global assessment of arthritis, baseline physician’s global assessment of arthritis, baseline patient global assessment of arthritis pain, baseline DAS28-CRP, baseline tender/painful joint count 28, baseline swollen joint count 28, and baseline CRP(three levels).

Figure 2: Mean Overall DAS28-CRP Change from Baseline over Time - Study B3281001



Source: FDA Statistical Reviewer

Component analysis of DAS28-CRP endpoint

The components of the DAS28-CRP endpoint include tender/painful joint count (28), swollen joint count (28), C-reactive protein (CRP) and patient's global assessment of arthritis (PGA). The analysis of DAS28 components show that for most of the components, the response rates were consistently higher in subjects receiving rituximab-US than subjects receiving rituximab-EU or PF-0528058 (Table 10).

Table 10: Component analysis of DAS28-CRP endpoint - study B3281001

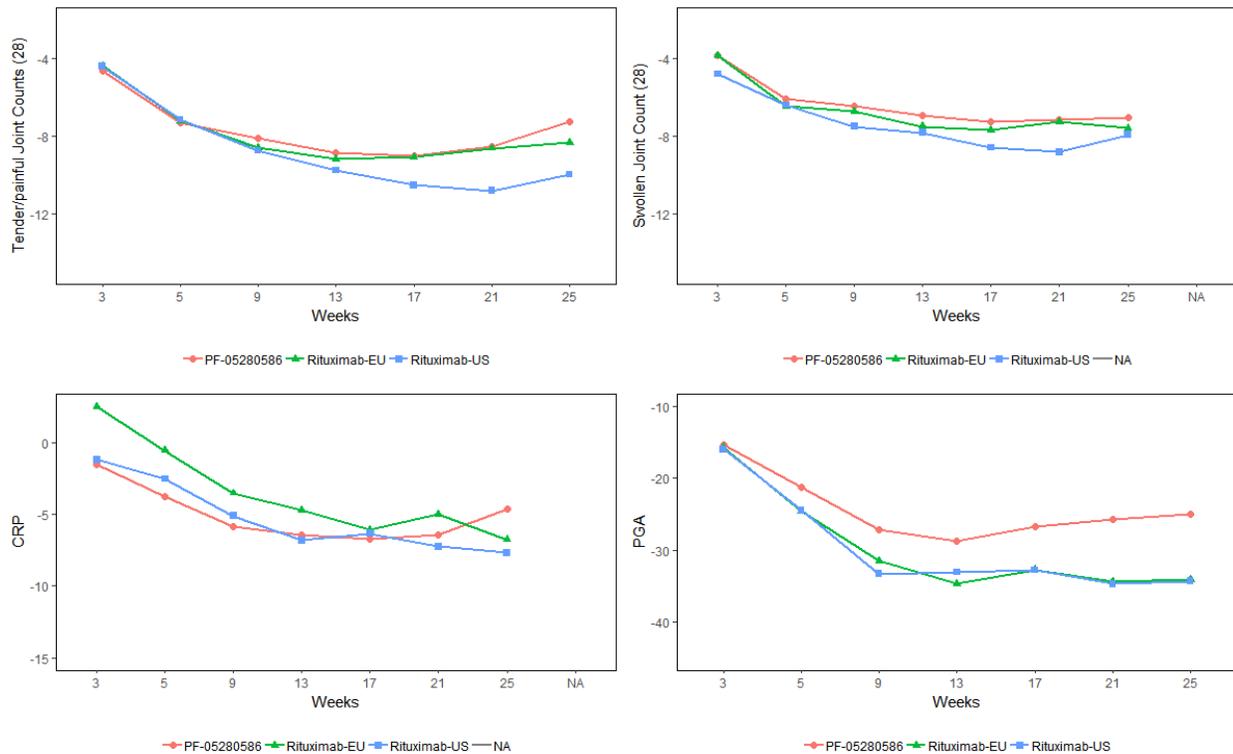
DAS28-CRP Components	Week	PF-05280586	Rituximab-EU	Rituximab-US
Tender/painful joint counts (28)	13	-8.9	-9.2	-9.8
	25	-7.3	-8.3	-10.0
Swollen joint count (28)	13	-7.0	-7.5	-7.8
	25	-7.1	-7.6	-7.9
hsC-Reactive Protein (hsCRP)	13	-6.5	-4.7	-6.8
	25	-4.7	-6.8	-7.7
PGA	13	-28.7	-34.7	-33.1
	25	-25.0	-34.2	-34.3

Source: FDA Statistical Reviewer

Change from Baseline in DAS28-CRP Components was evaluated by linear mixed-effect model with fixed effect variables of treatment, visit, treatment by visit, and baseline Components. Toeplitz covariance structure within subject is used.

Estimated mean change from baseline values are plotted across different treatment visits in each component of DAS28- CRP are shown in Figure 3

Figure 3: Components DAS28-CRP endpoint across visit - study B3281001



Source: FDA Statistical Reviewer

ACR20, ACR50 and ACR70 Response Rates

The proportions of ACR 20, 50 and 70 responders were compared using logistic regression by adjusting covariates; treatment, region, baseline RA duration, baseline CRP (three levels), baseline HAQ-DI, baseline RF status, baseline swollen joint count 66, baseline tender/painful joint count 68, baseline patient global assessment of arthritis, baseline physician’s global assessment of arthritis, and baseline patient global assessment of arthritis pain. In general, the proportion of ACR responders were highest in the rituximab-US group compared to the rituximab-EU or PF-05280586 groups.

The estimated proportions of ACR20 responders were 60.3%, 77.3%, and 74.9% at week 13 and 76.2%, 78.5%, and 91.5% at week 25 for subjects receiving PF-05280586, rituximab-EU, and rituximab-US respectively (Table 11).

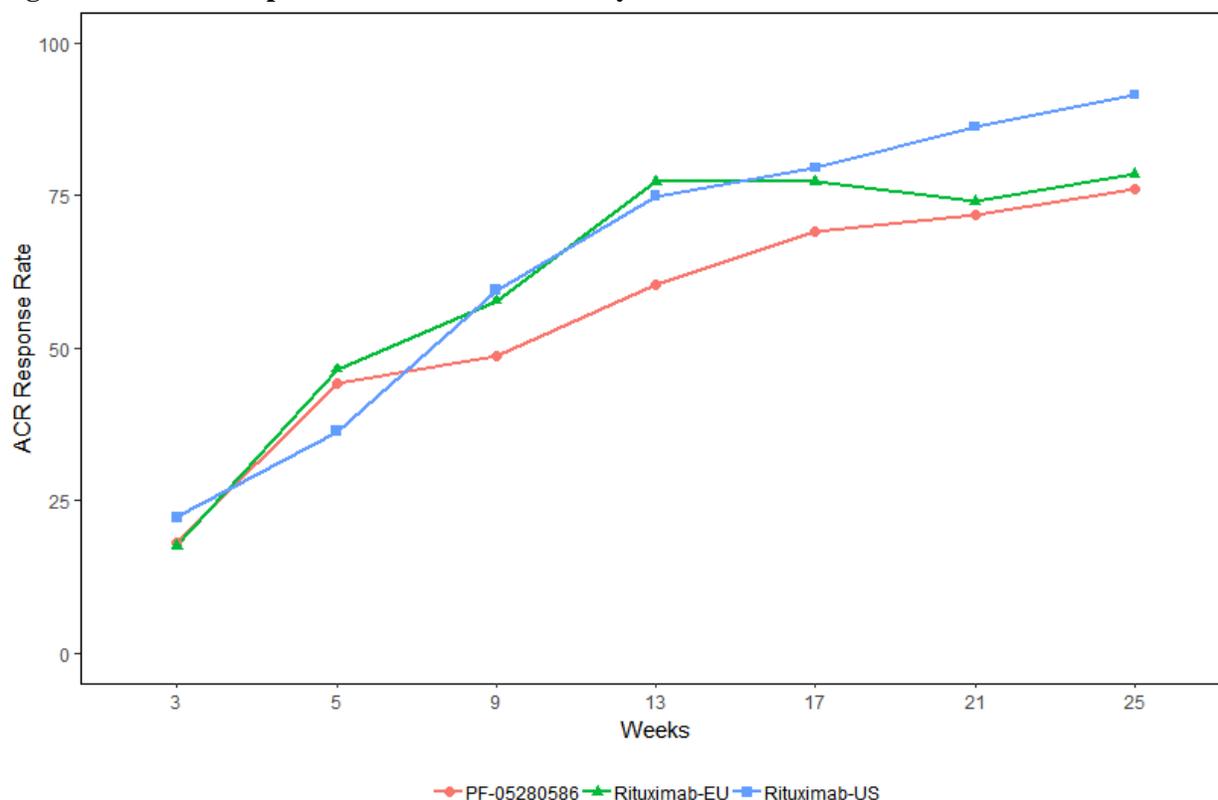
Table 11: ACR20 Response Rates by Treatment Group by Visit - study B3281001

Week	Estimated Response Rate (%)			Response Rate difference (%) (95% CI)	
	PF-05280586	Rituximab-EU	Rituximab-US	PF-05280586 Vs Rituximab-EU	PF-05280586 Vs Rituximab-US
13	60.3	77.3	74.9	-16.9 (-32.9, -0.9)	-14.5 (-31.7, 2.6)
17	69.0	77.3	79.6	-8.3 (-24.0, 7.4)	-10.6 (-27.2, 6.0)
21	71.9	74.1	86.3	-2.2 (-17.3, 12.8)	-14.4 (-29.5, 0.7)
25	76.2	78.5	91.5	-2.3 (-17.9, 13.3)	-15.3 (-31.5, 0.9)

Source: FDA Statistical Reviewer

ACR20 response rate increased over time across the three treatment arms. However, the response rate for PF-05280586 was found to be lower than the other two reference groups (Figure 4).

Figure 4: ACR20 Response Rate over Time - study B3281001



Source: FDA Statistical Reviewer

ACR50 response rate was higher for rituximab-US compared to the other two groups at Week 17 and thereafter. The estimated proportions of ACR50 responders were 34.1%, 36.5%, and 32.8% at Week 13 and 20.1%, 34.7%, and 39.3% at week 25 for subjects receiving PF-05280586, rituximab-EU, and rituximab-US respectively (Table 12).

Table 12: ACR50 Response Rates by Treatment Group by Visit - study B3281001

Week	Estimated Response Rate (%)			Response Rate difference (%) (95% CI)	
	PF-05280586	Rituximab-EU	Rituximab-US	PF-05280586 Vs Rituximab-EU	PF-05280586 Vs Rituximab-US
13	34.1	36.5	32.8	-2.3 (-18.7, 14.0)	1.3 (-16.3, 18.8)
17	28.3	38.8	52.9	-10.5 (-27.7, 6.7)	-24.6 (-44.3, -4.9)
21	29.2	37.2	49.9	-8.0 (-24.5, 8.6)	-20.7 (-39.6, -1.7)
25	20.1	34.7	39.3	-14.5 (-32.0, 3.0)	-19.2 (-39.4, 1.0)

Source: FDA Statistical Reviewer

Similar trends were observed in ACR70 endpoint with higher response rate for rituximab-US. The estimated proportions of ACR70 responders were 15.0%, 22.3%, and 21.4 at week 13 and

19.2%, 18.6%, and 21.8 at week 25 for subjects receiving PF-05280586, rituximab-EU, and rituximab-US respectively (Table 13).

Table 13: ACR70 Response Rates by Treatment Group by Visit - study B3281001

Week	Estimated Response Rate (%)			Response Rate difference (%) (95% CI)	
	PF-05280586	Rituximab-EU	Rituximab-US	PF-05280586 Vs Rituximab-EU	PF-05280586 Vs Rituximab-US
13	15.0	22.3	21.4	-7.4 (-20.1, 5.4)	-6.4 (-20.6, 7.8)
17	18.2	19.7	20.9	-1.5 (-14.7, 11.6)	-2.7 (-16.2, 10.8)
21	12.2	17.5	20.5	-5.3 (-16.8, 6.2)	-8.2 (-22.2, 5.8)
25	19.2	18.6	21.8	0.6 (-14.0, 15.2)	-2.6 (-17.9, 12.7)

Source: Statistical Reviewer

EULAR Response Rates

The analysis of EULAR endpoint were based on the response rate derivation (given in Table 8) and the summary of EULAR response over the visits are presented in Table 14. Despite some variations in the response rates, there were no obvious imbalances across the treatment groups, unlike the ACR responder rates or DAS28-CRP clinical responses even though all these endpoints capture very similar components and concepts of clinical response.

Table 14: Summary of EULAR Response Rates by Visit - study B3281001

Visit	PF-05280586 N=73	Rituximab-EU N=74	Rituximab-US N=73
Week 13			
Good Response	41.8	44.4	32.8
Moderate Response	38.8	37.5	44.8
No Response	19.4	18.1	22.4
Week 17			
Good Response	36.4	38	32.8
Moderate Response	45.5	39.4	53.7
No Response	18.2	22.5	13.4
Week 21			
Good Response	35	35.4	47.5
Moderate Response	51.7	46.2	39
No Response	13.3	18.5	13.6
Week 25 (EOT)			
Good Response	30	36.2	41.8
Moderate Response	50	46.6	43.6
No Response	20	17.2	14.5

Source: FDA Statistical Reviewer

Study B3281004

The details of study design are given in section 2.2. Overall, 185 subjects of the 220 subjects treated in the Study B3281001 were randomized and were included in the ITT Population of Study B3281004. Two of the 185 randomized subjects did not receive treatment in Study B3281004. A total of 183 subjects were included in the mITT population. A total of 183 subjects were treated in Course 1, 173 subjects treated in Course 2, and 164 subjects treated in Course 3.

The 59 subjects assigned to PF-05280586 in Study B3281001 were assigned to receive PF-05280586 throughout Study B3281004. The 60 subjects who previously received rituximab-US and the 66 subjects who previously received rituximab-EU in Study B3281001 were randomized (1:1) in a blinded manner to receive PF-05280586 or their previously assigned licensed product in Course 1. For the subsequent 2 treatment courses, all subjects (173 subjects) were assigned to receive PF-05280586 in a blinded manner. Approximately one-half of the subjects underwent a single transition from either US-licensed Rituxan or EU-approved MabThera to PF-05280586 at Course 1, and the remainder underwent a transition at Course 2; thus, at Courses 2 and 3, all subjects received only PF-05280586.

A total of 22 (11.9%) subjects were withdrawn from treatment for all five treatment groups combined before they received the full three courses of treatment and discontinued before completing the study.

Statistical Considerations

The reviewer has identified the following statistical issues in this submission.

- In study B3281001, the ACR20/50/70 response rates of the PF-05280586 treatment arm were numerically lower as compared with the responses in the rituximab-EU and rituximab-US treatment groups. In addition, the differences in ACR response rates appear to be more evident than the DAS28-CRP results.
- The applicant proposed that the numerical difference in ACR response in study B3281001 was due to an imbalance in baseline characteristics between rituximab-EU and rituximab-US and PF-05280586 study arms, with more severe disease activity in the rituximab-US compared to the PF-05280586 arm at baseline. Therefore, FDA recommended the applicant to perform a post-hoc analysis on the DAS28 and ACR20/50/70 clinical endpoints to evaluate the impact of baseline imbalances in the observed differences in the response rates.
- Study B3281001 was powered to show PK similarity between PF-05280586, rituximab-US, and rituximab-EU treatment groups and the efficacy was assessed as a secondary objective in both studies of B3281001 and B3281004. Furthermore, there were no pre-specified formal statistical testing procedures for comparatively evaluating efficacy in these studies, which limits statistical conclusions regarding efficacy based on the available data.

Summary and Conclusions

Study B3281001 was a randomized, double-blind, active-controlled study comparing the PK, PD, and safety of PF-05280586, US-licensed Rituxan, and EU-approved MabThera in subjects with active rheumatoid arthritis who had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

Study B3281001 was designed and powered to assess PK similarity, and efficacy was assessed as a secondary objective. While the study met its primary objectives of demonstrating PK similarity between the three products, some differences were observed in clinical outcomes, as described in Section 5 above. In considering whether the observed differences between the treatment groups represent meaningful differences, the team considered the following:

- Study B3281001 design: The study was designed and conducted as a PK similarity study with the primary objective to demonstrate PK similarity between PF-05280586, US-licensed Rituxan, and EU-approved MabThera. Secondary objectives included PK/PD modeling approaches to integrate PK and PD data and assessment of additional clinical response and health outcome endpoints. Study B3281001 was not designed for formal statistical evaluation of efficacy endpoints. The data on selected disease activity measures were collected as secondary endpoints and descriptive statistics, limiting conclusions based on statistical considerations regarding efficacy from this study.
- Sample size: Related to the bullet above, the sample size of the study, while sufficient for the assessment of PK similarity, was small (approximately 73 patients per arm). This is significantly smaller than the sample size needed to adequately assess efficacy endpoints using a pre-specified similarity margin in studies in RA (range of 200 to 300 patients per arm), also limiting the statistical conclusions regarding efficacy from this study.
- Baseline Differences: Notable differences in baseline disease characteristics were seen between the treatment arms (Table 6). For example, patients in US-licensed Rituxan arm

had a higher proportion of seropositive (RF+ and anti-CCP+) patients, had more swollen and tender joints along with a higher mean serum CRP compared to subjects in the comparative arms and had higher DAS28-CRP (6.22), compared to EU-approved MabThera (5.79) and PF-05280586 (5.69). These baseline differences raise questions of whether patients were inherently different between the treatment groups and warrant caution in the interpretation of the observed higher responses in the US-licensed Rituxan arm, compared with the EU-approved MabThera and PF-05280586 for some of the efficacy outcomes analyzed using descriptive and post-hoc analyses.

