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APPLICATION NUMBER:

761103Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review and Summary Review for Regulatory Action

Date	see stamp date
From	R. Angelo de Claro, M.D. (Cross-Discipline Team Leader) and Ann T. Farrell, M.D. (Division Director)
Subject	Cross-Discipline Team Leader Review and Summary Review for Regulatory Action
NDA/BLA # Supplement#	BLA 761103
Applicant	Pfizer, Inc.
Date of Submission	25 July 2018
BsUFA Goal Date	25 July 2019
Proprietary Name	Ruxience ¹
Code Name	PF-05280586 ¹
Nonproprietary Name	rituximab-pvvr ¹
Reference Product	US-licensed Rituxan
Dosage forms / Strength	Injection: 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL (10 mg/mL) solution in single-dose vials
Applicant's Proposed Indication(s)	The following indications for US-licensed Rituxan: <ul style="list-style-type: none"> • Non-Hodgkin's Lymphoma (NHL) • Chronic Lymphocytic Leukemia (CLL) • Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)
Recommendation on Regulatory Action	<i>Approval</i>
Recommended Indication	Same as Applicant's proposed indications

Material Reviewed/Review Discipline	Reviewers
DHP Clinical/Statistical Review	Clinical: Yvette Kasamon, MD / R. Angelo de Claro, MD Statistical: Kate Li Dwyer, PhD / Yeh-Fong Chen, PhD / Thomas Gwise, PhD
DPARP Clinical/Statistical Review	Clinical: Suzette Peng, MD / Rachel Glaser, MD Nikolay Nikolov, MD Statistical: Ginto Pottackal, PhD / Greg Levin, PhD
Clinical Pharmacology Review	Shalini Wickramaratne Senarath Yapa, PhD / Salah Hamed, PhD / Anshu Marathe, PhD

¹ For purposes of this review, the proposed product is referred to by either the proposed proprietary name, the proposed nonproprietary name, or the Applicant's descriptor PF-05280586. The proposed proprietary name, Ruxience, and the proposed nonproprietary name, rituximab-pvvr, are only conditionally accepted until the application is approved.

Material Reviewed/Review Discipline	Reviewers
Pharmacology-Toxicology Review	Pedro Del Valle, PhD / Christopher Sheth, PhD
Product Quality Review	Bazarragchaa Damdinsuren, PhD (Application Technical Lead) / refer to CMC review for full list
CMC Statistical	Chao Wang, PhD / Meiyu Shen, PhD
OSI	Min Lu, MD, MPH / Kassa Ayalew, MD, MPH
OSIS	Gajendiran Mahadevan, PhD / Amanda Lewin, PhD / Arindam Dasgupta, PhD
OSE/DMEPA	Nicole Garrison, PharmD, BCPS / Carlos M Mena-Grillasca, BS Pharm / Hina Mehta, PharmD / Danielle Harris, PharmD, BCPS
OPDP	Nisha Patel, PharmD
PLT	Susan Redwood, MPH, BSN, RN / Sharon R. Mills, BSN, RN, CCRP / LaShawn Griffiths, MSHS-PH, BSN, RN
RPM	Jennifer Lee, PharmD
Cross-Discipline Team Lead	R. Angelo de Claro, MD
Division Director (DHP)	Ann Farrell, MD

DHP, Division of Hematology Products; DPARP, Division of Pulmonary, Allergy, and Rheumatology Products; CMC, Chemistry, Manufacturing, and Control; OSI, Office of Scientific Investigations; OSIS, Office of Study Integrity and Surveillance; OSE, Office of Surveillance and Epidemiology; DMEPA, Division of Medication Error Prevention and analysis; OPDP, Office of Prescription Drug Promotion; PLT, Patient Labeling Team, RPM, Regulatory Project Manager

1. Regulatory Recommendation

Regulatory Recommendation: Approval

The Applicant is seeking licensure of Ruxience (rituximab-pvvr) as a biosimilar to US-licensed Rituxan for the Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) indications that are the same as those for the reference product, US-licensed Rituxan.

