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APPLICATION NUMBER:

761103Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology
351(k) Biosimilar Review

351(k) BLA Number	761103
Applicant	Pfizer, Inc.
Submission Date	July 25, 2018
Submission Type	Standard
Link to EDR	\\CDSESUB1\evsprod\BLA761103\761103.enx
Brand (Generic) Name	PF-05280586
Dosage Form and Strength	100 mg/10 mL (10 mg/mL) or 500 mg/50 mL (10 mg/mL) solution in a single-dose vial
Route of Administration	Intravenous
Proposed Indication(s)	<ul style="list-style-type: none"> • Non-Hodgkin’s Lymphoma • Chronic Lymphocytic Leukemia • Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies • Granulomatosis with Polyangiitis (Wegener’s Granulomatosis) and Microscopic Polyangiitis in adult patients in combination with glucocorticoids
Associated IND	IND 110426
Reference Product Information (U.S.-licensed)	
Brand (Generic) Name	Rituxan® (Rituximab)
Dosage Form and Strength	100 mg/10 mL and 500 mg/50 mL solution in a single-dose vial
OCP Review Team Signers	
OCP Review Team	Shalini Wickramaratne Senarath Yapa, Ph.D. Anshu Marathe, Ph.D./Salaheldin Hamed, Ph.D.

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1. EXECUTIVE SUMMARY

The Applicant, Pfizer, Inc., submitted this Biologic License Application (BLA) for PF-05280586 under Section 351(k) of the Public Health Service Act (42 U.S.C. 262(k)). PF-05280586 is a proposed biosimilar to the US-licensed Rituxan[®] (BLA 103705, Genentech), which has been licensed in the US since November 1997. The proposed indications for PF-05280586 is for the treatment of adult patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA) in combination with methotrexate (MTX) in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies, and granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids, which are the same as that indicated for US-licensed Rituxan[®].

The clinical development program for PF-05280586 included 3 clinical studies (Studies B3281001, B3281006, B3281004). Pharmacokinetic (PK) similarity of PF-05280586 to US-licensed Rituxan[®] was evaluated in a randomized, double-blind, parallel-group study to determine 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). Therapeutic similarity of PF-05280586 to EU-approved MabThera[®] was evaluated in a randomized, double-blind, comparative study to determine 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 (LTB) follicular lymphoma (FL) (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, since 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). The study also established the PK portion of the scientific bridge between PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®], which supports the use of EU-approved MabThera[®] in the comparative clinical study (Study B3281006). In Study B3281006, serum concentrations appeared to be comparable between PF-05280586 and EU-approved MabThera[®] up to Week 52 (end of study) in patients with CD20+ LTB FL.

Immunogenicity of PF-05280586 and EU-approved MabThera[®] was compared in Study B3281006. 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 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+ LTB FL.

1.1 Recommendations

The Office of Clinical Pharmacology has determined that PK similarity has been demonstrated between PF-05280586 and US-licensed Rituxan[®], and the PK results support a demonstration of no clinically meaningful differences between PF-05280586 and US-licensed Rituxan[®].

Review Issue	Recommendations and Comments
<p align="center">Pivotal evidence of PK similarity</p>	<p>PK similarity was demonstrated between PF-05280586 and US-licensed Rituxan[®]. In addition, the PK portion of the scientific bridge between PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] was also demonstrated. The 90% CI of the GMR for each product pairwise comparison for AUC_{0-inf}, AUC_{0-t}, and AUC_{0-2wk} were within the PK similarity acceptance criteria of 80 to 125% (Table 1)</p>
<p align="center">Evidence of immunogenicity comparability</p>	<p>Results from Study B3281006 indicate comparable incidences of ADA for PF-05280586 and EU-approved MabThera[®]</p>

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Clinical Pharmacology and Pharmacokinetics

PF-05280586 is a proposed biosimilar to US-licensed Rituxan[®] (rituximab), a genetically engineered chimeric murine/human monoclonal IgG₁ kappa antibody directed against the CD20 antigen. The molecular weight of rituximab is approximately 145 kD. Rituximab targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes, and upon binding, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity and antibody dependent cell mediated cytotoxicity (Rituxan[®] USPI). For the clinical pharmacology of US-licensed Rituxan[®] refer to the US product label (Rituxan[®] USPI).