- Inconsistent results depending on outcome measures of clinical response: There is inconsistency in the differences observed using some clinical response outcomes versus others, despite similar concepts captured by these outcome measures. For example, using DAS28-CRP as an outcome, the mean changes were very similar between PF-05280586 and EU-approved MabThera but different from US-licensed Rituxan, while using ACR20 response rates, the results were lower for PF-05280586 but similar between EU-approved MabThera and US-licensed Rituxan. This suggests that any observed differences are likely due to the difference in the precision and accuracy of various outcome measures used in the study and may not be considered as an evidence of true difference in efficacy.
- Further, clinical endpoints used in Study B3281001 are not sufficiently sensitive, in the context of this PK study design, to detect meaningful differences even across products with different mechanisms of action⁴ or significant differences in dosing and exposure.⁵

When taken together with (1) the considerations enumerated above, (2) the demonstration that PF-05280586 is highly similar to US-licensed Rituxan, (3) 3-way PK similarity between PF-05280586, US-licensed Rituxan, and EU-approved MabThera, and (4) the comparative clinical Study B3281006 data in LTB-FL, which support a demonstration of no clinically meaningful differences, the differences in ACR response rates observed in study B3281001 in RA do not preclude a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan.

PF-05280586 Clinical Program in RA: Clinical Safety

Categorization of Adverse Events

Standard definitions of adverse event (AE) and serious adverse event (SAE) were utilized. Severity of AEs was determined in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Treatment-emergent AEs were defined as any AEs that occurred during or after the first infusion of the study treatment or any pre-existing AEs that got worse on or after the first infusion of the study treatment. AEs were coded with Medical Dictionary for Regulatory Activities (MedDRA) version 16.0. Adverse events were collected from Day 1 through the treatment period (24 weeks). Long-term follow-up involved collecting SAEs every 3 months until CD19+ B-cell counts recovered to at least 50% of baseline or up to 1 year from Day 1.

⁴ Demin I, et al. Longitudinal model-based meta-analysis in rheumatoid arthritis: an application toward model-based drug development, *Clin Pharmacol Ther.* 2012 Sep;92(3):352-9

⁵ Mandema JW et al. A dose-response meta-analysis for quantifying relative efficacy of biologics in rheumatoid arthritis, *Clin Pharmacol Ther.* 2011 Dec;90(6):828-35

This memo will focus on the safety in study B3281001. A brief discussion of any change in safety after a single transition (particularly, infusion-related reactions) in study B3281004 will also be presented.

Adequacy of Safety Database

The majority of randomized subjects received a full dose of study drug on Day 1 and Day 15 in study B3281001. Only two subjects in the rituximab-US arm on Day 1 and one subject in the rituximab-EU arm on Day 15 received a partial dose of study drug. Therefore, there was no notable difference regarding study drug exposure across treatment arms.

Major Safety Results

Table 15 shows a summary of safety from study B3281001. In general, the number of subjects with AEs and TEAEs appeared to be similar across treatment arms. The proportion of subjects with any AEs, Serious AEs, and discontinuations secondary to AEs were overall low in number and similar across treatment arms.

Table 15. Summary of Safety in Study B3281001 (mITT Population)

	Rituximab-US N=73 n (%)	Rituximab-EU N=74 n (%)	PF-05280586 N=73 n (%)
Subjects with any AEs	45 (61.6)	41 (55.4)	50 (68.5)
Subjects with treatment-related AEs	18 (24.7)	17 (23.0)	22 (30.1)
Subjects with SAEs	4 (5.5)	1 (1.4)	5 (6.8)
Subjects with Discontinuations due to AEs	1 (1.4)	1 (1.4)	2 (2.7)

Discontinuations due to AEs defined as withdrawals before Day 15 dose.

Source: Protocol B3281001 Clinical Study Report. Table 22. Dated August 30, 2016; page 93.

Deaths

One death occurred during study. Subject (b) (6) was a 66 year-old, Caucasian female who received PF-05280586 and was diagnosed with a Grade 5 presumed bone neoplasm 51 days after the first dose of study drug. The subject was discontinued from the study and subsequently died.

Serious Adverse Events (SAEs)

The number of subjects with nonfatal SAEs was similar across treatment arms. However, the numbers were low, and, thus, it is difficult to make any conclusions. Table 16 presents the types of SAEs by Systemic Organ Class (SOC) and Preferred Term (PT). The SOC with the most SAEs was Infections and Infestations; these are described below under Serious Infections. There was 1 subject with heart failure in the US-licensed Rituxan group and 1 subject in the PF-05280586. Otherwise, the PTs occurred as single events.

Table 16. Treatment-Emergent Serious Adverse Events (SAEs) in Study B3281001 (mITT Population)

System Organ Class Preferred Term	Rituximab-US N=73 n (%)	Rituximab-EU N=74 n (%)	PF-05280586 N=73 n (%)
Subject with any SAEs	4 (5.5)	1 (1.4)	4 (5.5)
Blood and lymphatic system disorders			
Thrombocytopenic purpura	0	1 (1.4)	0
Cardiac disorders			
Cardiac failure	0	0	1 (1.4)
Cardiac failure congestive	1 (1.4)	0	0
Atrial flutter	1 (1.4)	0	0
Infections and infestations			
Arthritis bacterial	0	0	1 (1.4)
Bacterial sepsis	0	0	1 (1.4)
Septic shock	0	0	1 (1.4)
Pyelonephritis	1 (1.4)	0	0
Musculoskeletal and connective tissue disorders			
Arthropathy	1 (1.4)	0	0
Psychiatric disorders			
Intentional self-injury	0	0	1 (1.4)

A subject was counted once for each preferred term (PT).

Source: Protocol B3281001 Clinical Study Report. Table 28. Dated August 30, 2016; page 104.

Serious Infections

Serious infections are an AE of special interest (AESI). Three of the 4 serious infections occurred in subjects on PF-05280586, and one occurred in a subject in the Rituximab-US arm. Although there were more serious infections in the PF-05280586 arm, the types of infections were consistent with the known safety profile of US-licensed Rituxan.

No serious opportunistic infections were identified. There was 1 case of zoster in a subject on US-licensed Rituxan, but this was not considered serious.

Discontinuations due to Adverse Events

Four subjects in all treatment arms discontinued from the study due to a TEAE; specifically, these were withdrawals that occurred before the Day 15 dose of study treatment. Like the SAEs, the number of subjects who discontinued due to AEs was similar across study arms. However, the low numbers make it difficult to draw any conclusions.

The AEs, by PT, that lead to discontinuation are described below:

- Rituximab-US arm
 - One subject discontinued due throat irritation.
- Rituximab-EU arm
 - One subject discontinued after developing thrombocytopenia purpura (TTP).
- PF-05280586 arm
 - Two subjects discontinued due to AEs, one from bacterial sepsis and one from upper respiratory infection.

The applicant noted that no AEs led to dose reductions or temporary discontinuations. However, the infusion rate was reduced on Day 1 for 9 subjects (n=2 on US-licensed Rituxan, n=2 on EU-approved MabThera, n=5 on PF-05280586). These infusion rate reductions occurred on the Day 1 infusion, and the AEs for subjects on PF-05280586 included hypersensitivity, ear pruritus, and pruritus. These were similar to the type AEs that led to infusion rate reductions in the rituximab-US and rituximab-EU arms.

Common Adverse Events

The SOC with the mostly commonly reported AEs were Infections and Infestations (6 subjects in rituximab-US arm, 7 subjects in rituximab-EU arm, 9 subjects in PF-05280586 arm) and Gastrointestinal Disorders (3 subjects in rituximab-US, 6 subjects on rituximab-EU, 3 subjects on PF-05280586). The most common Preferred Terms (PTs) reported in all subjects were upper respiratory tract infection (n=6, 2.7%), pruritus (n=5, 2.3%), bronchitis (n=5, 2.3%), fatigue (n=4, 1.8%), and throat irritation (n=4, 1.8%). These occurred in similar numbers across treatment arms.

Laboratory Findings

For both hematology and chemistry mean values, there were no notable differences among treatment groups. Mean change from baseline were also small for both hematology and chemistry values.

Vital Signs/Electrocardiogram (ECG)/QT

Vital signs (including blood pressure, respiratory, pulse rate, and body temperature) were monitored at screening, Days 1 and 15, and Weeks 5, 9, 13, 17, 21, 25. Changes from baseline were small and not notably different across all treatment arms.

An ECG was obtained at screening and Week 25. Three subjects were determined to have a clinically significant abnormal ECG. Two of these subjects had an abnormal ECG at the end of treatment. One was in the EU-approved MabThera arm, and one was receiving PF-05280586. The subject on PF-05280586 was the one with the SAE of heart failure. This subject had a known history of coronary artery disease status post quadruple coronary artery bypass graft.

Adverse Events of Special Interest (AESI)

No AESIs were identified in the protocol for study B3281001. Rather, the applicant identified expected SAEs that would be anticipated in the study population, and they were handled as SAEs in the safety database. Infusions-related reactions (IRRs) and Hy's law were defined by the applicant and described below. Otherwise, for other AESIs, a review of the pertinent SOCs is reviewed below.

- **Infusion-related Reactions, including Anaphylaxis**

Any AEs occurring on the day of infusion were reviewed as potential infusion-related reactions (IRRs) and verified with the reporting investigator. IRRs occurred in all treatment arms at similar numbers, 10 subjects (13.7%) on rituximab-US, 5 subjects (6.8%) on rituximab-EU, and 10 subjects (13.7%) on PF-05280586.

The most common IRR by SOC was Respiratory, thoracic, and mediastinal disorders, occurring in 5 subjects (6.8%) on rituximab-US, 1 subject (1.4%) on rituximab-EU, and 2 subjects (2.7%) on PF-05280586. Ear pruritus (n=2 [2.7%] on PF-05280586), throat irritation (n=2 [2.7%] on rituximab-US, n=1 [1.4%] on rituximab-EU, n=1 [1.4%] on PF-05280586), and pruritus (n=1 [1.4%] on rituximab-US, n=1 [1.4%] on rituximab-EU, n=3 [4.1%] on PF-05280586) were the only AEs that occurred in more than 1 subject in any treatment arm.

- Hy's Law

Potential drug-induced liver injury involved changes in AST, ALT, and alkaline phosphatase, as defined by Hy's law. No cases of Hy's law were reported.

- Malignancies

Subjects who reported AEs that fall under the SOC Neoplasms benign, malignant, and unspecified (incl cysts and polyps) were low and similar across treatment arms (n=0 on rituximab-US, n=2 on rituximab-EU, n=2 on PF-05280586).

- Subjects on rituximab-EU reported a skin papilloma and basal cell carcinoma.
- The subjects on PF-05280586 reported bone neoplasm (described above under Death) and benign neoplasm of thyroid gland.

- HBV Reactivation

No subjects were diagnosed with HBV reactivation in study B3281001.

- Progressive Multifocal Leukoencephalopathy (PML)

No subjects were diagnosed with PML in study B3281001.

- Cardiovascular Events

The number of subjects AEs under the SOC Cardiac disorders is low and similar across treatment arms (n=3 on rituximab-US, n=1 on rituximab-EU, n=1 on PF-05280586).

- Subjects on US-licensed Rituxan reported AEs (by PT) of congestive cardiac failure, paroxysmal tachycardia, and atrial flutter.
- The subject on EU-approved MabThera had atrial fibrillation.
- The subject on PF-05280586 had AEs of extrasystole and cardiac failure.

- Hematologic Disorders

The number of subjects with AEs that fall under the SOC of Blood and lymphatic system disorders is similar across treatment arms (n=1 on rituximab-US, n=2 on rituximab-EU, n=1 on PF-05280586).

- The subject on rituximab-US had iron-deficiency anemia.
- The subjects on rituximab-EU had PTs of thrombocytopenia and thrombocytopenic purpura.
- The subject on PF-05280586 had a reported PT of anemia.

- Renal Disorders

One subject on rituximab-EU and one subject on PF-05280586 had AEs that fell under the SOC Renal and urinary disorders. The subject on rituximab-EU reported renal pain, and the subject on PF-05280586 reported nephrolithiasis and hematuria.

Immunogenicity

Anti-drug antibody (ADA) measurements were available for subjects from study B3281001 and B3281004. However, the incidence of immunogenicity must be interpreted with caution since the measurement of ADA in the clinical study samples from these studies were not performed adequately. The clinical pharmacology review team concluded that the immunogenicity data from studies B3281001 and B3281004 were not helpful for assessment of comparative immunogenicity in this clinical program. Instead, immunogenicity data from study B3281006 have been reviewed to support an assessment of comparative immunogenicity between PF-05280586 and US-licensed Rituxan. See clinical pharmacology review by Dr. Wickramaratne Senarath Yapa and OBP review by Dr. De Silva for details on the immunogenicity data (e.g., incidence of ADA, NAb, and impact on PK, activity and safety). This memo focused on any change in safety assessments, including potentially immune-mediated adverse events, in subjects who underwent a single transition from US-licensed Rituxan or EU-approved MabThera to PF-05280586. Any change in safety, particularly infusion-related reactions, may be helpful in determining whether there was any immunogenicity with clinically relevant consequences after single transition.

Additionally, the risk of worsening clinically relevant immunogenicity after a single transition from US-licensed Rituxan (or EU-approved MabThera) to PF-05280586 would be expected to be low for the following reasons:

- The intravenous route of administration (which provides for the lowest exposure to antigen-presenting cells of all the routes of administration)
- The immunosuppressive nature of US-licensed Rituxan, as a broad-spectrum B-cell depleting mAb, by targeting CD20
- The minor analytical differences between PF-05280586 and US-licensed Rituxan are not differences that are likely to provoke additional anti-product immunogenicity.

To further expand on the last bullet point, the structural differences between PF-05280586 and US-licensed Rituxan or EU-approved MabThera that could contribute to/result in a differential immune response would be related to attributes such as glycosylation, which can affect the conformation of the molecule, and oxidation and deamidation, which can impact stability (leading to fragments and/or aggregates) or could affect the conformation of the molecule. As discussed in the comparative analytical review by the product quality review team, PF-05280586 and US-licensed Rituxan (and EU-approved MabThera) have the same types of glycan species. Although there are small differences in the proportion of the various N-linked glycoforms per lot, a patient's immune system is not being exposed to new or unique antigens; simply different amounts of a given glycoform. Therefore, one would not expect PF-05280586 to be associated with any additional risk of immunogenicity based on this small difference in glycosylation. Additionally, comparative oxidation and deamidation levels, as well as fragments and aggregates, were assessed directly by multiple methods, and no significant differences were observed, again, leading one not to expect any additional risk of immunogenicity associated with PF-05280586.

Manufacturing process/stability/formulation-related differences may also have the potential to impact the immune response to the finished PF-05280586 drug product and US-licensed Rituxan (and EU-approved MabThera) drug product, such as IgG fragments and aggregates, and process-related impurities, such as residual host cell proteins, raw materials, or leachables. However, these were also extensively tested and comparatively assessed using multiple methods, and no significant differences were observed.

Therefore, based on the extensive comparative analytical and product quality data, the baseline concern regarding worsening clinically relevant immunogenicity after transitioning from US-licensed Rituxan to PF-05280586 would be low. This is consistent with the observed safety profile of subjects who transitioned from US-licensed Rituxan or EU-approved MabThera to PF-05280586 in Study B3281004, as discussed below.

Safety after Single Transition (Study B3281004)

Table 17 summarizes the safety after 1 course of study treatment in study B3281004. In general, there did not appear to be more TEAEs in subjects after a single transition. The proportion of subjects who were stayed on EU-approved MabThera in study B3281004 and reported a TEAE was 37.5%, whereas 54.5% of those who transitioned to PF-05280586 reported a TEAE. For subjects who were on US-licensed Rituxan, 53.3% of those who stayed on US-licensed Rituxan reported a TEAE, and 40.0% who transitioned to PF-05280586 reported a TEAE. These proportions were similar to those subjects who received PF-05280586 for both courses and who had a TEAE (55.2%).