Based on a totality of the evidence approach, the data and information submitted in the BLA support the licensure of Ruxience as a biosimilar to US-licensed Rituxan for the Applicant's proposed indications. The Applicant demonstrated that PF-05280586 is highly similar to US-licensed Rituxan notwithstanding minor differences in clinically inactive components, and that there are no clinically meaningful differences in terms of safety, purity and potency between PF-05280586 and US-licensed Rituxan. All review teams for BLA 761103 recommend approval.

Licensure of PF-05280586 as a biosimilar to US-licensed Rituxan for conditions of use that were not directly studied (*i.e.*, CLL, GPA/MPA, and NHL subtypes such as diffuse large B-cell lymphoma and advanced follicular lymphoma) in the clinical development program is supported by adequate justification for extrapolation (refer to Section 9 of this review).

The Applicant established a scientific bridge between PF-05280586, US-licensed Rituxan, and EU-approved MabThera because the comparative development program (nonclinical studies and comparative clinical efficacy/safety study in LTBFLL) used EU-approved MabThera as a comparator. A sufficient scientific bridge was established, which consisted of analytical and pharmacokinetic evaluations as is described in Sections 3 and 6 of this review.

2. Background

On July 25, 2018, Pfizer, Inc. (Applicant) 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). Rituximab (US-licensed Rituxan) was first approved in the US in November 1997. It was approved in Europe (EU) in February 1998 and 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 modified the requested indications for their product.³ The requested indications now are:

- Non-Hodgkin's Lymphoma (NHL)
- Chronic Lymphocytic Leukemia (CLL)
- Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA)

The full wording of the the NHL, CLL, and GPA/MPA indications for US-licensed Rituxan is listed below:

Non-Hodgkin's Lymphoma (NHL)

RITUXAN is indicated for the treatment of adult patients with:

- 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 a rituximab product 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)

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.

chemotherapy.

- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Chronic Lymphocytic Leukemia (CLL)

RITUXAN is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of adult patients with previously untreated and previously treated CD20-positive CLL.

Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA)

RITUXAN, in combination with glucocorticoids, is indicated for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

Regulatory Background

The Biologics Price Competition and Innovation Act of 2009 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 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, 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 "totality of the evidence" submitted as part of this application to support the approval of PF-05280586 include the following:

- A comprehensive analytical characterization of PF-05280586, US-licensed Rituxan, and EU-approved MabThera which included comparative characterization of physicochemical attributes and comparative functional assessments.
- The nonclinical studies included a single-dose IV study and a 4-week repeat-dose IV study in adult 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) evaluated comparative efficacy, safety, and immunogenicity of PF-05280586 compared to 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-Rituxan has been previously licensed.

3. Product Quality

Source: Product Quality and CMC Statistics Review

Product Quality Review Team Recommendation: Approval

CMC Statistics Review Team Recommendation: Approval

- General product quality considerations

Rituximab-pvvr (PF-05280586) is a chimeric monoclonal IgG1 antibody, and the rituximab-pvvr drug product, Ruxience, has been developed as a proposed biosimilar to US-licensed Rituxan.

Rituximab-pvvr binds to CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, and malignant B cells. Upon binding to CD20, rituximab-pvvr mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC), signaling induced cell death (apoptosis), and antibody dependent cellular phagocytosis (ADCP), which are applicable to mechanisms of action of rituximab in B cell malignancies and in autoimmune diseases.

The rituximab-pvvr molecule is constructed as a chimera of mouse variable regions binding human CD20 on framework and constant regions of human IgG1, and has one N-linked glycosylation site on each heavy chain CH2 domain. The Fc regions of the heavy chains retain Fc effector functions important in the mechanism of action of rituximab.

Rituximab-pvvr is produced in genetically engineered CHO (b) (4) cells. Rituximab-pvvr drug product, Ruxience, is manufactured to the same concentration and presentation, but uses different formulation excipients than those used for US-licensed Rituxan. Ruxience is a sterile, preservative-free, clear to slightly opalescent, colorless to pale brownish-yellow solution for intravenous (IV) infusion and supplied in single-dose vials containing PF-05280586 at 100 mg/10 mL or 500 mg/50 mL.