Study B3281001, conducted in 220 patients with active RA, demonstrated that the 90% CI for the GMR of AUC_{0-inf}, AUC_{0-t}, and AUC_{0-2wk} were within the PK similarity acceptance criteria of 80

to 125% for the pairwise comparisons among PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] (Table 1). Since the pairwise comparisons met the PK similarity criteria between PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®], a scientific PK bridge was established to support the relevance of the data generated using EU-approved MabThera[®] in the comparative clinical study (Study B3281006). For details refer to Section 3.2.4.

Table 1: 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-inf}	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-inf}	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-inf}	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: Study B3281001, Clinical Study Report, Summarized data from Table 17, Page 75

In Study B3281006, serum concentrations assessed from Day 1 up to Week 52 (end of study) were overall comparable between the PF-05280586 and EU-approved MabThera[®] treatment groups in patients with CD20+ LTB FL (n=394). For details refer to Sections 3.2.4.

The incidence of immunogenicity at Week 52 (end of study) in patients with CD20+ LTB FL for PF-05280586 and EU-approved MabThera[®] was 21.5% and 20.4%, respectively, and therefore was comparable between the treatment groups (Study B3281006). An impact of ADA on the PK of PF-05280586 and EU-approved MabThera[®] was observed with lower serum concentrations in ADA+ patients 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+ LTB FL.

Overall, the submitted clinical pharmacology data support a demonstration of PK similarity between PF-05280586 and US-licensed Rituxan[®].

2.2 Outstanding Issues

None from a clinical pharmacology perspective.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Regulatory Background

3.1.1 Describe relevant regulatory history for the review of this 351(k) BLA

PF-05280586 is being developed as a proposed biosimilar to US-licensed Rituxan[®]. The Applicant is seeking licensure for the same indications as for US-licensed Rituxan[®], except for the indications protected by orphan designation or other exclusivity status. During the clinical development program for PF-05280586, the Applicant had the following key regulatory interaction with the Agency, a) FDA General Advice (November 3, 2011) to discuss the importance of a 3-arm PK study with PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] to provide bridging data and to discuss the PK, PD, and efficacy endpoints of the study, b) Pre-IND meeting (October 10, 2012) to discuss the clinical data requirements for the different indications, c) BPD Type 3 meeting (August 6, 2014) to seek advice on the data generated and on the design of the comparative clinical ‘Phase 3’ study, d) BPD Type 2 meeting (May 18, 2017) to seek advice on the aspects of the BLA filing strategy and submission format, and e) BPD Type 4 meeting (March 8, 2018) to discuss the proposed content of the planned BLA.

3.2 Clinical Pharmacology Review Questions

3.2.1 What are the design features of the clinical pharmacology and/or clinical studies to support biosimilarity?

The clinical development program for PF-05280586 included three clinical studies (Table 2). Study B3281001 was the pivotal 3-way PK bridging study in patients with active RA. Pharmacokinetic comparison between PF-05280586 and EU-approved MabThera[®] was also assessed in patients with CD20+ LTB FL in the comparative clinical study, Study B3281006. An additional study, Study B3281004, was an extension study for patients with active RA who had participated in Study B3281001 to evaluate the safety, tolerability, immunogenicity, efficacy, PK, and PD of PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®]. The clinical pharmacology review focuses on the pivotal PK similarity study (B3281001) and the PK and immunogenicity from Study B3281006. Refer to the Clinical Review by Dr. Peng for further details on Study B3281004.