Table 17. Summary of TEAEs after Course 1 in Study B3281004 (mITT Population)

B3281001 Treatment	PF-05280586	Rituximab-EU		Rituximab-US	
B3281004 Treatment	P N=58 n (%)	E N=32 n (%)	P N=33 n (%)	U N=30 n (%)	P N=30 n (%)
Subjects with any TEAE	32 (55.2)	12 (37.5)	18 (54.5)	16 (53.3)	12 (40.0)
Subjects with Serious TEAEs	4 (6.9)	2 (6.3)	2 (6.1)	1 (3.3)	2 (6.7)
Subjects with Discontinuations secondary to TEAEs	1 (1.7)	1 (3.1)	0	0	1 (3.3)

E=EU reference product; U=US reference product; P=PF-05280586.

Source: Protocol B3281004 Clinical Study Report. Table 22. Dated June 18, 2018; page 95.

Serious Adverse Events

It is notable that, in the rituximab-US and rituximab-EU arms, the number of subjects with SAEs was similar whether subjects transitioned to PF-05280586 or not.

- PF-05280586 for both studies: The SAEs reported were pneumonia, urinary tract infection, syncope, and chronic obstructive pulmonary disease.
- Rituximab-EU for both studies: The SAEs reported were TIA, hydronephrosis, and ureterolithiasis.
- Rituximab-EU for study B3281001 → PF-05280586 for the first course in study B3281004: The reported SAEs were anemia and pneumonia.
- Rituximab-US for both studies: The reported SAEs were inguinal hernia and umbilical hernia.

- Rituximab-US for study B3281001 → PF-05280586 for the first course in study B3281004: The reported SAEs were pancreatitis and bacterial arthritis.

Discontinuations due to TEAEs

Three subjects experienced AEs leading to discontinuation. These did not occur more frequently in subjects who underwent a single transition. One subject who had received PF-05280586 for both study B3281001 and B3281004 experienced a “rash papular.” One subject who had received rituximab-EU for both studies experienced a transient ischemic attack (TIA). One subject who had received rituximab-US in study B3281001 and transitioned to PF-05280586 in study B3281004 experienced a bacterial arthritis.

Infusion-related Reactions (IRRs)

After a single transition, there did not appear to be more IRRs. Table 18 shows the numbers of subjects with IRRs after a single transition and the types of IRRs by PT. The overall numbers of IRRs after the first course of study treatment in study B3281004 were low, so it is difficult to make conclusions. However, there did not appear to be any difference between those who stayed on US-licensed Rituxan or EU-approved MabThera and those who transitioned to PF-05280586. No subjects who received EU-approved MabThera in study B3281001 experienced an IRR in study B3281004. For subjects who received US-licensed Rituxan in B3281001, 1 subject reported an IRR in each arm. One subject experienced a hot flush amongst those who stayed on treatment, and one subject experienced ear pain and oropharyngeal pain amongst those who transitioned to PF-05280586. Taking into account exposures in this extension study, the incidence of IRRs per 100 patient-years also did not appear to differ amongst those subjects who underwent a single transition.

Table 18. Infusion-related Reactions (TEAEs by PT) after Course 1 in Study B3281004 (mITT Population)

B3281001	PF-05280586	Rituximab-EU		Rituximab-US	
B3281004	P N=58 29.134 PY n (n/PY*100)	E N=32 14.612 PY n (n/PY*100)	P N=33 16.638 PY n (n/PY*100)	U N=30 13.974 PY n (n/PY*100)	P N=30 14.669 PY n (n/PY*100)
Subjects with any IRR TEAE	2 (6.9)	0	0	1 (7.2)	1 (6.8)
IRR by Preferred Term					
Ear pain	0	0	0	0	1 (6.8)
Oropharyngeal pain	0	0	0	0	1 (6.8)
Throat irritation	1 (3.4)	0	0	0	0
Rash papular	1 (3.4)	0	0	0	0
Hot flush	0	0	0	1 (7.2)	0

E=EU reference product; U=US reference product; P=PF-05280586.

Source: Protocol B3281004 Clinical Study Report. Table 34. Dated June 18, 2018; page 121-122.

Of note, after the second course of treatment in study B3281004 when all subjects received PF-05280586, the number of IRRs remained low, but there was no major difference between

subjects who transitioned to and subjects who received another course of PF-05280586. This is shown in Table 19.

Table 19. Infusion-related Reactions after Course 2 in Study B3281004 (mITT Population)

B3281001	PF-05280586	Rituximab-EU		Rituximab-US	
B3281004	PP N=54 53.287 PY n (n/PY*100)	EP N=30 28.003 PY n (n/PY*100)	PP N=31 31.466 PY n (n/PY*100)	UP N=29 27.546 PY n (n/PY*100)	PP N=29 28.512 PY n (n/PY*100)
Subjects with any IRR TEAE	2 (3.8)	0	1 (3.2)	1 (3.6)	1 (3.5)

E=EU reference product; U=US reference product; P=PF-05280586.

Source: Protocol B3281004 Clinical Study Report. Table 35. Dated June 18, 2018; page 123-124.

Overall Summary of Safety and Immunogenicity

The safety data of PF-05280586 in subjects with RA in studies B3281001 and B3281004 are supportive of the conclusions of no clinically meaningful differences in terms of safety between PF-05280586 and US-licensed Rituxan in study B3281006 (subjects with LTB-FL). The safety database for PF-05280586 is adequate to provide a descriptive comparison between products. In general, the numbers of SAEs and AEs leading to discontinuation were similar whether subjects received PF-05280586, EU-approved MabThera, and US-licensed Rituxan.⁶ Additionally, the types of AEs were similar to the known safety profile of US-licensed Rituxan. The safety data support the demonstration that there are no clinically meaningful differences between PF-05280586 and US-licensed Rituxan in the RA population studied. In addition, transitioning of nontreatment naïve patients, i.e., patients previously treated with EU-approved MabThera or US-licensed Rituxan to PF-05280586 does not appear to result in an increase of clinically significant adverse reactions. The FDA safety analyses are generally consistent with the applicant's.

One of the objectives of study B3281004 was evaluation of the immunogenicity and safety after a single transition from EU-approved MabThera or US-licensed Rituxan to PF-05280586. The immunogenicity data (incidence of ADAs) cannot be interpreted from the RA studies because the measurement of ADA in the clinical study samples was not performed adequately. However, as discussed above, the baseline concern for a worsening immunogenic response upon transition from US-licensed Rituxan and EU-approved MabThera to PF-05280586 is low, because the differences between PF-05280586 and Rituxan and MabThera are not of the nature that would be likely to provoke a worsening immunogenic response. When taken together with the comparative immunogenicity data in Study B3281006 (in LTB-FL), and the comparative safety in Study B3281004, including the safety after patients underwent transitioning from US-licensed Rituxan and EU-approved MabThera to PF-05280586, we believe there is sufficient information in this submission to conclude there are no clinically meaningful differences, including with respect to immunogenicity, between PF-05280586 and US-licensed Rituxan.

⁶ FDA-approved Rituxan labeling.

6. Extrapolation of Data to Support Biosimilarity in Non-oncology Conditions of Use

The applicant is seeking licensure of PF-05280586 for the indications of CLL, NHL, GPA, and MPA, which are previously licensed for US-licensed Rituxan. The PF-05280586 clinical program, however, provides clinical efficacy and safety data primarily from clinical studies in patients with RA and LTB-FL with the comparative clinical study B3281006 conducted in subjects with LTB-FL. The Division of Hematology Products (DHP) has determined that the data from this oncology study support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan and will address the considerations that support licensure of PF-05280586 for the oncology indications sought for licensure. The discussion of extrapolation to NHL and CLL is provided in the DHP review by Dr. Yvette Kasamon.

The Agency has determined that it may be appropriate for a biosimilar product to be licensed for one or more conditions of use for which the reference product is licensed or approved, based on the totality of the data, including data from clinical study(ies) performed in another condition of use. This concept of extrapolation is described in the *Guidance for Industry: Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (April 2015)*. The applicant needs to provide sufficient scientific justification for extrapolation, which should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action (MOA) in each condition of use for which licensure is sought
- The pharmacokinetics (PK) and bio-distribution of the product in different patient populations
- The immunogenicity of the product in different patient populations
- Differences in expected toxicities in each condition of use and patient population
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought

As a scientific matter, the FDA has determined that differences between conditions of use with respect to the factors addressed in a scientific justification for extrapolation do not necessarily preclude extrapolation. The applicant provided an extrapolation rationale consistent with the principles outlined in the above Guidance, for the indications for which US-licensed Rituxan is approved and which are not subject to regulatory exclusivity, i.e., NHL, CLL, RA, GPA, and MPA. Of these, DPARP reviewed the scientific justification for the non-oncology indications, i.e., RA, GPA, and MPA. The justification includes the following:

- Mechanism of action: The primary mechanisms of action (MOA) of rituximab include antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), signaling induced cell death (apoptosis), and antibody-dependent cellular phagocytosis (ADCP). The published scientific literature indicates that these Fab- and Fc-mediated interactions are important for the MOA of rituximab in rheumatic disease

indications as well as oncology indications.^{7,8,9} The *in vitro* data provided by Pfizer demonstrated similar activity for these mechanisms, supporting the demonstration that PF-05280586 and US-licensed Rituxan utilize the same MOAs. Therefore, the data and information submitted related to MOA are supportive.

- PK similarity was demonstrated between PF-05280586 and US-licensed Rituxan using a repeat intermittent dosing in patients with RA (Study B3281001). Further, the product quality review team concluded that PF-05280586 is highly similar to US-licensed Rituxan based on comparative analytical data and that there are no product-related attributes that would increase the uncertainty that the PK may differ between PF-05280586 and US-licensed Rituxan in the indications sought for licensure. Thus, a similar PK profile would be expected between PF-05280586 and US-licensed Rituxan in patients with indications being sought for licensure but not directly studied, i.e., GPA and MPA.
- Immunogenicity: Immunogenicity (ADA) of US-licensed Rituxan has been characterized. Similar immunogenicity was demonstrated between PF-05280586 and US-licensed Rituxan in LTB-FL, a reasonably sensitive patient population, as discussed in the section on Immunogenicity Assessment above. Importantly, across all US-licensed Rituxan-approved indications, the incidence of ADA (referred to as HACA in the FDA-approved-Rituxan labeling) formation was relatively low (1.1% in NHL, 11% in RA, and 23% in GPA/MPA) and was not associated with clinically relevant sequelae¹⁰. Further, no analytical differences were seen in attributes that could potentially impact immunogenicity. Thus, as the analytical data support the demonstration that PF-05280586 is highly similar to US-licensed Rituxan and as PK similarity was also demonstrated between these products, a similar immunogenicity profile would be expected between PF-05280586 and US-licensed Rituxan in the non-oncology indications DPARP reviewed in this BLA.
- Expected toxicities: The safety profile of US-licensed Rituxan is well characterized across its approved indications. No nonclinical biologically or toxicologically relevant differences in incidence or severity of microscopic findings were observed between PF-05280586 and EU-approved MabThera in a repeat-dose toxicity study in animals. The clinical safety profiles of PF-05280586 and EU-approved MabThera or US-licensed Rituxan showed no clinically meaningful differences and were consistent with the established safety profile of US-licensed Rituxan. As analytical similarity and PK similarity were demonstrated between PF-05280586 and US-licensed Rituxan, a similar safety profile would be expected between PF-05280586 and US-licensed Rituxan in indications being sought for licensure but not directly studied, i.e., GPA and MPA.

⁷ Taylor RP, Lindorfer MA, Drug insight: the mechanism of action of rituximab in autoimmune disease-the immune complex decoy hypothesis, *Nat Clin Pract Rheumatol*. 2007 Feb;3(2):86-95

⁸ Seyfizadeh N et al, A molecular perspective on rituximab: A monoclonal antibody for B cell non Hodgkin lymphoma and other affections, *Crit Rev Oncol Hematol*. 2016 Jan;97:275-90

⁹ Jaglowski SM1, Byrd JC, Rituximab in chronic lymphocytic leukemia, *Semin Hematol*. 2010 Apr;47(2):156-69.

¹⁰ FDA-approved Rituxan labeling

Based on the above considerations, the available data and information in Pfizer's BLA, and the FDA's previous finding of safety and efficacy for the approved indications for US-licensed Rituxan, DPARP concludes that the applicant provided sufficient scientific justification for extrapolation of the data and information submitted in the application to support licensure of PF-05280586 as a biosimilar for the non-oncology indications being sought for licensure, and for which US-licensed Rituxan has been previously licensed.

7. Advisory Committee Meeting

This application is the second 351(k) BLA filed for a proposed biosimilar to rituximab. Therefore, an Advisory Committee (AC) meeting was not deemed necessary.

8. Other Relevant Regulatory Issues

Financial Disclosures

The applicant has adequately disclosed financial interests/arrangements with clinical investigators in accordance with 21 CFR Part 54 and *Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosures by Clinical Investigators*. The applicant has submitted Form FDA 3454 and 3455 for all covered studies, including studies B3281001, B3281004, and B3281006. No clinical investigators were full-time or part-time employees of Pfizer. None of the 1,335 clinical investigators required Due Diligence activities. Twenty-nine of the 1,335 investigators had financial information to disclose. Pfizer provided details regarding procedures designed to minimize the potential of bias in the data during the conduct of the studies, including processing, analyzing, and reporting the data.

Other GCP issues in RA clinical program

The applicant noted that the studies were 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 (ICH) Good Clinical Practice (GCP) guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

In study B3281001, the applicant acknowledged that there were 10 protocol deviations impacting subject eligibility, but GCP compliance was maintained. Although these patients entered the study without meeting inclusion/exclusion criteria (e.g., RF seronegative, no previous TNF inhibitor treatment, positive hepatitis B/C, history of recurrent inflammatory joint disease other than RA), they were included in the PP population. Study B3281004 also had protocol deviations, the most frequent regarding laboratory samples (e.g., unstable or missing samples), but the applicant again noted that GCP compliance was maintained.

OSI audits

The Office of Scientific Investigations (OSI) inspected 2 clinical sites where studies B3281001 and B3281004 were performed. These 2 sites (Dr. Maria Greenwald in Palm Desert, CA, and Dr. Robert Shurmer in Battle Creek, MI) were selected based on enrolling the highest number of subjects (n=23 and 15, respectively). At Dr. Greenwald's site, there were findings of under-reporting of non-serious adverse events, PK sampling outside of the specified window, and correction to some source documents initialed but not dated. OSI concluded that these findings appeared to be clinically insignificant and unlikely to impact data reliability nor compromise the rights, safety, and welfare of subjects in the study. No significant observations were identified at Dr. Shurmer's site. The final classification for the inspection was No Action Indicated (NAI).

The OSI investigators concluded, and we agree, that the data submitted from these clinical sites were reliable in support of the requested indication under this BLA.

See OSI review by Dr. Min Lu for a detailed summary of the inspections.

9. Labeling

- Proprietary name

The proprietary name for PF-05280586 will be RUXIENCE. This name was reviewed by the Division Medication Error Prevention and Analysis (DMEPA) who did not have any concerns and concluded that it is acceptable.

- Non-proprietary name

Per the FDA's *Guidance for Industry: Nonproprietary Naming of Biological Products: Update* (March 2019), the non-proprietary name for PF-05280586 needs a distinguishing suffix. The proposed non-proprietary name with suffix is "rituximab-pvvr" and is conditionally acceptable. This will be updated throughout the label.

- The labeling negotiations are ongoing at the time of this review.

10. DPARP Summary of Findings from PF-05280586 Clinical Program in RA

The product quality review team has determined, and we agree, that, the comparative analytical assessment presented in the BLA is acceptable to support the following conclusions:

- PF-05280586 is highly similar to US-licensed Rituxan.
- The analytical component of the scientific bridge has been established to scientifically justify the relevance of data generated using the EU-approved MabThera to support the demonstration of biosimilarity of PF-05280586 to US-licensed Rituxan.

The clinical pharmacology review team has concluded, and we agree, that

- PK similarity has been demonstrated between PF-05280586 and US-licensed Rituxan.
- The PK component of the scientific bridge has been established to scientifically justify the relevance of data generated using the EU-approved MabThera to support the demonstration of biosimilarity of PF-05280586 to US-licensed Rituxan.
- PK results support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan.