Fill size and dosage forms:

- 100 mg/10 mL (10 mg/mL concentration), single-dose vial, injection
- 500 mg/50 mL (10 mg/mL concentration), single-dose vial, injection

Dating period:

- 100 mg/10 mL Drug Product: 24 months when stored at 2-8 °C
- 500 mg/50 mL Drug Product: 24 months when stored at 2-8 °C
- Drug Substance (b) (4) months when stored at (b) (4) °C

The OPQ (Office of Pharmaceutical Quality) review of manufacturing has determined that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing as submitted in the BLA submission are sufficient to assure a consistent and safe product. The drug substance manufacturing process is robust for inactivation and removal of adventitious agents.

Conclusion: OPQ recommends approval of BLA 761103 for Ruxience manufactured by Pfizer, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of Ruxience is well-controlled and leads to a product that is pure and potent. The comparative analytical assessment as presented in the BLA supports that:

- The biological product, rituximab-pvvr, 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 support the relevance of data generated using the EU-approved MabThera to the assessment of biosimilarity.
- 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 requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act to demonstrate that the “strength” of the proposed biosimilar product is the same as the reference product.

- Highly Similar Determination

To support a demonstration that Ruxience (PF-05280586) is highly similar to US-licensed Rituxan, and to establish the analytical portion of the scientific bridge, Pfizer performed a comparative analytical assessment using up to 15 independent drug substance and drug product lots of PF-05280586, up to 55 lots of US-licensed Rituxan, and up to 65 lots of EU-approved MabThera. Molecular attributes of the product are each assigned to risk categories based on potential impact to safety, efficacy, PK/PD, and immunogenicity. Attribute similarity was evaluated using statistical methods proposed by the Applicant, which were appropriately justified (Table 1 of CMC ATL review). CDC, ADCC, apoptosis, and binding to CD20 activities reflect the mechanism of action for rituximab and were classified as “Tier 1” quality attributes to be comparatively evaluated using statistical equivalence testing. The similarity data package (analytical data provided in the original submission and in response to information requests) was generated using methods that are appropriately validated or qualified for their intended purpose.

OBP and CMC statistics reviewed and analyzed the comparative analytical data for four quality attributes: CDC, ADCC, CD20, and apoptosis. Assuming that sample handling does not affect quality attributes, FDA analysis of the data show that equivalence criteria were met and these results support a demonstration that PF-05280586 is highly similar to US-licensed Rituxan.

The strength of US-licensed Rituxan is labeled in mass per unit volume (mg/mL). US-licensed Rituxan is filled into vials with volumes of 100 mg in 10 mL and 500 mg in 50 mL. Ruxience is seeking approval for the same strength as US-licensed Rituxan.

Comparative protein concentration (mg/mL), reviewed as part of the analytical similarity assessment, and extractable volume and fill weight data (b) (4) were used to inform the assessment of whether the proposed presentation of Ruxience has the same strength as the presentation of US-licensed Rituxan. Based on the similarity and manufacturing data, the 100 mg/10 mL and 500 mg/50 mL of Ruxience vial presentations have the same total content of drug substance in units of mass in a container and the same concentration of drug substance in units of mass per unit volume as the respective presentations of US-licensed Rituxan. The strength(s) proposed for Ruxience, 100 mg/10 mL (10 mg/mL) and 500 mg/50 mL, meet the requirement under section 351(k)(2)(A)(i)(IV) of the PHS Act to demonstrate that the “strength” of the proposed biosimilar product is the same as the reference product.

- Facilities review/inspection

During the review cycle, a Pre-License Inspection (PLI) of (b) (4) was conducted from (b) (4) by OPQ/OFP/DIA and OPQ/OBP. This inspection covered the drug substance manufacturing and the testing laboratories. A FDA 483 with four observations was issued at the completion of the inspection. The inspection was classified as voluntary action indicated (VAI). In the firm’s written response, the firm has committed to taking appropriate corrective actions to address the deficiencies, and FDA found the response to be adequate. OPF/DIA recommends an approval of the (b) (4) drug substance facility regarding BLA 761103.