Table 2: Summary of Clinical Studies

Study	Design/Objectives	Patient Population	Dosing Regimen
Pivotal Clinical Pharmacology Study			
B3281001 Phase 1/2	3-way PK similarity; Randomized, double-blind, parallel-group, controlled study <u>Primary Objective:</u> To demonstrate PK similarity of PF-	Patients with active RA on a background of MTX who had an inadequate response to 1 or more TNF antagonist therapies PF-05280586, n=73 ^a	1000 mg of PF- 05280586, US- licensed Rituxan [®] , or EU- approved MabThera [®] on

	05280586, US-licensed Rituxan [®] , and EU-approved MabThera [®] <u>Secondary Objectives:</u> PK, PD, safety, tolerability, immunogenicity, clinical response endpoints	US-licensed Rituxan [®] , n=73 ^a EU-approved MabThera [®] , n=74 ^a	Days 1 and 15 via IV infusion
Comparative Clinical Study			
B3281006 Phase 3	Therapeutic similarity; Randomized, double-blind, comparative study <u>Primary Objective:</u> To compare efficacy of PF-05280586 to EU-approved MabThera [®] <u>Secondary Objectives:</u> Safety, immunogenicity, PK, PD	Patients with CD20+ LTB FL in the first-line treatment setting PF-05280586, n=196 ^b EU-approved MabThera [®] , n=198 ^b	375 mg/m ² of BSA of PF-05280586 or EU-approved MabThera [®] on Days 1, 8, 15, 22 (4 weekly doses) via IV infusion
Extension Clinical Study			
B3281004	Extension study for patients who participated in Study B3281001 <u>Objectives:</u> To provide continued treatment access to patients who participated for at least 16 weeks in Study B3281001; safety, tolerability, and immunogenicity of PF-05280586 after transition from a licensed rituximab product to PF-05280586; biomarker and efficacy endpoints	Patients with active RA on a background of MTX who had an inadequate response to 1 or more TNF antagonist therapies when entering Study B3281001 PF-05280586, n=58 ^c US-licensed Rituxan, n=60 ^c EU-approved MabThera, n=65 ^c	Up to 3 courses of treatment Each course: 1000 mg of PF-05280586, US-licensed Rituxan [®] or EU-approved MabThera [®] on Days 1 and 15 of a 24-week course

^a Number of patients randomized

^b Number of patients assigned to study treatment

^c Number of patients treated

Source: Summarized information from the Clinical Study Reports of Studies B3281001, B3281006, and B3281004

3.2.2 What are the endpoints in the clinical pharmacology and/or clinical studies to support biosimilarity?

The following PK parameters, AUC_{0-inf}, AUC_{0-t}, AUC_{0-2wk}, and C_{max}, were assessed in Study B3281001. Pharmacodynamic endpoints, clinical response, safety, and immunogenicity were also evaluated in the study. The pre-specified PK similarity acceptance criteria was that the 90% CI for the GMR of PF-05280586 to US-licensed Rituxan[®], PF-05280586 to EU-approved MabThera[®], and EU-approved MabThera[®] to US-licensed Rituxan[®] fall within 80 to 125% interval for the PK endpoints. The margin proposed by the Applicant was acceptable.

The PK sampling schedule in Study B3281001 was as follows, Day 1 pre-dose (within 1 hour prior to start of infusion), during the infusion (at 3 (± 0.17) hour), immediately prior to the end of infusion (at 4.25 (-0.25) hour), Days 4, and 8, Day 15 within 1.5 hour prior to the start of the second infusion, during the infusion (1.5 (± 0.17) hour), immediately prior to the end of the second infusion (3.25 (-0.25) hour), and Days 18, 22, 29, 57, 85 (Week 12). The PK sampling duration was adequate to characterize the PK in patients with active RA since it was approximately 5 times the mean elimination half-life (range: 424 to 456 hours (17.6-19 days) for PF-05280586, US-licensed Rituxan[®], EU-approved MabThera[®]).

An additional PK analysis (post-hoc) was performed for Study B3281001 to calculate exposure parameters based on concentration-time data from Day 1 up to Week 24. In addition to the aforementioned PK sampling schedule, a single PK sample was collected at the nominal time of Week 24. The following exposure parameters were estimated – $AUC_{t,0-24wk}$, AUC_{0-24wk} , and $AUC_{0-inf, 24wk}$, and the 90% CI for the GMR of PF-05280586 to US-licensed Rituxan[®], PF-05280586 to EU-approved MabThera[®], and EU-approved MabThera[®] to US-licensed Rituxan[®] for the PK parameters were also reported.