The DHP clinical review team has concluded, and we agree, that this application provides sufficient evidence of no clinically meaningful differences in safety and efficacy between PF-05280586 and US-licensed Rituxan in patients with follicular lymphoma. The determination of no clinically meaningful differences with respect to clinical efficacy, safety, and immunogenicity is established, in part, based on overall response rate (ORR) in the dedicated comparative clinical Study B3281006, a randomized, double-blind, study evaluating 4 weekly doses of PF-05280586 vs. EU-approved MabThera in patients with previously untreated, low tumor burden follicular lymphoma (LTB-FL).

The clinical program in RA supporting this application consisted of two studies, Study B3281001 and Study B3281004, a continuation of Study B3281001. Study B3281001 was a randomized, double-blind, active-controlled study comparing the PK, PD, and safety of PF-05280586, US-licensed Rituxan, and EU-approved MabThera in subjects with active rheumatoid arthritis who had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Study B3281001 was designed and powered to assess PK similarity, and efficacy was assessed as a secondary objective. While the study met its primary objectives of demonstrating PK similarity between the three products, some differences were observed in clinical outcomes. The differences in clinical efficacy observed in Study B3281001 in RA (detailed in Section 5 above) do not preclude a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan when taken together with the following: (1) the considerations about the study enumerated in the summary and conclusions sub-section of Section 5 above, (2) the demonstration that PF-05280586 is highly similar to US-licensed Rituxan, (3) PK similarity between PF-05280586, US-licensed Rituxan, and EU-approved MabThera, and (4) no clinically meaningful differences observed regarding safety, efficacy and immunogenicity in the dedicated comparative clinical Study B3281006 in LTB-FL..

The analysis of the data in RA indicates a safety profile of PF-05280586 similar to that of US-licensed Rituxan. There were no notable differences between PF-05280586, EU-approved MabThera, or US-licensed Rituxan in treatment-emergent adverse events, serious adverse events, adverse events leading to discontinuations, or deaths between the treatment groups. The safety risks identified are consistent with the known adverse event profile of US-licensed Rituxan. The safety data support the demonstration that there are no clinically meaningful differences between PF-05280586 and US-licensed Rituxan in the RA population studied. In addition, a single transition of nontreatment naïve patients, i.e., patients previously treated with EU-approved MabThera or US-licensed Rituxan, to PF-05280586 did not result in an increase of clinically significant adverse reactions.

The applicant has provided a data package sufficient to address the scientific considerations for extrapolation of data and information submitted in the application to support licensure of PF-05280586 as a biosimilar for the indications for which US-licensed Rituxan is currently licensed and for which the applicant is seeking licensure.

11. Appendix

Efficacy Endpoints utilized in Studies B3281001 and B3281004

DAS28-CRP

The Disease Activity Score (DAS) assessment is a continuous composite measured derived using differential weighting given to each component. The 4 components assessed as part of DAS28-CRP include in the following:

- Tender/painful joint count (28 joints assessed)
- Swollen joint count (28 joints assessed)
- hsCRP (high-sensitivity C-Reactive Protein, measured from a central laboratory)
- Patient's Global Assessment of Arthritis VAS (Visual Analog Scale from 0-100 mm)

The formula for calculation of DAS28-CRP is the following:

$$\text{DAS28-CRP} = 0.56 \sqrt{\text{DAS28 tender joint count}} + 0.28 \sqrt{\text{DAS28 swollen joint count}} + 0.36 (\ln \text{CRP [mg/L]} + 1) + 0.014 (\text{GH}) + 0.96$$

Several of the secondary endpoints utilized specific DAS28-CRP scores to define a meaningful measurement.

- **EULAR** (European League Against Rheumatism) **response** is a reduction in DAS28-CRP ≥ 1.2 .
- **LDAS** (low disease activity) is a DAS28-CRP ≤ 3.2 .
- **DAS remission** is defined as a DAS28-CRP < 2.6 .

ACR Assessments

The American College of Rheumatology (ACR) definition for improvement in RA is calculated as a percent improvement in number of tender and swollen joint counts and percent improvement in 3 of the 5 other ACR core measures.

All the components that contribute to the ACR assessment include the following:

- Tender/painful joint count (68 joints assessed)
- Swollen joint count (66 joints assessed)
- Patient's assessment of arthritis pain
- PGA (Patient's Global Assessment) of arthritis
- PhGA (Physician's Global Assessment) of arthritis
- CRP
- HAQ-DI (Health Assessment Questionnaire-Disability Index, described below)

ACR20 is a categorical variable indicating a 20% improvement in number of affected joints and 20% improvement in 3 of the 5 other ACR core measures. ACR50 and ACR70 are, thus, 50% and 70% improvement in the same parameters, respectively.

Health Assessment Questionnaire-Disability Index (HAQ-DI)

The HAQ-DI assesses the degree of difficulty a subject has experienced during the past week in 8 domains of daily living activities: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and other activities. Each activity category consists of 2-3 items. For each question in the questionnaire, the level of difficulty is scored from 0 (“no difficulty”) to 3 (“unable to do”). Any activity that requires assistance from another individual or requires the use of an assistive device adjusts to a minimum score of 2 to represent a more limited functional status.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SUZETTE W PENG
07/22/2019 12:47:19 PM

GINTO J POTTACKAL
07/23/2019 08:00:13 AM

PEILING YANG
07/23/2019 08:21:52 AM

NIKOLAY P NIKOLOV
07/23/2019 08:51:29 AM
Signed under the authority, delegated by Dr. Sally Seymour, Division Director, DPARP.

Clinical and Statistical Review
 Yvette Kasamon, MD (clinical)
 Kate Li Dwyer, PhD (statistics)
 BLA 761103
 Ruxience (PF-05280586)

CLINICAL and STATISTICAL REVIEW

Application Type	Original BLA
Application Number	761103
Priority or Standard	Standard
Submit Date	7/25/2018
Received Date	7/25/2018
BsUFA Goal Date	7/25/2019
Division/Office	DHP / OHOP
Reviewer Names	Clinical: Yvette Kasamon, MD R. Angelo de Claro, MD (Team Leader) Statistics: Kate Li Dwyer, PhD Yeh-Fong Chen, PhD (Team Leader) Thomas E. Gwise, PhD (Deputy Division Director)
Review Completion Date	March 27, 2019
Established/Proper Name	PF-05280586 (rituximab-xxxx)*
(Proposed) Trade Name	Ruxience
Applicant	Pfizer, Inc.
Dosage Form	Intravenous infusion
Applicant Proposed Dosing Regimen(s)	<ul style="list-style-type: none"> NHL: 375 mg/m² once weekly for 4 or 8 doses (monotherapy), or on Day 1 of each chemotherapy cycle for up to 8 doses; maintenance 375 mg/m² every 8 weeks for 12 doses CLL: 375 mg/m² the day prior to initiating FC, then 500 mg/m² on Day 1 of Cycles 2-6
Applicant Proposed Indications/Populations	<ul style="list-style-type: none"> Non-Hodgkin's Lymphoma (NHL) <ul style="list-style-type: none"> Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent. Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab products in combination with chemotherapy, as single-agent maintenance therapy. Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy. Previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens. Chronic Lymphocytic Leukemia (CLL)

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

	- Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).
Recommendation on Regulatory Action	The data indicate no clinically meaningful differences between PF-05280586 and Rituxan. Refer to CMC and CDTL reviews as to whether PF-05280586 is highly similar to Rituxan.
Recommended Indications/Populations	As proposed by Applicant

*The review was completed prior to designation of the suffix.

Table of Contents

Glossary.....	7
1. Executive Summary	8
1.1. Product Introduction.....	8
1.2. Conclusions on the Substantial Evidence of Effectiveness	8
1.3. Benefit-Risk Assessment	8
1.4. Patient Experience Data.....	8
2. Therapeutic Context	9
2.1. Analysis of Condition.....	9
2.2. Analysis of Current Treatment Options	9
3. Regulatory Background	9
3.1. U.S. Regulatory Actions and Marketing History.....	9
3.2. Summary of Presubmission/Submission Regulatory Activity	9
3.3. Foreign Regulatory Actions and Marketing History.....	10
4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	10
4.1. Office of Scientific Investigations (OSI)	10
4.2. Product Quality	10
4.3. Clinical Microbiology	10
4.4. Nonclinical Pharmacology/Toxicology	10
4.5. Clinical Pharmacology	10
4.6. Devices and Companion Diagnostic Issues	10
5. Sources of Clinical Data and Review Strategy	11
5.1. Table of Clinical Studies.....	11
5.2. Review Strategy.....	11
6. Review of Relevant Individual Trials Used to Support Efficacy	12
6.1. Study B3281006	12
6.1.1. Study Design	12

6.1.2. Study Results	19
7. Integrated Review of Effectiveness	35
7.1. Assessment of Efficacy Across Trials	35
7.2. Integrated Assessment of Effectiveness	35
8. Review of Safety	35
8.1. Safety Review Approach	35
8.2. Review of the Safety Database	36
8.2.1. Overall Exposure	36
8.2.2. Relevant Characteristics of the Safety Population	36
8.2.3. Adequacy of the Safety Database	37
8.2.4. Issues Regarding Data Integrity and Submission Quality	37
8.2.5. Categorization of Adverse Events	37
8.2.6. Routine Clinical Tests	37
8.3. Safety Results	37
8.3.1. Deaths	37
8.3.2. Serious Adverse Events	37
8.3.3. Dropouts and/or Discontinuations Due to Adverse Effects	37
8.3.4. Significant Adverse Events	37
8.3.5. Treatment-Emergent Adverse Events and Adverse Reactions	37
8.3.6. Laboratory Findings	38
8.3.7. Vital Signs	39
8.3.8. Electrocardiograms / QT	39
8.3.9. Immunogenicity	40
8.3.10. Safety Analyses by Demographic Subgroups	40
8.4. Additional Safety Explorations	40
8.4.1. Human Carcinogenicity or Tumor Development	40
8.4.2. Human Reproduction and Pregnancy	40
8.4.3. Pediatrics	40
8.5. Safety in the Postmarket Setting	41
8.5.1. Safety Concerns Identified Through Postmarket Experience	41

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

8.5.2. Expectations on Safety in the Postmarket Setting	41
8.6. Integrated Assessment of Safety	41
9. Advisory Committee Meeting and Other External Consultations.....	41
10. Labeling Recommendations	41
10.1. Prescription Drug Labeling	41
11. Risk Evaluation and Mitigation Strategies (REMS)	41
12. Postmarketing Requirements and Commitments.....	41
Appendices.....	42
12.1. References	42
12.2. Financial Disclosure	42
12.3. Grouping of Preferred Terms for Safety Analysis.....	43

Table of Tables

Table 1: Handling of Missing Assessments and Censoring Rules for PFS	17
Table 2: Selected Potentially Important Protocol Deviations (Study B3281006).....	20
Table 3: Patient Disposition (Study B3281006)	21
Table 4: Reasons for Exclusion from PP Population (Study B3281006)	22
Table 5: Demographics of ITT Population (N = 394)	22
Table 6: Disease Characteristics of ITT Population	23
Table 7: Summary Statistics of Response by Treatment at Week 26 – Central Review (ITT)	24
Table 8: Summary Statistics of Response by Treatment at Week 26 – Central Review (PP)	25
Table 9: Summary Analysis of PFS Results – Central Review (ITT)	26
Table 10: Summary of Censoring Reasons for PFS – Central Review (ITT)	28
Table 11: Summary of Censoring Distribution for PFS – Central Review (ITT)	28
Table 12: Summary Analysis of DOR – Central Review (Response Evaluable Population).....	29
Table 13: Time Point Estimates for DOR – Central Review (Response Evaluable Population)	30
Table 14: Summary of Censoring Distribution for DOR (Response Evaluable Population)	31
Table 15: ORR at Week 26 by Demographic Subgroups – Central Review (ITT)	34
Table 16: ORR at Week 26 by Baseline Assessments – Central Review (ITT)	34
Table 17: Exposure in Safety Population (N = 393)	36
Table 18: All-Cause AEs Reported in > 5% of Patients (Study B3281006)	38
Table 19: Laboratory Abnormalities in > 5% of Patients by Maximum Postbaseline Grade.....	39
Table 20: Safety According to Demographic Subgroups	40

Table of Figures

Figure 1. Study B3281006 Schema	12
Figure 2. Modified KM Plot of PFS – Central Review (ITT).....	27
Figure 3. Modified KM Plot of DOR – Central Review (Response Evaluable Population)	30
Figure 4. Modified KM Plot for TTF – Central Review (ITT)	33

Glossary

ADA	anti-drug antibody
ANC	absolute neutrophil count
AR	adverse reaction
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
DOR	duration of response
FL	follicular lymphoma
FLIPI2	Follicular Lymphoma International Prognostic Index 2
HR	hazard ratio
IR	information request
IRC	independent review committee
IRR	infusion-related reaction
ITT	intention-to-treat
IWG	international working group
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NHL	non-Hodgkin lymphoma
LTB	low tumor burden
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PP	per protocol
PR	partial response
PT	preferred term
SAE	serious adverse event
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	stable disease
SOC	system organ class
TE	treatment-emergent
TEAE	treatment-emergent adverse event
ULN	upper limit of normal

1. Executive Summary

1.1. Product Introduction

PF-05280586 (rituximab-xxxx; Ruxience) is a chimeric immunoglobulin G1 kappa (IgG1 κ), CD20-directed monoclonal antibody (mAb) that has been developed as a proposed biosimilar to US-licensed Rituxan (reference product), with the same proposed hematologic malignancies indications and dosing as the reference product.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This application provides sufficient evidence of no clinically meaningful differences in efficacy between PF-05280586 and Rituxan in patients with follicular lymphoma. Efficacy is based on overall response rate (ORR) in Study B3281006, a randomized, double-blind, phase 3 trial evaluating 4 weekly doses of PF-05280586 vs. Rituximab-EU (MabThera) in patients with previously untreated, low tumor burden follicular lymphoma (FL). The primary endpoint was ORR per central review at week 26, with a prespecified equivalence margin of (-16%, 16%).

In the PF-05280586 arm (N = 196), ORR was 76% (90% CI: 70, 81) with a CR rate of 26%; in the Rituximab-EU arm (N = 198), ORR was 71% (90% CI: 65, 76) with a CR rate of 29%. The difference in ORR (PF-05280586 minus Rituximab-EU) was 4.66% (90% CI: -2.73%, 12.07%) and thus was within the prespecified equivalence margin. The hazard ratios (HRs) for progression-free survival (PFS) and duration of response (DOR) favored the Rituximab-EU arm at 1.39 and 1.49, respectively. However, the confidence intervals are broad, and the study was not designed to demonstrate equivalence in secondary efficacy endpoints.

Provided that PF-05280586 is highly similar to Rituxan, the data would support approval of PF-05280586 as a biosimilar for the same hematologic malignancies indications as Rituxan, which include B-cell non-Hodgkin lymphomas (NHLs) and chronic lymphocytic leukemia (CLL).

1.3. Benefit-Risk Assessment

In Study B3281006, the safety profile of PF-05280586 was similar to that of Rituximab-EU, with no clinically meaningful differences. Provided that PF-05280586 is highly similar to Rituxan, the benefit-risk of PF-05280586 is favorable in its intended populations and comparable to the benefit-risk of Rituxan.

1.4. Patient Experience Data

Patient experience data was not submitted as part of this application.

2. Therapeutic Context

2.1. Analysis of Condition

Rituximab has a central role in the treatment of nearly all B-cell NHLs and CLL. Addition of rituximab to cytotoxic chemotherapy, both in the front-line and later-line settings, has improved ORR, PFS, and overall survival (OS) in various contexts, including in patients with FL, diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma, and CLL.

2.2. Analysis of Current Treatment Options

Six CD20-directed monoclonal antibodies are available for the treatment of B-cell malignancies: rituximab, rituximab and hyaluronidase, ofatumumab, obinutuzumab, ibritumomab tiuxetan (a radioimmunoconjugate), and the Rituxan biosimilar, rituximab-abbs (Truxima). Rituximab-abbs received FDA approval in 11/2018 for the 3 Rituxan indications involving low-grade or follicular NHL.

In addition to non-malignant indications (rheumatoid arthritis, granulomatosis with polyangiitis or microscopic polyangiitis, and pemphigus vulgaris), Rituxan is approved for:

- NHL:
 - Relapsed or refractory, low grade or follicular, CD20-positive B-cell NHL as a single agent.
 - Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to rituximab products in combination with chemotherapy, as single-agent maintenance therapy.
 - Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line cyclophosphamide, vincristine, and prednisone (CVP) chemotherapy.
 - Previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin, vincristine, and prednisone) (CHOP) or other anthracycline-based chemotherapy regimens.
- CLL: Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC).