Analytical similarity data of this BLA was inspected as part of inspection of Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC (Andover, MA) which was conducted from January 14 to 18, 2019 by ORA and OPQ/OBP. There was a two-item FDA Form 483 issued at the conclusion of the inspection and the inspection was classified as VAI. In the firm’s written response, the firm has committed to taking appropriate corrective actions to address the deficiencies, and the responses are adequate.

- Other notable issues: Immunogenicity Assays

The immunogenicity assay review identified that the measurement of anti-drug antibodies (ADA) in the clinical study samples from Studies B3281001 and B3281004 (in subjects with RA) was not performed adequately. Additionally, the ADA assays have insufficient drug tolerance to assure sensitive detection of ADA in clinical samples collected during the dosing period of Study B3281006 (subjects with LTBF). The neutralizing antibody (NAb) assay used also has insufficient assay sensitivity to assure detection of neutralizing antibodies that may be present in clinical samples.

CDTL Comment: Refer to OBP’s immunogenicity assay review memo for more details on the assay validation issues affecting the reliability of ADA results for Studies B3281001 and B3281004 identified during the review. Because the clinical pharmacology review team concluded that the immunogenicity data from studies B3281001 and B3281004 were not helpful for assessment of comparative

immunogenicity, comparative immunogenicity data from Study B3281006 was considered. Because the OBP Immunogenicity assay review noted assay drug tolerance issues during the dosing period for Study B3281006, data from samples collected after the final dose where drug concentrations were at or below the assay drug tolerance level were reviewed. See Section 8 (Safety) of this memo for a discussion of the immunogenicity assessment between PF-05280586 and US-licensed Rituxan.

4. Clinical Microbiology

Not applicable

5. Nonclinical Pharmacology and Toxicology

Source: Pharmacology/ Toxicology Review

Pharmacology/Toxicology Team Recommendation: Approval

PF-05280586 is a genetically engineered chimeric mouse/human immunoglobulin G1kappa (IgG1k) monoclonal antibodies directed against the CD20 antigen with the intended effect of depleting B cells. CD20 is a 32-kDa, non-glycosylated transmembrane phosphoprotein, located on the surface of normal precursor-B cells, mature B lymphocytes and malignant B cells but it is not located on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal cells. CD20 does not internalize upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, consequently, does not compete for antibody binding. Upon binding, PF-05280586 initiates multiple immune effector functions including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC) leading to target cell lysis.

Pfizer conducted a GLP-compliant comparative nonclinical single-dose toxicokinetic and tolerability study and a GLP-compliant 4-week toxicity and toxicokinetic study in cynomolgus monkeys that included a comparison of the potential toxicity, local tolerance, hematology and immunophenotyping assessment of absolute lymphocyte counts and B cells as PD biomarker, PK/TK, and immunogenicity of PF-05280586 and EU-approved MabThera. The studies compared the effects of PF-05280586 to EU-approved MabThera, but not US-licensed Rituxan because, according to Pfizer, the physicochemical and functional data showed that PF-05280586, US-licensed Rituxan, and EU-approved MabThera were all similar to each other in the in vitro assays that evaluated biological activity and Fc-based functionality. PF-05280586 and EU-approved MabThera were administered by the IV route because it is consistent with the clinical route of administration. PF-05280586 and EU-approved MabThera produced similar PD effects and safety data in both toxicity and toxicokinetic studies in monkeys. No biologically-relevant or systemic exposure differences occurred between test articles. In addition, the in vitro pharmacology of PF-05280586, as compared to US-licensed Rituxan and EU-approved MabThera, was assessed with respect to its Fab and Fc-based functionality in several functional and binding assays (see product quality review). In vivo primary and secondary PD studies were not conducted.

Pharmacology/Toxicology Review Team Conclusion: From the perspective of nonclinical pharmacology and toxicology, the data support a demonstration of biosimilarity to US-licensed Rituxan.

CDTL Comment: The primary role of nonclinical studies was to support initiation of clinical studies with PF-05280586.

6. Clinical Pharmacology

Source: Clinical Pharmacology Review

Clinical Pharmacology Team Recommendation: Approval

The clinical development program for PF-05280586 included 3 clinical studies: B3281001, B3281006, and B3281004.

- Pharmacokinetic (PK) similarity of PF-05280586 to US-licensed Rituxan was evaluated in a randomized, double-blind, parallel-group study to compare the PK, safety, pharmacodynamics (PD), clinical response endpoints, and immunogenicity of PF-05280586, US-licensed Rituxan, and EU-approved MabThera following IV infusion of 1000 mg on Days 1 and 15 in patients with active RA (n=220, Study B3281001).
- PF-05280586 and EU-approved MabThera were evaluated in a randomized, double-blind, comparative study to compare the efficacy, safety, immunogenicity, PK, and PD of PF-05280586 and EU-approved MabThera following IV infusion of 375 mg/m² of body surface area (BSA) on Days 1, 8, 15, 22 in patients with CD20+ low tumor burden follicular lymphoma (LTBFL) (n=394, Study B3281006).
- An extension study, Study B3281004, was conducted in patients with active RA who had participated in Study B3281001 to evaluate the efficacy, safety, tolerability, immunogenicity, PK, and PD of PF-05280586, US-licensed Rituxan, and EU-approved MabThera.

The clinical pharmacology review focuses only on the PK similarity study (B3281001) and the PK and immunogenicity data from Study B3281006.

Pharmacokinetic similarity was demonstrated between PF-05280586 and US-licensed Rituxan in Study B3281001; the 90% confidence interval (CI) for the geometric mean ratios (GMR) of PF-05280586 to US-licensed Rituxan, PF-05280586 to EU-approved MabThera, and EU-approved MabThera to US-licensed Rituxan for AUC_{0-inf}, AUC_{0-t}, and AUC_{0-2wk} were all within the PK similarity acceptance criteria of 80 to 125% (Table 1 of clinical pharmacology review). The results from the study also established the PK portion of the scientific bridge between PF-05280586, US-licensed Rituxan, and EU-approved MabThera, which supports the relevance of data generated from studies using EU-approved MabThera as the comparator to the assessment of biosimilarity. In the comparative clinical study B3281006, serum concentrations of PF-

05280586 and EU-approved MabThera were comparable up to Week 52 (end of study) in patients with CD20+ LTBFL.

Immunogenicity of PF-05280586 and EU-approved MabThera was compared in Study B3281006. Assay drug tolerance issues resulted in limited sensitivity to detect ADAs in clinical samples collected during the dosing period. Therefore, immunogenicity was assessed using data from samples collected after the final dose where drug concentrations were at or below the assays drug tolerance level. The overall incidence of immunogenicity at Week 52 (end of study) was comparable between PF-05280586 and EU-approved MabThera (at Week 52: percentage of anti-drug antibody positive (ADA+) patients was 21.5% and 20.4% in the PF-05280586 and EU-approved MabThera groups, respectively). An impact of ADA on the PK of PF-05280586 and EU-approved MabThera was observed with lower serum concentrations of study drug in ADA+ patients when compared to ADA- patients; however, there was no apparent difference in the PK among the treatment groups in ADA+ patients. No apparent impact of ADA was observed on efficacy and safety in patients with CD20+ LTBFL.

Clinical Pharmacology Conclusion: The Office of Clinical Pharmacology has determined that the PK and immunogenicity results support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan, and add to the totality of the evidence to support a demonstration of biosimilarity between PF-05280586 and US-licensed Rituxan.