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

None

3.2. Summary of Presubmission/Submission Regulatory Activity

A scientific bridge was established between US-licensed Rituxan and EU-licensed MabThera (also referred to as Rituximab-EU) in that the two products were, per the Applicant, demonstrated to be indistinguishable at the analytical and clinical PK data levels. This scientific

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

bridge provided justification for use of either US-licensed Rituxan or EU-licensed MabThera as a comparator in the PF-05280586 development program. FDA agreed that EU-licensed MabThera could be used as the comparator in the non-clinical study and the comparative clinical study to demonstrate the relative efficacy and safety of PF-05280586 and EU-licensed MabThera.

3.3. **Foreign Regulatory Actions and Marketing History**

None

4. **Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety**

4.1. **Office of Scientific Investigations (OSI)**

Inspection of individual clinical sites for Study B3281006 was not requested, as no one particular site contributed more than 3.6% of the patients randomized. Bias was reduced by the study being double-blind and by the primary efficacy endpoint being based on IRC assessment. For this study, OSI investigated the Applicant and determined that no action was indicated.

4.2. **Product Quality**

No major issues. The neutralizing antibody assay was not informative. However, this is not expected to impact the determination of whether the study drug shows clinically meaningful differences with Rituxan in patients with B-cell malignancies.

4.3. **Clinical Microbiology**

No major issues

4.4. **Nonclinical Pharmacology/Toxicology**

No issues

4.5. **Clinical Pharmacology**

No major issues were identified with the PK data. FDA requested an expanded evaluation of anti-drug antibody (ADA) samples, the results of which are pending.

4.6. **Devices and Companion Diagnostic Issues**

Not applicable

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Study B3281006 is the basis of the BLA for the hematologic malignancies indications:

Trial	Population	Design	Regimen	1 ^o Endpoint	# of Patients
B3281006 (NCT02213263)	Previously untreated, low-tumor burden FL	Multicenter randomized (1:1), double-blind, phase 3 study	375 mg/m ² IV of PF-05280586 or Rituximab-EU on days 1, 8, 15, 22	ORR per IRC at week 26 ^a	ITT: 394 (PF-05280586: 196, Rituximab-EU: 198) Safety: 393 (196, 197)

^a Cut-off dates:

26-week CSR (primary efficacy and safety): 23 Oct 2017

52-week CSR (secondary efficacy endpoints, safety update): 19 Apr 2018

5.2. Review Strategy

Study B3281006 is the basis for all efficacy and safety assessments for the hematologic malignancies indications. The clinical reviewer evaluated data analysis datasets (Legacy format), clinical study reports (CSRs), the summary of clinical efficacy (SCE), summary of clinical safety (SCS), integrated summary of safety (ISS), individual patient narratives, and the 120-day safety and efficacy update. The Statistical reviewer focused on efficacy assessment, through assessing data quality, verifying the Applicant's results, and conducting additional sensitivity analyses to assess the robustness of the efficacy results.

Week 26 CSR and related datasets with the data cutoff date of 23 Oct 2017, protocol and amendments, SAP and amendments under original submission date 25 Jul 2018 are located at:

<\\CDSESUB1\evsprod\BLA761103\0001>

4-Month Safety Update, Final (Week 52) CSR and related datasets with the data cutoff date of 19 Apr 2018 under submission date 16 Nov 2018 are located at:

<\\CDSESUB1\evsprod\BLA761103\0009>

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study B3281006

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 initiation: 30 Sept 2014

Last patient's last visit: 19 Apr 2018

Study status: ended (database lock, 18 May 2018)

Data cutoff dates:

23 Oct 2017: primary efficacy (week 26) and safety

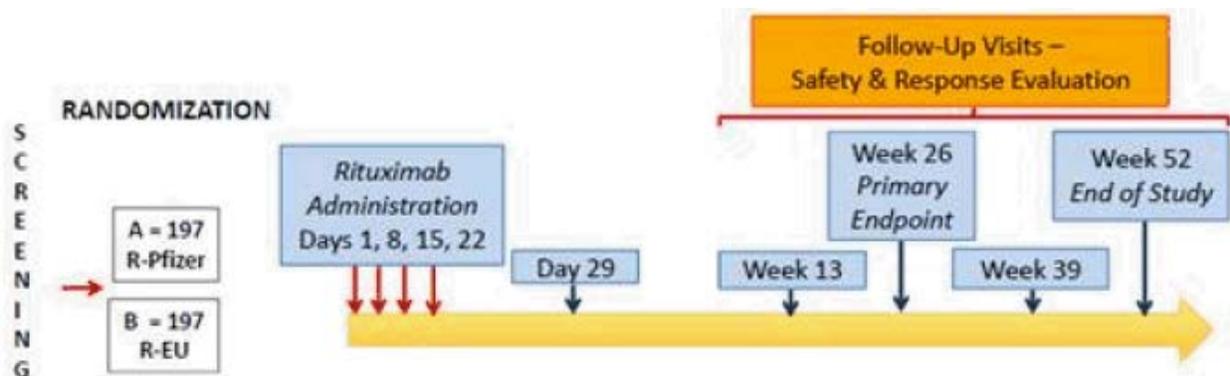
19 Apr 2018: longer-term efficacy (week 52) and safety

6.1.1. Study Design

This is a randomized, double-blind, phase 3 trial evaluating the efficacy, safety, PK and immunogenicity of PF-05280586 (Ruxience) vs. Rituximab-EU (MabThera) in patients with CD20-positive, low tumor burden FL in the first-line treatment setting.

The study design is depicted in Figure 1 below. Week 1–4 was designated as the Study Period, and Week 5-52 as the Follow-up Period.

Figure 1. Study B3281006 Schema



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

Source: Week 26 CSR, Section 9.1

Randomization and Stratification

Patients were randomized in a 1:1 ratio to receive either PF-05280586 or Rituximab-EU.

Randomization was stratified by Follicular Lymphoma International Prognostic Index 2 (FLIPI2)

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

(low, intermediate, and high risk). Overall 394 patients were enrolled globally (196 patients in the PF-05280586 group and 198 patients in the Rituximab-EU group).

Key Eligibility Criteria

- Age \geq 18 with stage II, III, or IV, CD20+ follicular lymphoma Grade 1-3a, with no previous systemic treatment (localized radiotherapy permitted)
- Low tumor burden defined as:
 - LDH and β 2-microglobulin \leq 1.5 x ULN
 - Largest mass $<$ 7 cm; \leq 3 nodal sites with diameter $>$ 3 cm; spleen \leq 16 cm by CT
 - No clinically significant serous effusions on chest radiography
 - No complications such as organ compression or impairment
 - No B symptoms
- Candidate for rituximab monotherapy
- ECOG PS $<$ 2
- Labs:
 - $<$ 5000/ μ L circulating lymphoma cells
 - Hemoglobin \geq 9.0 g/dL, ANC \geq 1500/ μ L, platelets \geq 75,000/ μ L
- No hep B, hep C, HIV, or active uncontrolled infection

Study Treatment

Dose-schedule: PF-05280586 or MabThera 375 mg/m² IV on Days 1, 8, 15 and 22 (one cycle)

Infusion rates:

- Dose 1: start 50 mg/hr, after 30 min increase rate by 50 mg/hr increments every 30 min to maximum of 400 mg/hr.
- Subsequent doses: start 100 mg/hr, after 30 min increase rate by 100 mg/hr increments every 30 min to max of 400 mg/hr.

Premedications:

- All patients should receive 100 mg IV methylprednisolone or equivalent, to be completed at least 30 min prior to start of infusion. An antipyretic and antihistamine should be administered before each infusion. Any reduction in premedications after the first infusion must follow local labeling and regulations.

Evaluations

Following baseline PET and CT, imaging (PET/CT or CT) was required every \sim 3 months starting with week 13 (week 13, 26, 39, and 52), with week 52 being end of study. PET was required for confirmation of CR per investigator. The study is considered complete when the last randomized patient completes the Week 52 visit.

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

Objectives

Primary Objective:

- To compare the efficacy of PF-05280586 to Rituximab-EU when administered as a first-line treatment to patients with CD20-positive, LTB FL.

Secondary Objectives:

- To evaluate the safety of PF-05280586 and Rituximab-EU.
- To evaluate the population 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 patients receiving PF-05280586 and Rituximab-EU.

Study Endpoints

Primary Endpoint

- Overall Response Rate (ORR), defined as the proportion of patients achieving either complete response (CR) or partial response (PR) at Week 26 based on central review, in accordance with 2007 International Working Group criteria.

Secondary Endpoints

- Safety
- Progression-Free Survival (PFS)
- Complete or Partial Response (CR/PR) rate at Week 26;
- Duration of response (DOR)
- Time to Treatment Failure (TTF)
- Overall survival (OS)
- Peak and trough PF-05280586 and Rituximab-EU concentrations
- CD19-positive B-cell counts
- Incidence of anti-drug antibodies (ADA), including neutralizing antibodies (NAb), and safety associated with immune response

Statistical Analysis Plan

Statistical Hypothesis

The primary endpoint is ORR at Week 26. The primary hypothesis for this endpoint is:

$$TEST\ 1: H_{0c}: \theta_1 - \theta_2 \geq D_{ub} \text{ vs. } H_{1c}: \theta_1 - \theta_2 < D_{ub}$$

$$TEST\ 2: H_{0d}: \theta_1 - \theta_2 \leq D_{lb} \text{ vs. } H_{1d}: \theta_1 - \theta_2 > D_{lb}$$

Where θ_1 is the ORR at Week 26 for patients randomized to PF-05280586, θ_2 is the ORR at

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

Week 26 for patients randomized to Rituximab-EU, D_{ub} is the largest acceptable difference for equivalence, and D_{lb} is the smallest acceptable difference for equivalence. In this study, $D_{ub} = 16\%$ and $D_{lb} = -16\%$.

Determination of Sample Size

Sample size was calculated based on the primary endpoint of ORR at Week 26. The hypothesis to be tested is that the difference between the ORR of PF-05280586 versus that of Rituximab-EU is within a prespecified margin of (-16%, 16%). A sample size of 394 patients (197 patients per treatment arm) was planned in order to provide approximately 93% power for achieving equivalence (with 2.5% type I error rate) under the specified margin between the ORR of PF-05280586 and that of Rituximab-EU, assuming an ORR of 77% in both treatment arms.

Equivalence Margin

The Applicant conducted an extensive, systematic literature search for rituximab in FL. The Ardeshta et al (2014) study was the only randomized trial which compared rituximab alone with watchful waiting (WW) in the first-line setting. In this study, at Month 7 the response rate to rituximab therapy (weekly for 4 weeks) was estimated to be 77% and the response rate in the WW arm was estimated to be 6%. The difference (rituximab - WW) was estimated to be 71% with a 95% CI of (60%, 79%). Based on these results, the equivalence margin of (-16%, 16%) preserved at least 73% efficacy.

Statistical Reviewer Comment:

- **The Agency agreed with the Applicant's prespecified analysis plan and the equivalence margin. In addition to the 95% CIs, the statistical reviewer conducted analyses to provide the 90% CIs.**

Analysis Populations

The Intent-to-Treat (ITT) Population was defined as all patients who were randomized. Patients were analyzed according to the treatment they were randomized to receive, regardless of any dosing errors. The ITT Population was primary for the efficacy analyses.

The modified ITT (mITT) Population was defined as all patients who were randomized and received at least 1 dose of study treatment (PF-05280586 or Rituximab-EU). The mITT Population was primary for the biomarker data analyses.

The Response Evaluable Population was defined as all patients in the ITT Population who received at least 1 dose of study treatment (PF-05280586 or Rituximab-EU), had adequate disease assessment at baseline, and at least 1 post-baseline response assessment. The Response Evaluable Population was used for the analysis of DOR.

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

The Per Protocol (PP) Population was defined as all randomized patients who receive 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. The PP Population was used for sensitivity analyses of the efficacy endpoints.

Analyses of the Primary Efficacy Endpoint

The primary efficacy analysis for equivalence was performed after all randomized patients had the opportunity to complete their Week 26 visit and the assessment of overall response in the ITT population. The FLIPI2 categorization (low, intermedia, and high) was considered as the stratification factor. The point estimate for the difference in ORR between PF-05280586 and rituximab EU was computed using the stratified Mantel-Haenszel method. The 95% confidence interval for the difference was calculated using the asymptotic stratified method proposed by Miettinen and Nurminen (1985).

Equivalence is considered established if the 95% confidence interval of the difference (PF-05280586 minus Rituximab-EU) in ORR at Week 26 was within the prespecified margin of (-16%, 16%) in the ITT population. These analyses were also conducted in the per-protocol population as sensitivity analyses.

The endpoints of CR and PR at Week 26 were analyzed in a similar fashion as ORR.

For ORR, CR or PR, a missing value was defined as no post-baseline response assessment either due to lost to follow-up or withdrawal by patient or other reasons. In the primary analysis, if a post-dose response assessment was missing, the overall response was imputed as a non-responder instead of a missing value.

Subgroup analysis by age, gender, race and region, Ann Arbor Staging classification, bone marrow involvement, as well as by baseline FLIPI2 categorization was performed on the primary endpoint, the ORR at Week 26 (ITT).

Analyses of the Secondary Efficacy Endpoints

PFS was defined as the time from the date of randomization to first progressive disease (PD) or death due to any cause in the absence of documented PD. Progression was based on the central review assessments. A log-rank test stratified by FLIPI2 risk was used to compare the treatment groups with respect to PFS at a 2-sided alpha level of 0.05. Progression-free survival was also summarized using the Kaplan-Meier method. The Kaplan-Meier estimates for the 1-year PFS rates, 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. Censoring for the PFS endpoint is summarized in Table 1.

Table 1: Handling of Missing Assessments and Censoring Rules for PFS

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 is earlier	Progressed (event)

Source: SAP

Duration of Response (DOR) was defined as the time from date of the first documentation of overall response (CR or PR) to the first documentation of progressive disease (PD) or to death due to any cause in the absence of documented PD. The analysis for DOR was based on central review assessment and the response-evaluable population. DOR was analyzed in a similar fashion as for PFS.

The CR/PR rate at Week 26 were analyzed in a similar fashion as for ORR.

Time to Treatment Failure (TTF) was defined as the time from date of randomization to first progression of disease based on central review, death due to any cause, or permanent discontinuation from treatment, or discontinuation from study for any reason, whichever comes first. The censoring mechanisms for TTF are similar to those described above for PFS with the exception that permanent discontinuation from treatment or discontinuation from study was considered as treatment failure. TTF was analyzed in a similar fashion as for PFS.

Overall Survival (OS) was defined as the time from date of randomization to date of death due to any cause. Patients were censored for this endpoint on the date of the last recorded visit if they did not die. OS was analyzed in a similar fashion as for PFS.

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

Changes to the Statistical Analysis Plan (SAP)

There were no changes to the planned analyses.

Protocol Amendments

Of 4 protocol amendments, Amendment 1 was substantive but predated study initiation. The following other amendments are considered substantive:

Amendment	Notable changes
Amendment 3 (4 Dec 2014)	<ul style="list-style-type: none">• Test for circulating lymphoma cells at screening• Exclude patients with prior allergy or hypersensitivity to any type of mAb
Amendment 4 (19 Apr 2016)	<ul style="list-style-type: none">• Allow recipients of prior localized radiotherapy for FL• Allow patients with LDH up to 1.5 x ULN• Clarify that lesions must be measurable via imaging• Remove requirement for steroid premedication 30 minutes before infusion as appropriate timing depends on route. Premedications may be administered per institutional standard.• Local lab may be used for eligibility or safety monitoring if not feasible to use central lab.

Source: FDA analysis

Clinical reviewer comment:

- **The clarification that disease must be radiographically measurable at baseline occurred late in the course of the study. A leading reason for patients being unevaluable for response was the lack of radiographically evaluable disease. Thirty patients overall (17%), including 16 (10%) in the PF-05280586 arm and 14 (7%) in the comparator arm were not evaluable for the week 26 assessment by central review and thus were excluded from the per-protocol population.**

SAP Amendments

The SAP was amended two times prior to the database snapshot and unblinding the trial. The key features of each amendment are listed below:

Amendment	Notable changes
Amendment 1 (1 Nov 2016)	<ul style="list-style-type: none"> • Confirmed that the assessment of efficacy will be based on central review data. • Modified censoring rules • Added subgroup analyses of efficacy
Amendment 2 (13 Nov 2017)	<ul style="list-style-type: none"> • Clarified exclusion criteria for the Per Protocol Analysis Population • Added that the stratified Mantel-Haenszel method will be used to obtain the corresponding estimated treatment group difference for the analysis of response data (including the primary endpoint) • Updated the censoring rules for progression free survival • Added the statistical specifications for programmatically determining which events are consistent with Sampson’s Criteria. • Local lab may be used for eligibility or safety monitoring if not feasible to use central lab.