7. Clinical/Statistical- Efficacy

Source: DPARP Division Memo and DHP clinical/statistical review

DHP Clinical/Statistical Recommendation: Approval

DPARP Clinical/Statistical Recommendation: Approval

DPARP Clinical/Statistical Review

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 in the context of a 351(k) program, 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 response outcomes (refer to Section 5 of the DPARP Division Memo). In considering whether the observed differences between the treatment groups represent clinically 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, as well as to establish the PK portion of the scientific bridge, between PF-05280586, US-licensed Rituxan, and EU-approved MabThera. Secondary objectives included: PK/PD modeling approaches to

integrate PK and PD data, to assess additional clinical response and health outcome endpoints. Study B3281001 was not designed for formal (i.e., statistical) comparative evaluation of efficacy. The data on selected disease activity measure were collected as secondary endpoints and descriptive statistics, limiting conclusions based on statistical considerations from this study.

- **Sample size:** Related to 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 similarity with respect to clinical efficacy using a pre-specified similarity margin in studies in subjects with RA (range of 200 to 300 subjects per arm), which also limits the clinical efficacy statistical conclusions from this study.
- **Baseline Differences:** Notable differences in baseline disease characteristics were seen between the treatment arms (refer to Table 6 of DPARP Division Memo). 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 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 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 outcome versus others, despite similar concepts captured by these outcome measures. For example, using DAS28-CRP as a 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 variability of the outcome used.
- **Further, clinical endpoints used in Study B3281001 are not sufficiently sensitive, in the context of this PK study design, to detect clinically meaningful differences even across products with different mechanisms of action,⁴ or significant differences in dosing and exposure.⁵**

Based on the above considerations, the differences in clinical efficacy observed in Study B3281001 in subjects with RA, when taken together with the demonstration of analytical and PK similarity between PF-05280586, US-licensed Rituxan, and EU-approved MabThera, and the similarity in clinical efficacy in the comparative clinical Study B3281006 in LTBFL, do not

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

preclude a demonstration of no clinically meaningful differences between PF-05280586, and US-licensed Rituxan.

DHP Clinical/Statistical Review

Efficacy was evaluated based on overall response rate (ORR) in Study B3281006, a randomized, double-blind comparative clinical study evaluating 4 weekly doses of PF-05280586 vs. EU-approved MabThera in patients with previously untreated, low tumor burden follicular lymphoma (LTBFL). The primary endpoint was ORR per central review at week 26, with a prespecified similarity margin of (-16%, 16%). Secondary efficacy endpoints, which included progression-free survival (PFS) and duration of response (DOR), did not have prespecified margins.

In the PF-05280586 arm (N = 196), ORR was 76% (90% CI: 70, 81) with a CR rate of 26%; in the EU-MabThera arm (N = 198), ORR was 71% (90% CI: 65, 76) with a CR rate of 29%. The difference in ORR (PF-05280586 minus EU-MabThera) was 4.66% (90% CI: -2.73%, 12.07%) and thus was within the prespecified similarity margin. The hazard ratios (HRs) for the secondary endpoints of progression-free survival (PFS) and duration of response (DOR) favored the EU-MabThera arm at 1.39 and 1.49, respectively. However, the confidence intervals were broad (data not shown; refer to the Primary Clinical and Statistical review dated 3/28/19), and, as stated above, the study was not designed to demonstrate equivalence in the secondary efficacy endpoints.

The application provides sufficient evidence of no clinically meaningful differences with respect to efficacy between PF-05280586 and US-licensed Rituxan in patients with follicular lymphoma, and supports licensure of PF-05280586 for the same hematologic malignancies indications as US-licensed Rituxan, which include B-cell non-Hodgkin lymphomas (NHLs) and chronic lymphocytic leukemia (CLL).

***CDTL Comment:** The relevance of clinical data generated using EU-MabThera in the comparative clinical study in LTBFL (Study B3281006) to the assessment of biosimilarity is justified because a scientific bridge was established between US-licensed Rituxan, EU-approved MabThera, and the proposed biosimilar PF-05280586. An adequate scientific bridge was established based on analytical and pharmacokinetic comparisons between PF-05280586 and US-licensed Rituxan, PF-05280586 and EU-approved MabThera, and EU-approved MabThera and US-licensed Rituxan.*

8. Safety

Source: DPARP Division Memo and DHP clinical/statistical review

DHP Clinical Recommendation: Approval

DPARP Clinical Recommendation: Approval

DPARP Safety Review

The comparative safety data in subjects with RA from 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 LTBFL). The safety database included in the application 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. Additionally, the types of AEs were similar to the known safety profile of US-licensed Rituxan. The safety data generated from the studies in patients with RA support the demonstration that there are no clinically meaningful differences between PF-05280586 and US-licensed Rituxan. 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 as compared to patients who continued on their original treatment. 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 a single transition from US-licensed Rituxan or EU-approved MabThera to PF-05280586 is low, because the differences between PF-05280586 and US-licensed Rituxan and EU-approved 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 (subjects with LTBF), and the comparative safety in Study B3281004, including the safety after patients who 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.

DHP Safety Review

The safety analysis considered all-causality treatment-emergent adverse events (TEAEs) in recipients of any study drug in Study B3281006. The Applicant used the full 52-week study period for safety reporting and analyses. Two clinical study reports and sets of data were submitted, encompassing the 26-week and 52-week analyses.

Baseline demographic and disease characteristics were similar between treatment arms. The number of patients exposed to study treatment was sufficient for safety review. Of the 393 patients with LTBF treated on Study B3281006, $\geq 99\%$ received the planned 4 doses of study treatment.

In Study B3281006, the safety profile of PF-05280586 was similar to that of EU-approved MabThera, with no notable differences between treatment arms.

CDTL Comment: Review of immunogenicity data and cross-analyses with clinical data showed no notable differences in immunogenicity profiles between PF-0520586 and EU-approved MabThera. At Week 52, ADA formation was 21.5% in the PF-05280586 group and 20.4% in the EU-approved MabThera group in Study B3281006 (described in Section 6 of this review), thus demonstrating that the population studied in B3281006 was a sensitive population to assess for differences in immunogenicity. As discussed above (Section 7 of this review), use of EU-approved MabThera is acceptable because the Applicant provided sufficient data to establish the scientific bridge. Although the product quality team noted issues with the sensitivity of the immunogenicity

assays to detect ADAs in clinical samples taken during the dosing period (Section 3 of this review), comparative immunogenicity assessed at timepoints following the dosing period show that ADA incidence is comparable between PF-05280586 and EU-approved MabThera in Study B3281006. To address the NAb assay sensitivity issue, the Applicant submitted adequate justification, which included discussion of results from Studies B3281001 and B3281006. The Applicant stated that the results from these studies do not indicate a decrease in treatment response over time, as would be expected if neutralizing ADAs were present at a level of clinical significance. Based on totality of information submitted by the Applicant, FDA agrees with the Applicant's justification in this case and concludes that additional evaluation of neutralizing ADAs is not necessary to further inform on the immunogenicity assessment of PF-05280586.

9. Considerations for Extrapolation of Biosimilarity

The Applicant submitted the following scientific justifications (Section 2.5.6.3 of Clinical Overview in BLA) for extrapolation of data and information to support licensure of PF-05280586 (code name for Ruxience [rituximab-pvvr]) as a biosimilar to US-licensed Rituxan for the following indications previously licensed for US-licensed Rituxan: Non-Hodgkn Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), and Granulomatosis with Polyangiitis and Microscopic Polyangiitis (GPA/MPA).