Source: FDA analysis

6.1.2. Study Results

6.1.2.1 Study Conduct

Compliance with Good Clinical Practices

The Applicant indicated that the study was conducted in accordance with good clinical practices.

Financial Disclosure

Refer to Appendix.

Data Quality and Integrity – Reviewers’ Assessment

The quality of the original data submission and the additional submissions in response to our IRs were adequate to evaluate and review the submission in general.

Protocol Violations / Deviations

Notably, most patients (83%) had at least one potentially important protocol deviation, as defined in the SAP. Table 2 summarizes the potentially important deviations reported in ≥ 5% of patients.

Table 2: Selected Potentially Important Protocol Deviations (Study B3281006)

Protocol Deviation ^a	% of Patients with Deviation	
	PF-05280586 (N = 196)	Rituximab-EU (N= 198)
Any major deviation	81	85
Investigational product	27	28
Actual dose differed by ≥ 5% from planned dose	12	13
Missing documentation, e.g. infusion start/stop times	9	10
Randomization incorrectly stratified	4	4
Concomitant medications	19	19
Required premedication incorrectly dosed	11	12
Required premedication not taken	6	5
Procedures / tests	39	38
CT done without contrast (no allergy)	11	10
Missed or unevaluable FDG-PET at follow-up	9	8
Missed or unevaluable CT at follow-up	6	9
Required site not imaged on CT	7	5
Non-protocol required procedures completed	6	7
Individual assessment missed within a given procedure	5	4
Laboratory assessments	60	58
Lab test not done as specified / unable to analyze	26	24
Lab test not done	9	14
Lab sample lost / received late / unable to analyze	4	7
PK sample not properly collected or handled	20	23
PK sample not collected	6	5
Unable to analyze immunogenicity / CD19+ B-cell samples	28	18
Informed consent deviations	20	22
Other		
Adherence to contraception not documented	7	6

Source: 52-week CSR, Table 9

^a Represents deviations reported in ≥ 5% of patients, unless a lower threshold was relevant to the review.

Clinical reviewer comments:

- **The large number of potentially important protocol deviations raises concern about the quality of study oversight.**
- **Although the frequencies and types of deviations were balanced in the treatment arms, some analyses, including efficacy and PK assessments, may have been affected. From a clinical standpoint, however, the deviations are deemed unlikely to impact the overall conclusions about efficacy and safety.**

6.1.2.2 Patient and Treatment Characteristics

Disposition

Of 627 patients screened, 394 were randomized and comprise the ITT efficacy population; 393 were treated and comprise the safety population (Table 3).

Table 3: Patient Disposition (Study B3281006)

Parameter	Patients Per Arm	
	PF-05280586	Rituximab-EU
Randomized	196	198
Analyzed for safety	196	197
Completed treatment	194	196
Discontinued due to related AE	2	1
Analyzed for efficacy (% of randomized pts)		
ITT	196 (100%)	198 (100%)
Per-protocol ^a	166 (85%)	176 (89%)
Response-evaluable ^b	192 (98%)	196 (99%)
Study completed	170 (87%)	170 (86%)
Study discontinued (% of randomized pts)	26 (13%)	28 (14%)
PD or insufficient response	17 (9%)	24 (12%)
Protocol violation	1 (< 1%)	0 (0%)
Patient decision or loss to follow-up	5 (3%)	3 (2%)
AE of any cause	3 (2%)	1 (< 1%)

Source: 52-week CSR, Tables 6 and 7

^a For sensitivity analyses

^b For analysis of DOR

The most frequent reason for exclusion from the PP Population was no evaluable Week 26 assessment. There were 20 (10.2%) patients in the PF-05280586 group and 14 (7.1%) patients in the Rituximab-EU group who had no evaluable Week 26 assessment.

Table 4: Reasons for Exclusion from PP Population (Study B3281006)

	PF-05280586 N = 196 n (%)	Rituximab-EU N = 198 n (%)
Number (%) of patients excluded from the PP Population	30 (15.3%)	22 (11.1%)
Reasons		
No evaluable Week 26 assessment	20 (10.2%)	14 (7.1%)
No measurable disease at baseline as assessed	13 (6.6%)	9 (4.5%)
Others	2 (1%)	0

Source: 52-week CSR, Table 10

Demographic and Other Baseline Characteristics

Table 5 and Table 6 summarize demographic and disease characteristics of the ITT population. The median age was 60, with 135 patients (34%) being aged ≥ 65 , and 77% of patients were white.

Overall, 27% of patients had stage II disease, 44% stage III, and 29% stage IV, with a similar distribution in the treatment arms. The FLIPI2 distribution (randomization stratification factor) was also comparable, with 28% having low-risk disease, 66% intermediate-risk, and 6% high-risk. All patients had a $\beta 2$ -microglobulin level $\leq 1.5 \times$ ULN, and 98% had a normal LDH. Per protocol, all patients had an ECOG performance status of 0 or 1.

Table 5: Demographics of ITT Population (N = 394)

Parameter		PF-05280586 (N = 196)		Rituximab-EU (N = 198)	
Age, y	Median (range)	59	(25-85)	60	(21-93)
	≥ 65	67	(34%)	68	(34%)
Sex	Male	86	(44%)	92	(46%)
Race	White	158	(81%)	146	(74%)
	Black	1	(< 1%)	0	(0%)
	Asian	30	(15%)	44	(22%)
	Other	7	(4%)	8	(4%)
Ethnicity	Hispanic/Latino	31	(16%)	26	(13%)
Region	US	25	(13%)	19	(10%)

Source: CSR

Table 6: Disease Characteristics of ITT Population

Parameter	PF-05280586 (N = 196)		Rituximab-EU (N = 198)	
Years since diagnosis				
Median (range)	0.2	(0, 10.5)	0.2	(0, 8.6)
Mean (SD)	0.7	(1.3)	0.7	(1.3)
ECOG performance status				
0	171	(87%)	169	(85%)
1	25	(13%)	28	(14%)
Missing	0	(0%)	1	(< 1%)
FLIPI risk category				
Low	91	(46%)	89	(45%)
Intermediate	72	(37%)	77	(39%)
High	33	(17%)	32	(16%)
FLIPI2 risk category				
Low (0)	54	(28%)	58	(29%)
Intermediate (1-2)	133	(68%)	127	(64%)
High (3-5)	9	(5%)	13	(7%)
Stage				
II	52	(27%)	54	(27%)
III	89	(45%)	85	(43%)
IV	55	(28%)	59	(30%)
Bone marrow biopsy result				
Positive	53	(27%)	56	(28%)
Negative	142	(72%)	142	(72%)
Indeterminate	1	(< 1%)	0	(0%)

Source: 26-week CSR, Tables 14.1.2.1.1 and 14.1.2.2

Patient Treatment

As summarized in Section 8.2.1, >99% of patients treated received the planned 4 doses of mAb.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Refer to Section 6.1.1 for required concomitant medications and for reported deviations from the treatment plan.

6.1.2.3 Efficacy Results – Primary Endpoint

Primary Analysis

The primary efficacy endpoint was ORR which was defined as the proportion of patients within each treatment group that achieved CR or PR at Week 26 based on central review in the ITT population, in accordance with the revised response criteria for malignant lymphoma. Summary statistics of responses by treatment at Week 26 was presented in Table 7. The ORR difference was 4.66% with 90% CI of (-2.73%, 12.07%) by FDA’s analysis and 95% CI of (-4.16%, 13.47%) by Applicant’s analysis. In both the FDA analysis and the Applicant’s analysis, the entire 95% and 90% CIs lay within the equivalence margin of (-16%, 16%). Therefore, the study demonstrated the equivalence between the PF-05280586 and Rituximab-EU using ORR.

Table 7: Summary Statistics of Response by Treatment at Week 26 – Central Review (ITT)

	PF-05280586 (N=196)	Rituximab-EU (N=198)	Trt Difference (95% CI) (90% CI) * (PF-05280586 - Rituximab-EU)
ORR (CR +PR)	148 (75.5)	140 (70.7)	4.66 (-4.16, 13.47) (-2.73, 12.07) *
CR	51 (26.0)	57 (28.8)	-2.80 (-11.60, 6.03) (-10.18, 4.61) *
PR	97 (49.5)	83 (41.9)	7.46 (-2.41, 17.18) (-0.83, 15.64) *
Stable Disease	20 (10.2)	36 (18.2)	-8.0
Progressive Disease	6 (3.1)	8 (4.0)	-1.0
Unevaluable	6 (3.1)	4 (2.0)	1.0
Missing	16 (8.2)	10 (5.1)	3.1

* 90% confidence interval

Source: FDA analysis

Statistical reviewer comment:

- **A total of 22 (11.2%) patients in the PF-05280586 arm and 14 (7.1%) patients in the Rituximab-EU arm had either unevaluable or missing Week 26 assessments.**

Sensitivity Analysis

ORR by treatment at Week 26 was also conducted in the PP population. The entire 95% and 90% CIs lay within the equivalence margin of ± 16%, indicating the primary analysis findings are robust for the study population (ITT vs. PP).

Table 8: Summary Statistics of Response by Treatment at Week 26 – Central Review (PP)

	PF-05280586 (N=166)	Rituximab-EU (N=176)	Trt Difference (95% CI (90% CI) * (PF-05280586 - Rituximab-EU)
ORR (CR +PR)	143 (86.1)	138 (78.4)	7.49 (-0.67, 15.80) (0.67, 14.46) *
CR	46 (27.7)	55 (31.3)	-3.87 (-13.45, 5.83) (-11.91, 4.27) *
PR	97 (58.4)	83 (47.2)	11.36 (0.72, 21.74) (2.43, 20.10) *

* 90% confidence interval

Source: FDA analysis

Clinical reviewer comments:

- **The Applicant had indicated, in the application orientation and pre-BLA meetings, that 100% of patients had primary efficacy data for the 26-week analysis. However,**
 - **22/196 patients (11%) in the PF-05280586 group (ITT) and 14/198 patients (7%) in the Rituximab-EU group were not evaluable for the primary efficacy endpoint, with a leading reason being failure to obtain imaging within the specified time frame (source: FDA analysis).**
 - **For the 52-week analysis, 164/196 patients (84%) in the PF-05280586 group and 162/198 (82%) in the Rituximab-EU group had the required Week 52 assessments needed to determine overall response per central review, and**
 - **For responding patients, 147/165 responders (89%) in the PF-05280586 group, and 141/166 responders (85%) in the Rituximab-EU group had the Week 52 disease assessments needed for central review (source: response to 29 Nov 2018 IR).**

Complete or Partial Response (CR/PR) at Week 26

As presented in Table 7, the proportion of patients in the ITT Population achieving a CR at Week 26 was 51 (26.0%) patients in the PF-05280586 arm and 57 (28.8%) patients in the Rituximab-EU arm, with 97 (49.5%) patients in the PF-05280586 arm and 83 (41.9%) patients in the Rituximab-EU arm achieving a PR at Week 26. The analysis of CR showed a difference of -2.80% (PF-05280586 minus Rituximab-EU), with a 95% CI of (-11.60%, 6.00%) and a 90% CI of (-10.18%, 4.61%).

The analysis of PR showed a difference of 7.46% (PF-05280586 minus Rituximab-EU), with a 90% CI of (-0.83%, 15.64%). The percentage of all patients who achieved CR or PR at Week 26 was comparable between the 2 treatment arms. Sensitivity analysis of CR in PP population (**Table 8**) was consistent with that of the ITT Population. Note that there were 11.36% more patients in the PF-05280586 arm who achieved PR than that of the Rituximab-EU arm in the PP

population.

6.1.2.4 Efficacy Results – Secondary Endpoints

Time to event endpoints including PFS, DOR, TTF and OS based on the cut-off date of 19 April 2018 were analyzed with the Kaplan-Meier method. Cox model was used to estimate the hazard ratio and its 95% CIs for the treatment difference.

Study B3281006 is a 52 Week study with the last assessment scheduled on Week 52 ± 14 Days. All patients except one had follow-up time up to 441 days (14.5 months). A patient (ID (b) (6)) was last assessed at Day 574 (18.9 months) with death event in the Rituximab-EU arm. Because the follow-up time for this patient was well beyond the Week 52 assessment window, we considered this patient as an outlier. Therefore, we changed this patient status to censored at month 15 with study completion without progression/death in the FDA analysis for time-to-event efficacy endpoints of PFS, DOR and TTF.

A. Progression-Free Survival

Table 9 summarizes the PFS results based on central review assessment using Kaplan-Meier plot and Cox regression method, after changing one patient to censored with no event at month 15.

Table 9: Summary Analysis of PFS Results – Central Review (ITT)

	PF-05280586 (N=196)	Rituximab-EU (N=198)
Patients with event, n (%)	37 (18.9)	28 (14.1)
Progression, n (%)	36 (97.3)	27 (96.4)
Death, n (%)	1 (2.7)	1 (3.6)
Number censored, n (%)	159 (81.1)	170 (85.9)
Median PFS (months) (95% CI)	-	. [12.6, .]
Median PFS follow-up (95% CI)	11.8 [11.8, 11.9]	11.8 [11.7, 11.8]
Probability of being event-free at 6 months (95% CI)	96.8 [94.3, 99.3]	95.6 [82.7, 98.6]
Probability of being event-free at 1 year (95% CI)	78.2 [70.2, 84.2]	83.0 [75.0, 88.6]
HR (95% CI)	1.39 (0.85, 2.29)	

Source: FDA analysis

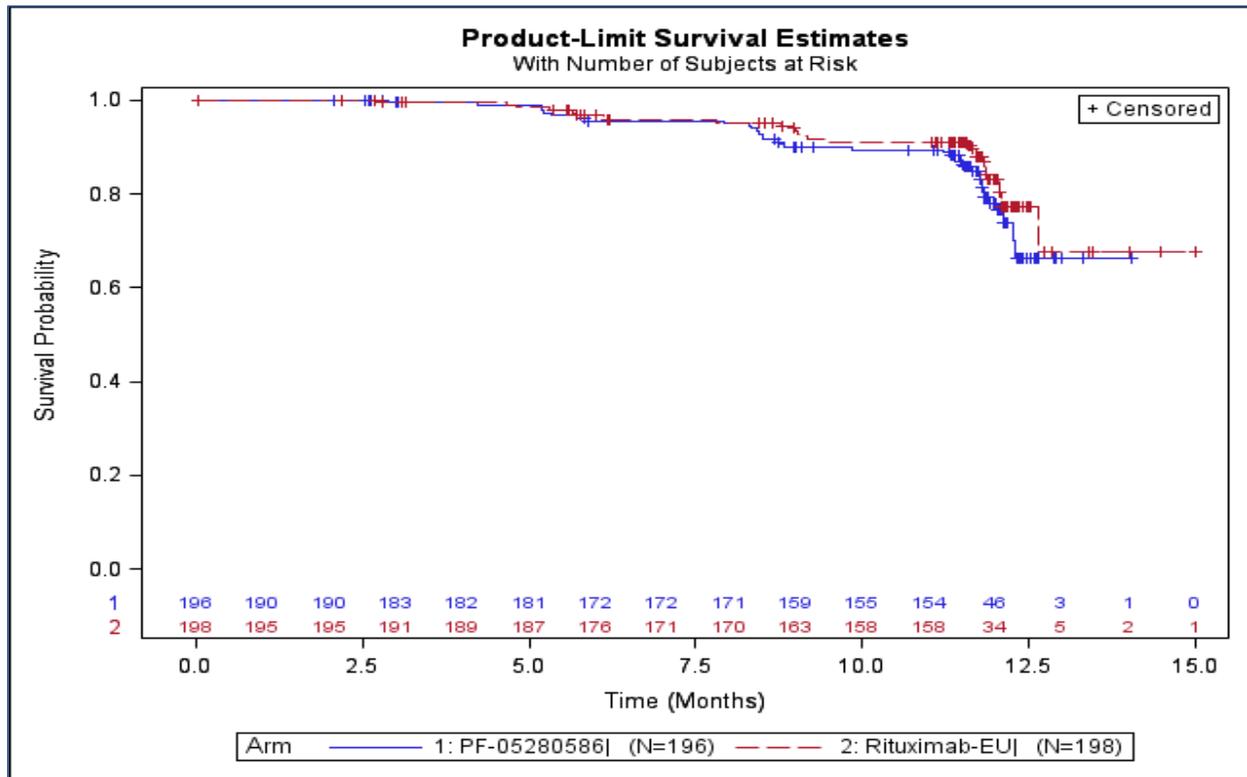
Statistical reviewer comments:

- **As of time of data cut-off (19 Apr 2018), there were 37 (18.9%) patients in the PF-05280586 arm progressed including one death; there were 28 (14.1%) patients in the Rituximab-EU treatment arm progressed with one death at Day 574 (18.9 months). The percentage of patients who were being event-free at month 6 and 1 year were comparable between the 2 treatment arms.**

- **The median PFS has not yet been reached for either treatment arm based on the currently available data after changing one patient to censored, and the hazard ratio between the study arms, estimated using the Cox’s regression model adjusted for stratification factor FLIPI risk group, was 1.39 with 95% CI of (0.85, 2.29), favoring Rituximab-EU arm. The median follow-up time for PFS are 11.8 month for both treatment arms.**

Figure 2 shows the modified Kaplan-Meier plot of PFS after changing the status of one patient as of cut-off of 19 Apr 2018. The KM plot for PFS was close to identical between the two arms until month 10, and then start diverging from month 10.

Figure 2. Modified KM Plot of PFS – Central Review (ITT)



Source: FDA analysis

Per central review assessment, 159 patients in PF-05280586 arm and 170 patients in Rituximab-EU arm have been censored. The reasons for censoring are summarized in Table 10. Among these censored patients, 139 (87.4%) patients in PF-05280586 arm and 150 (88.2%) patients in Rituximab-EU arm were censored due to the study completion without progression/death.

Table 10: Summary of Censoring Reasons for PFS – Central Review (ITT)

	PF-05280586 (N=196)	Rituximab-EU (N=198)
Number censored, n (%)	159	170
No baseline assessment	0	1 (<1.0)
No post-baseline assessment	6 (3.8)	2 (1.2)
Early study discontinuation without PD	14 (8.8)	17 (10.0)
Study completion without progression/death	139 (87.4)	150 (88.2)

Source: FDA analysis

Clinical reviewer comments:

- **The Applicant indicated no ongoing plans for further follow-up of efficacy. Once the database was locked on 18 May 2018, the study ended (source: response to 29 Nov 2018 IR).**
- **Estimation of PFS was limited by the short follow-up time.**

Table 11 shows the reviewer’s summary of censoring distribution by treatment. The censoring distribution was similar between the two treatment groups. Over 85% of the patients were censored after month 11, these are due to study completion without progression or death.

Table 11: Summary of Censoring Distribution for PFS – Central Review (ITT)

Month	PF-05280586 (N=196)			Rituximab-EU (N=198)		
	# of patients at risk at the beginning of time interval	# of events within the time interval	# of patients censored within the time interval	# of patients at risk at the beginning of time interval	# of events within the time interval	# of patients censored within the time interval
0 -< 6	196	8	16	198	6	16
6 -< 11	172	11	7	176	10	8
11 -< 12	154	14	94	158	8	116
12 +	46	4	42	34	3	31

Source: FDA analysis

B. Duration of response

Table 12 shows summary analysis of DOR for the response analysis. For patients who achieved ORR, there are numerically more PD events in the PF-05280586 arm than those from the Rituximab-EU arm (17.0% vs. 11.4%). The median DOR has not yet been reached for either treatment arm at the end of the study. The median follow-up time for DOR are similar between two treatment arms.

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

Per central review assessment, 137 patients in PF-05280586 arm and 147 patients in Rituximab-EU arm have been censored. Among these censored patients, 127 (92.7%) patients in PF-05280586 arm and 136 (92.5%) patients in Rituximab-EU arm were censored due to the study completion without PD.

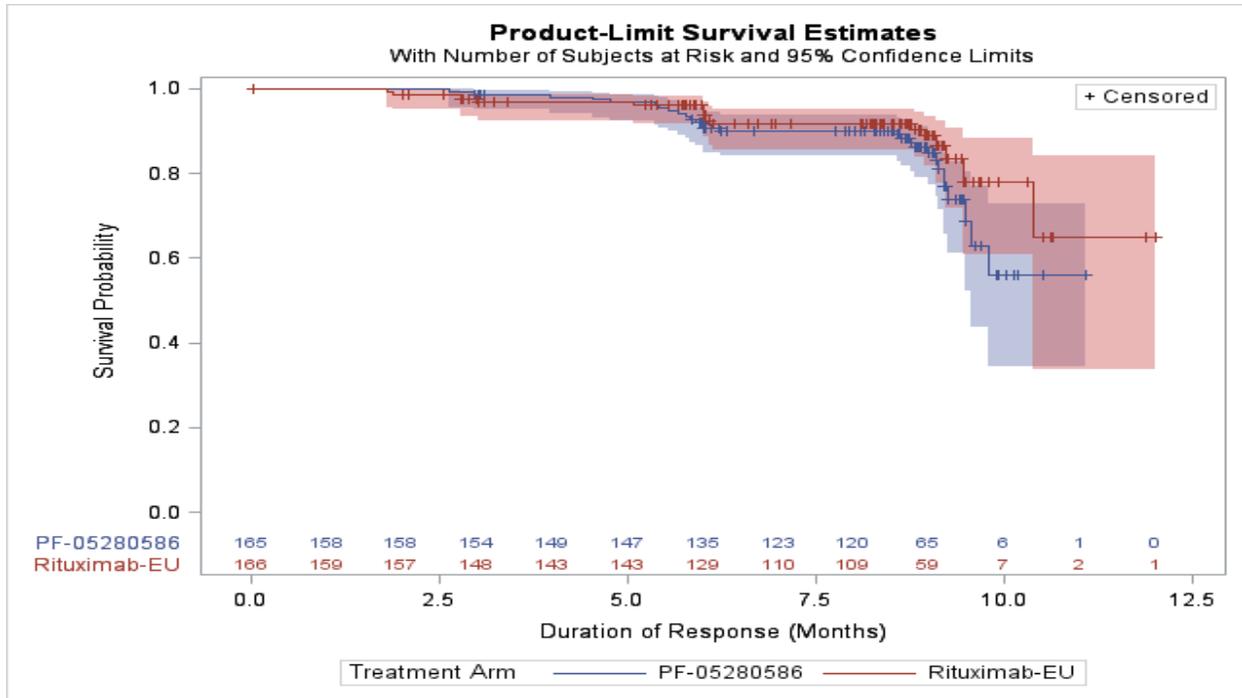
Table 12: Summary Analysis of DOR – Central Review (Response Evaluable Population)

	PF-05280586 (N=165)	Rituximab-EU (N=155)
Patients with event, n (%)	28 (17.0)	19 (11.4)
Progression, n (%)	28 (100)	18 (94.7)
Death, n (%)	0	1 (5.3)
Number censored, n (%)	137	147
Early study discontinuation without PD	10 (7.3)	11 (7.5)
Study completion without PD	127 (92.7)	136 (92.5)
Median DOR (month) (95% CI)	- [9.6, -]	- [10.4, -]
Median Follow-up for DOR (95% CI)	8.9 (8.8, 9.0)	8.8 (8.6, 8.9)
HR (95% CI)	1.49 (0.82, 2.70)	

Source: FDA analysis

The modified Kaplan-Meier plot of DOR by treatment arm after changing one patient to censored with PD at month 12 is presented in Figure 3. 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 1.49, with a 95% CI of (0.82, 2.70), favoring Rituximab-EU.

Figure 3. Modified KM Plot of DOR – Central Review (Response Evaluable Population)



Source: FDA analysis

Statistical Reviewer Comments:

- The KM plot for DOR is similar between the two arms until month 8, and then start separating. The PF-05280586 arm shows numerically shorter DOR than that of Rituximab-EU from the KM plot survival analysis. The reliable estimation of DOR was limited by the short follow-up.

To further explore the differences in DOR between the two treatment arms, FDA conducted additional analysis to obtain the time point estimation and censoring distribution for DOR.

Table 13: Time Point Estimates for DOR – Central Review (Response Evaluable Population)

Duration of Overall Response	PF-05280586 (N=165)	Rituximab-EU (N=166)
Month 6, (95% CI)	92.1% (87.9%, 96.4%)	96.1% (93.0%, 99.2%)
Month 8, (95% CI)	90.0% (85.3%, 94.8%)	91.6% (87.0%, 96.2%)
Month 10, (95% CI)	55.9% (36.1%, 75.6%)	78.0% (64.4%, 91.5%)

Source: FDA analysis

Statistical Reviewer Comments:

- Although the median follow-up time for DOR (Table 12) are almost identical among two treatment arms, only 55.9% (95% CI: 36.1% to 75.6%) patients in the PF-05280686 arm had durable response up to 10 months compared to 78.0% (95% CI: 64.4% to 91.5%) of patients in the Rituximab-EU arm.

Table 14 shows FDA’s summary of censoring distribution of DOR between the two treatment arms. Although the estimated median follow-up for DOR is about 9 months for both treatment arms, there were more PD events in the PF-05280586 arm than these of Rituximab-EU arm at month 4-6 and 9-10.

Table 14: Summary of Censoring Distribution for DOR (Response Evaluable Population)

Month ^a	PF-05280586			Rituximab-EU		
	# of responders at the beginning of time interval	# of PD events	# of patients censored within the time interval	# of responders at the beginning of time interval	# of PD events	# of patients censored within the time interval
0 -< 2	165	0	7	166	2	7
2 -< 4	158	3	6	157	3	11
4 -< 6	149	9	5	143	1	13
6 -< 8	135	3	12	129	6	14
8 -< 9	120	4	51	109	2	48
9 -< 10	65	9	50	59	3	49
10 +	6	0	6	7	1	6

^a Measured from the date of first documentation of response (PR or CR) to the first documentation of PD or to death due to any cause.

Source: FDA analysis

Because DOR appeared shorter in the PF-05280586 arm, FDA requested that the Applicant provide justification that these findings do not preclude demonstration of no clinically meaningful differences. In response to this 25 Mar 2019 midcycle communication, the Applicant acknowledged the observed difference, but indicated that the study was not designed to formally demonstrate equivalence in the secondary endpoints, and that

- The comparison between the two treatment groups was not statistically significant (HR 1.49, p=0.185), and the CI for the HR was relatively wide (0.823, 2.704).
- The number of patients at risk and number of events dropped precipitously after Month

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

9, which increased variability and separation at the end of the KM curves, and further underscored the fact that the study was not designed to estimate those time points at the end of the KM curves. The numbers at risk dropped from 124 patients at Month 9 to 13 patients at Month 10, and there is not enough information at the latter time points to permit interpretation of differences across treatment groups.

Clinical Reviewer Comments:

- **The Applicant's justification is sufficient. Demonstrating equivalence in PFS would require a larger study with longer follow-up.**

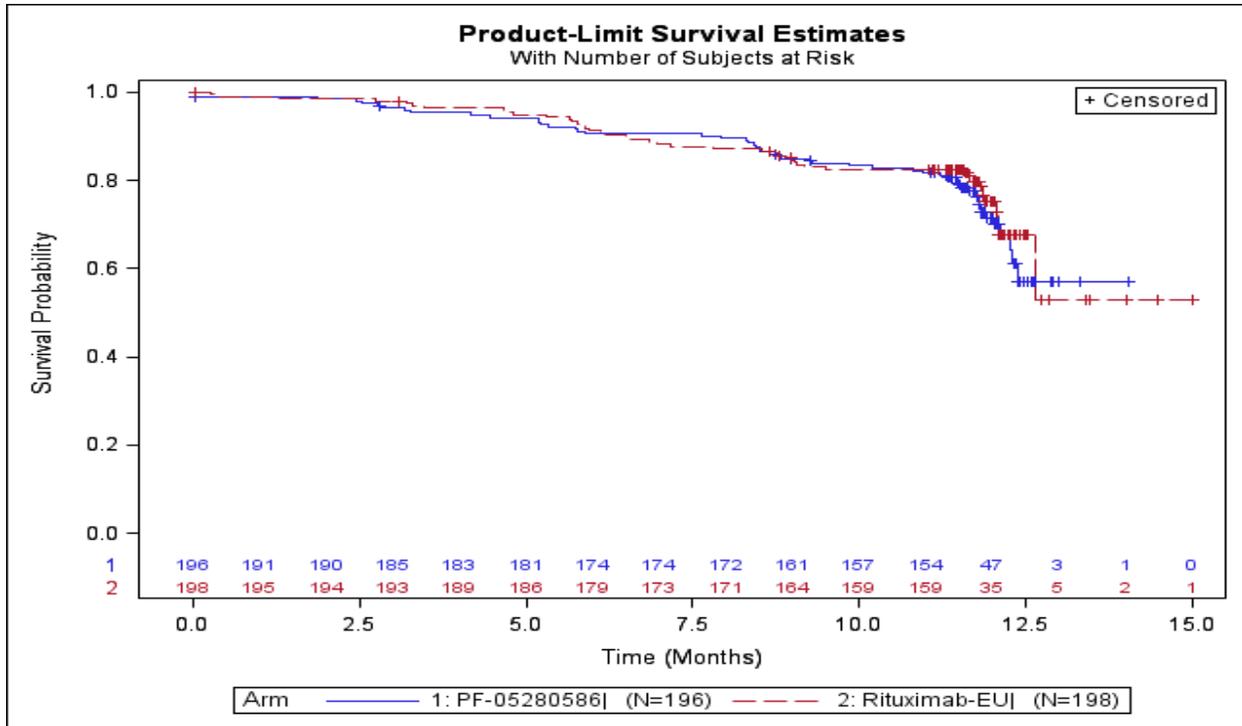
Statistical Reviewer' Comments:

- **Because having a response is a treatment related outcome, comparisons of duration of response across treatment arm are difficult to interpret. The Applicant's justification for DOR is sufficient.**

C. Time to Treatment Failure

The modified Kapan-Meier plot of TTF by treatment arm after changing one patient to censored with PD at month 15 is presented here.

Figure 4. Modified KM Plot for TTF – Central Review (ITT)



Source: FDA analysis

Statistical Reviewer Comments:

- The median TTF has not yet been reached for either treatment arm based on the currently available data after changing one patient to censored. The KM plot for TTF was similar between the two arms. The hazard ratio when comparing TTF between PF-05280586 and Rituximab-EU was 1.16, with a 95% CI of (0.79, 1.72).

D. Overall Survival

As of the data cut-off (19 Apr 2018), there was 1 death in the Rituxan -EU treatment arm. The median time of OS is not estimable in either treatment arm. The final data set is not mature for evaluation of OS.

6.1.2.5 Subpopulations

The primary endpoint of ORR was analyzed in the subgroups of gender, age, race and geographic region using 90% CI. The results are summarized in Table 15. Although interpretation of these results was limited by the small sample size, the 90% CI interval was outside the equivalence margins of $\pm 16\%$ in some subgroups. Further, point estimates of ORR differences vary among regions (-4.4% US, 11.6% Europe, -15.8% Latin America and 1.9% Asia).

Table 15: ORR at Week 26 by Demographic Subgroups – Central Review (ITT)

	PF-05280586 (N=196)	Rituximab-EU (N=198)	Difference (90% CI)
Male	64/86 (74.4)	62/92 (67.4)	7.03 (-4.13,18.19)
Female	84/110 (76.4)	78/106 (73.6)	2.78 (-6.92,12.47)
Age<60	79/99 (79.8)	68/96 (70.8)	8.96 (-1.15,19.08)
Age>=60	69/97 (71.1)	72/102 (70.6)	0.55 (-10.1,11.14)
White	117/158 (74.1)	100/146 (68.5)	5.56 (-2.98,14.10)
Asian	24/30 (80.0)	34/44 (77.3)	2.73 (-13.2,18.61)
Other	7/8 (87.5)	6/8 (75.0)	10.71 (-22.6,43.99)
United States	16/25 (64.0)	13/19 (68.4)	-4.42 (-28.0,19.18)
Europe	92/118 (78.0)	73/110 (66.4)	11.60 (1.89,21.31)
Latin America	13/19 (68.4)	16/19 (84.2)	-15.8 (-38.1,6.50)
Asian	20/26 (76.9)	30/40 (75.0)	1.92 (-15.7,19.57)

Source: FDA analysis

Subgroup analyses by baseline disease characters are presented in Table 16. There are no statistical differences between two treatment arms by Ann Arbor Staging classification and bone marrow involvement. However, the point estimates of the ORR differences in FLIPI2-Low (16.09) and FLIP2-High (23.93) patients exceeded the equivalence margin of $\pm 16\%$.