- The mechanisms of action of rituximab include antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, apoptosis, and antibody-dependent cellular phagocytosis. Based on information in published literature, the relevant target molecule (CD20) for each of these mechanisms of action is the same across all indications for which US-licensed Rituxan is approved, including NHL, CLL, and GPA/MPA. Comparative analytical data provided by the Applicant support that PF-05280586 has the same mechanism(s) of action as US-licensed Rituxan. The foregoing supports the extrapolation of data and information to the indications for which the Applicant is seeking licensure (*i.e.*, CLL, GPA/MPA, and NHL subtypes such as diffuse large B-cell lymphoma and advanced follicular lymphoma).
- PK similarity was demonstrated between PF-05280586 and US-licensed Rituxan in Study B3281001 in subjects with RA. In Study B3281006, serum concentrations were comparable between PF-05280586 and EU-approved MabThera up to Week 52 (end of study) in patients with CD20+ LTBFL. Conditions which might impact PK are not expected to differ across the indications for which US-licensed Rituxan is approved. Therefore, a similar PK profile would be expected between PF-05280586 and US-licensed Rituxan in indications for which the Applicant is seeking licensure .
- LTBFL is considered a sensitive population for detecting potential differences in immunogenicity following treatment. The clinical immunogenicity results from Study B3281006 in patients with LTBFL support a demonstration that there are no clinically meaningful differences in terms of immunogenicity between PF-05280586 and US-licensed Rituxan. There are no data to suggest that the mechanism of ADA formation differs between LTBFL and other indications for which the Applicant is seeking licensure and for which US-licensed Rituxan is licensed. Therefore, the incidence of

immunogenicity for PF-05280586 would be expected to be similar in each of the indications for which the Applicant is seeking licensure.

- The available safety data of the reference product does not indicate that there are any notable differences in expected toxicities for each condition of use and patient population for which US-licensed Rituxan was previously licensed and for which the Applicant is seeking licensure.

***CDTL Comment:** The Applicant's proposed scientific justifications noted above are sufficient to support extrapolation of data and information in the application to support licensure of PF-05280586 under section 351(k) of the PHS Act for the indications for which the Applicant is seeking licensure.*

10. Advisory Committee Meeting

The Application was not discussed at an Advisory Committee meeting.

11. Pediatrics

The Agency has determined at this time that no pediatric studies will be required under the Pediatric Research Equity Act (PREA) for this BLAs. Refer to memo dated July 22, 2019.

12. Other Relevant Regulatory Issues

- Application Integrity Policy (AIP): No issues.
- Exclusivity or Patent Issues of Concern: Refer to Purple Book at <https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or> for a list of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations.
- Financial Disclosures: In accordance with 21 CFR 54.4, the Applicant submitted the required financial disclosure requirement and certification for clinical studies B3281001, B3281004, and B3281006. The Applicant included details regarding procedures designed to minimize the potential of bias in the data during the conduct of the trials, including processing, analyzing, and reporting the data.
- Other GCP Issues: None
- Office of Scientific Investigation (OSI) Audits: OSI inspected the Applicant for Study B3281006, and final classification is No Action Indicated (NAI). OSI inspected 2 clinical sites for Study B3281001, and the final classification for the 2 clinical sites is No Action Indicated.
- Other outstanding regulatory issues: None

13. Labeling

- Proprietary name: The conditionally accepted proprietary name for PF-05280586 is RUXIENCE. This name was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA) who did not have any concerns that the proposed name is misleading and concluded that it is acceptable.
- Nonproprietary name: Per the FDA’s *Guidance for Industry: Nonproprietary Naming of Biological Products: Update* (March 2019), the nonproprietary name for PF-05280586 should include a distinguishing suffix. The proposed nonproprietary name is “rituximab-pvvr” and is conditionally acceptable.
- All the review teams participated with the labeling discussions and negotiations. The Agency provided labeling recommendations consistent with current FDA labeling practice.

14. Postmarketing Recommendations

Risk Evaluation and Management Strategies (REMS): The review teams did not identify a need for REMS to ensure the safe use of Ruxience.

Postmarketing Requirements (PMRs) and Commitments (PMCs):

Product quality team recommended the following PMC: Re-evaluate the drug product lot release and stability acceptance criteria for the FcγRIIIa reporter gene assay after release data from 30 drug product lots derived from independent drug substance batches are available and with consideration of available stability data. The final report should include the corresponding data, the analysis thereof, and any proposed changes to the drug product release or stability specifications resulting from the assessment.

Refer to action letter for final wording.

15. Recommended Comments to the Applicant

None

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/

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