Table 16: ORR at Week 26 by Baseline Assessments – Central Review (ITT)

	PF-05280586 (N=196)	Rituximab-EU (N=198)	Difference (90% CI)
FLIPI2 - Low Risk	45/54 (83.3)	39/58 (67.2)	16.09 (2.96,29.22)
FLIPI2 - Intermediate	96/133 (72.2)	94/127 (74.0)	-1.84 (-10.9,7.21)
FLIPI2 - High	7/9 (77.8)	7/13 (53.8)	23.93 (-8.27,56.13)
Stage II	34/52 (65.4)	36/54 (66.7)	-1.28 (-16.4,13.85)
Stage III/IV	114/144 (79.2)	104/144 (72.2)	6.94 (-1.34,15.23)
Positive Bone Marrow Biopsy	41/53 (77.4)	40/57 (70.2)	7.18 (-6.56,20.92)
Negative Bone Marrow Biopsy	107/143 (74.8)	100/141 (70.9)	3.90 (-4.77,12.58)

Source: FDA analysis

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable

7.2. Integrated Assessment of Effectiveness

Study B3281006 demonstrates equivalence between PF-05280586 and MabThera for ORR for patients with previously untreated, low tumor burden FL. The difference in ORR was within the prespecified equivalence margin of (-16%, 16%), and the CR rates were similar. In the PF-05280586 arm, ORR was 76% (90% CI: 70 to 815) with a CR rate of 26%. In the MabThera arm, ORR was 71% (90% CI: 65, 76) with a CR rate of 29%. The difference in ORR between treatment arms (PF-05280586 minus Rituximab-EU) was 4.66% with a 90% CI of (-2.73%, 12.07%) and 95% CI of (-4.16%, 13.47%), which are within the prespecified equivalence margin.

On PFS analysis shows that 37 (18.9%) and 28 (14.1%) patients experienced a PD event on the PF-05280586 arm and Rituximab-EU arm, respectively. Evaluation of PFS in the ITT population demonstrated numerically more PD events in the PF-05280586 arm, with a HR of 1.39 (95% CI: 0.85, 2.29) in favor of MabThera. The PF-05280586 arm also had numerically shorter DOR than that of MabThera on Kaplan-Meier analysis with a HR of 1.49 (95% CI: 0.82, 2.70) in favor of MabThera. The PFS and DOR data are, however, immature, and due to the study design, they cannot be reliably estimated or compared.

Although subgroup analyses for ORR by region and FLIPI2 did not show consistency, the study was not powered to detecting the same magnitude of treatment effect. The results of the subgroup analyses therefore do not change the overall determination of efficacy.

Based on ORR, the results support the claim that there are no clinically meaningful differences in efficacy between PF-05280586 and rituximab in patients with previously untreated, low tumor burden FL. Study B3281006 was not designed to address whether there are clinically meaningful differences in durability of response.

8. Review of Safety

8.1. Safety Review Approach

The safety analysis considers all-causality treatment-emergent AEs (TEAEs) in recipients of any study drug in Study B3281006. TEAEs were defined as AEs that are new or worsened from baseline grade or are unknown to have worsened from baseline. AEs related to the underlying disease were discounted from the safety analysis. For increased sensitivity, FDA used a combination of individual MedDRA preferred terms (PTs) and custom groupings of PTs as

Clinical and Statistical Review
 Yvette Kasamon, MD (clinical)
 Kate Li Dwyer, PhD (statistics)
 BLA 761103
 Ruxience (PF-05280586)

defined in the Appendix. All presented analyses use the FDA grouping.

The Applicant used the full 52-week study period for safety reporting and analyses. The clinical reviewer used JMP 13 to conduct safety analyses using the data analysis datasets. Two CSRs and sets of data were submitted, encompassing the 26-week and 52-week analyses. Apart from deaths, the safety analysis is based on the 26-week datasets.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The number of patients exposed to study treatment was sufficient for safety review. Of the 393 patients with FL treated on Study B3281006, $\geq 99\%$ received the planned 4 doses of mAb (Table 17).

Table 17: Exposure in Safety Population (N = 393)

	PF-05280586 (N = 196)		Rituximab-EU (N = 197)	
Total doses received				
1	2	(1%)	0	
2	0		1	(< 1%)
3	0		0	
4	194	(99%)	196	(> 99%)
Doses within protocol-specified window ^a				
4	186	(95%)	189	(96%)
Patients with dose interruption				
Dose 1	42	(21%)	53	(27%)
Dose 2	4	(2%)	2	(1%)
Dose 3	2	(1%)	1	(< 1%)
Dose 4	3	(2%)	1	(< 1%)

Source: 26-week CSR, Table 14.4.1.1

^a Relative to first dose, dose 2 was due within 8 +/- 1 days, dose 3 within 15 +/- 1 days, and dose 4 within 22 +/-1 days.

8.2.2. Relevant Characteristics of the Safety Population

Characteristics of the safety population and primary efficacy population are virtually identical, as the safety population has 1 fewer patient.

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

8.2.3. Adequacy of the Safety Database

The safety database was generally adequate for review.

8.2.4. Issues Regarding Data Integrity and Submission Quality

The submitted data were of acceptable quality. There were no concerns regarding data integrity.

8.2.5. Categorization of Adverse Events

AEs were graded using NCI CTCAE version 4.03 and were classified using MedDRA terminology. Mapping of verbatim terms to PTs was generally appropriate.

8.2.6. Routine Clinical Tests

The schedule of routine clinical testing was sufficient for safety review.

8.3. Safety Results

8.3.1. Deaths

As of the 52-week data sets, no study treatment-related deaths were reported in either arm. One patient in each arm died of disease progression.

8.3.2. Serious Adverse Events

At least one SAE was reported in 14 patients (7%) in the PF-05280586 arm and 12 patients (6%) in the Rituximab-EU arm. Infection was the leading cause in both arms, with at least one infection SAE reported in 4 recipients (2%) of PF-05280586 and 3 recipients (2%) of Rituximab-EU (source: FDA analysis). A particular pattern of SAEs was not observed. The PF-05280586 arm had no infusion-related SAEs; in the Rituximab-EU arm, SAEs included 1 IRR and 1 case of serum sickness.

8.3.3. Dropouts and/or Discontinuations Due to Adverse Effects

Less than 1% of the overall safety population discontinued study treatment due to an adverse reaction. Refer to the summary of patient disposition in Section 6.1.2.2 (Table 3).

8.3.4. Significant Adverse Events

Refer to Section 8.3.2 for a review of SAEs. No grade 4 AEs were reported in the PF-05280586 arm, and 1 grade 4 AE (neutropenia) was reported in the Rituximab-EU arm.

8.3.5. Treatment-Emergent Adverse Events and Adverse Reactions

Table 18 summarizes AEs reported in > 5% of patients in either arm, regardless of attribution. Most AEs were grade 1-2. Infusion-related reactions (IRRs) were the leading cause of AEs overall, occurring in > 25% of the safety population, and had a similar incidence and grade distribution in the two arms. In the PF-05280586 arm, the PT of IRR was reported in 50 patients (26%): 10 patients (5%) with maximum grade 1, 35 (18%) grade 2, and 5 (3%) grade 3. The

Rituximab-EU arm had an observed 4% higher incidence of IRRs, which were reported in 59 patients (30%): 8 patients (4%) with maximum grade 1, 50 (25%) grade 2, and 1 (< 1%) grade 3. The rates of treatment interruption due to AEs were similar (Table 17).

The incidences and grade distributions of AEs were generally similar in the treatment arms. In addition to IRRs, commonly reported ($\geq 10\%$) AEs in the PF-05280586 arm included fatigue or asthenia, upper respiratory tract infection, and abdominal pain.

Table 18: All-Cause AEs Reported in > 5% of Patients (Study B3281006)

PT or Grouped PT	PF-05280586 (N = 196)			Rituximab-EU (N = 197)		
	% Any Grade	% G1-2	% G3 ^a	% Any Grade	% G1-2	% G3 ^a
IRR	26	23	3	30	29	< 1
Fatigue or asthenia	11	11	0	13	12	< 1
Upper resp. tract infection	11	11	< 1	11	11	< 1
Abdominal pain	10	9	< 1	4	4	0
Headache	9	9	0	10	9	1
Nausea	7	7	0	9	9	0
Rash	7	7	< 1	5	5	0
Pruritus	7	7	0	11	11	0
Cough	7	7	0	6	6	0
Diarrhea	7	7	0	6	6	< 1
Throat irritation	7	7	< 1	5	5	0
Pyrexia	6	6	< 1	5	5	0

Source: FDA analysis

Bolded terms have a $\geq 2.0\%$ higher incidence of any-grade AEs in the PF-05280586 arm.

^a None grade 4

8.3.6. Laboratory Findings

The arms had similar laboratory findings, with most abnormalities being maximum grade 1-2 (Table 19). In the PF-05280586 arm, common ($\geq 10\%$) all-grade hematology abnormalities included neutropenia, lymphopenia, and anemia, with < 1% of patients reported to have grade 3 neutropenia. Elevations of AST and ALT, all grade 1-2, were also common.

Table 19: Laboratory Abnormalities in > 5% of Patients by Maximum Postbaseline Grade

	PF-05280586 (N = 196)			Rituximab-EU (N = 197)		
	% Any Grade	% G1-2	% G3-4 ^a	% Any Grade	% G1-2	% G3-4
HEMATOLOGY						
Leukopenia	22	22	0	25	24	< 1
Neutropenia	20 ^b	19	< 1	18	17	2
Lymphopenia	19	17	2	18	16	2
Anemia	10 ^b	10	0	8	8	0
Thrombocytopenia	6	6	0	6	5	< 1
CHEMISTRY^c						
ALT increase	18	18	0	19	19	< 1
AST increase	11	11	0	13	13	0
Alk phos increase	6	6	0	8	8	0
Bilirubin increase	6	6	0	8	8	0

Source: FDA analysis

^a None grade 4

^b Difference in arms < 2.0%

^c See note below regarding creatinine.

In addition, grade 1-2 creatinine elevations occurred in 68% of recipients of PF-05280586 and 71% of recipients of Rituximab-EU based on CTCAE v 4.03, in which any creatinine elevation >1 to 1.5 x ULN is grade 1 (including values in the normal range). Using CTCAE v 5 (which does not regard values < 1.5 x ULN as grade 1), grade ≥ 1 creatinine elevations were rare.

Reviewer comment:

- **Given the rarity of grade 4 neutropenia reported, the incidence of late-onset neutropenia is likely underestimated.**

8.3.7. Vital Signs

Mean changes from baseline in vital sign values were comparable between treatment groups (source: 26-week CSR, Section 12.5.1).

8.3.8. Electrocardiograms / QT

No clinically significant EKG abnormalities were reported in either treatment group (source: 26-week CSR, Section 12.5.2). On FDA analysis, the arms had similarly low (< 5%) incidences of cardiac arrhythmia AEs (high-level grouped term).

8.3.9. Immunogenicity

Refer to the clinical pharmacology review. Per the Applicant’s analysis (source: Week 52 CSR, Section 11.4.4), 14 (7%) patients in the PF-05280586 group and 17 (9%) in the Rituximab-EU group had a positive ADA test (titer ≥ 1.88) at baseline. Post treatment, the incidence of ADA increased throughout the study and was similar between treatments. Overall, there were 43 (22%) patients in the PF-05280586 group and 39 (20%) patients in the Rituximab-EU group with at least 1 post-dose sample that tested positive for ADA. Overall, the incidence of immune-based AEs between ADA positive and ADA negative patients was comparable (source: Week 52 CSR, Table 14.3.7.2.3).

8.3.10. Safety Analyses by Demographic Subgroups

In the PF-05280586 arm, the incidences of having an SAE or grade ≥ 2 AE were numerically higher (absolute difference, 5-6%) in patients aged ≥ 65 than in patients aged < 65 (Table 20). There are insufficient data to evaluate safety differences according to race.

Table 20: Safety According to Demographic Subgroups

Parameter			PF-05280586 (N = 196)	
Age	Any SAE	≥ 65	7 / 67	(10%)
		< 65	7 / 129	(5%)
	Grade ≥ 2 AE	≥ 65	41 / 67	(61%)
		< 65	71 / 129	(55%)
Sex	Any SAE	Male	6 / 86	(7%)
		Female	8 / 110	(7%)
	Grade ≥ 2 AE	Male	48 / 86	(56%)
		Female	56 / 110	(51%)

Source: FDA analysis

8.4. Additional Safety Explorations

8.4.1. Human Carcinogenicity or Tumor Development

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of rituximab.

8.4.2. Human Reproduction and Pregnancy

No clinical data with study drug. Based on human data, rituximab can cause B-cell lymphocytopenia in infants exposed to rituximab in-utero.

8.4.3. Pediatrics

No clinical data with study drug. There are no pediatric lymphoma data in the Rituxan PI. On first interim analysis (310 patients), a randomized study in pediatric aggressive B-cell NHL and

Clinical and Statistical Review
Yvette Kasamon, MD (clinical)
Kate Li Dwyer, PhD (statistics)
BLA 761103
Ruxience (PF-05280586)

B-ALL, comparing standard chemotherapy with vs. without rituximab, was terminated early because of superior EFS in the rituximab arm (Minard-Colin et al 2016).

8.5. Safety in the Postmarket Setting

8.5.1. Safety Concerns Identified Through Postmarket Experience

Not applicable

8.5.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be consistent with the known safety profile of US-licensed Rituxan.

8.6. Integrated Assessment of Safety

In adults with low-tumor burden FL, the safety profile of PF-05280586 was similar to that of Rituximab-EU. These data support the determination of no meaningful differences in these products in terms of safety in the patient population studied. Overall, the observed safety profile of PF-05280586 is consistent with the known safety profile of US-licensed Rituxan.

9. Advisory Committee Meeting and Other External Consultations

The application was not presented to the Oncologic Drug Advisory Committee or other external consultants because it did not raise significant efficacy or safety issues for the proposed indications.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Should this application be approved, the prescribing information for Ruxience would mirror that of Rituxan, with the same proposed hematologic malignancies indications and dosing as the reference product.

11. Risk Evaluation and Mitigation Strategies (REMS)

Based on the observed safety profile of PF-05280586, safety issues can be adequately managed through appropriate labeling and routine post-marketing surveillance, without the need for a REMS.

12. Postmarketing Requirements and Commitments

None recommended by the clinical review team.

Appendices

12.1. References

Minard-Colin V et al. Results of the randomized Intergroup trial Inter-B-NHL Ritux 2010 for children and adolescents with high-risk B-cell non-Hodgkin lymphoma (B-NHL) and mature acute leukemia (B-AL): Evaluation of rituximab (R) efficacy in addition to standard LMB chemotherapy (CT) regimen. 2016 ASCO Annual Meeting. J Clin Oncol 34, 2016 (suppl; abstr 10507)

Miettinen O, Numinen M. Comparative Analysis of Two Rates. Statistics in Medicine 1985;4(2):213-26.

Ardeschna KM, Smith P, Norton A, et al. Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: a randomised controlled trial. Lancet 2003;362(9383):516–22.

12.2. Financial Disclosure

Covered Clinical Study: B3281006

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Total number of investigators identified: <u>895</u>		
Number of investigators who are Applicant employees (both full-time and part-time): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>4</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>0</u> Significant payments of other sorts: <u>4</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
Is an attachment provided with details of the disclosable interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u> *		

* None had missing financial disclosure information

12.3. Grouping of Preferred Terms for Safety Analysis

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper, Abdominal discomfort	
Cardiac arrhythmias	High-level group term	
Cough	Cough, Productive cough, Upper airway cough syndrome	
Dyspnea	Dyspnea, Dyspnea exertional	
Fatigue or asthenia	Fatigue, Asthenia, Lethargy	Malaise
Headache	Headache, Head discomfort, Migraine, Tension headache	
Hypertension	Hypertension, Blood pressure increase	
Hypotension	Hypotension, Blood pressure decrease	
Musculoskeletal pain	Musculoskeletal chest pain, Musculoskeletal pain, Musculoskeletal discomfort	Back pain, Bone pain, Pain in extremity, Arthralgia, Spinal pain, Neck pain, Flank pain
Neutropenia	Neutropenia, Neutrophil count decreased ^a	
Pruritus	Pruritus, Pruritis allergic	Localized sites of pruritus
Rash	Rash, specific types of rash (e.g., erythematous, maculopapular, pruritic), Dermatitis, Dermatitis allergic, Drug eruption	Drug hypersensitivity, Dermatitis contact, Folliculitis, Urticaria
Upper respiratory tract infection	Upper respiratory tract infection, Viral upper respiratory tract infection, Nasopharyngitis, Pharyngitis, Sinusitis, Acute sinusitis, Viral sinusitis	Rhinitis, Rhinitis allergic, Rhinorrhea, Laryngitis, Upper respiratory tract inflammation, Respiratory tract infection

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

YVETTE L KASAMON
03/27/2019 08:28:41 PM

KATE L DWYER
03/28/2019 10:31:38 AM

YEH FONG CHEN
03/28/2019 10:53:52 AM

THOMAS E GWISE
03/28/2019 11:15:44 AM

ROMEO A DE CLARO
03/28/2019 01:51:18 PM