B-cell kinetics such as B-cell depletion or recovery are known PD characteristics for US-licensed Rituxan[®]. Circulating CD19+ B-cell counts (a surrogate marker for CD20+ B-cells) versus time profiles in patients with active RA in Study B3281001 is shown in Figure 1. A rapid depletion of CD19+ B-cells was observed following dose administration on Day 1 in the PF-05280586, US-licensed Rituxan[®], EU-approved MabThera[®] groups, and in all treatment groups the CD19+ B-cell counts remained decreased for the duration of the study. Despite these observations, the correlation between B-cell kinetics and efficacy outcomes is known to be inconsistent. Therefore, B-cell kinetic data is considered exploratory and was not used for supporting similarity assessment for PF-05280586 and US-licensed Rituxan[®].

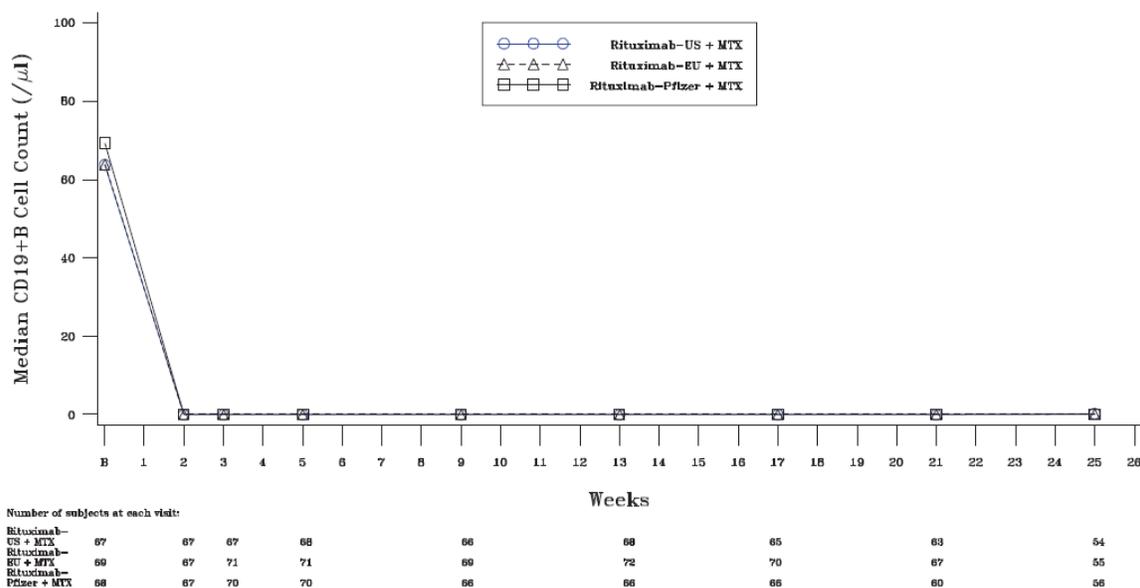


Figure 1: Median CD19+ B-Cell Counts versus Time (mITT Population)

Note: PF-05280586 is reported as rituximab-Pfizer in the Figure

Source: Study B3281001, Clinical Study Report, Figure 4, Page 78

In Study B3281006, the primary efficacy endpoint was overall response rate (ORR) at Week 26 of PF-05280586 versus EU-approved MabThera[®]. Safety, immunogenicity, PK and PD was also evaluated in the study.

3.2.3 Are the pharmacologically active moieties of the proposed biosimilar and the reference product in plasma (or other biological matrix) appropriately identified and measured to assess the PK parameters?

Yes. Concentration of PF-05280586 and rituximab in human serum was measured using a validated enzyme-linked immunosorbent assay (ELISA) method. Refer to Appendix 4.1 for further details.

3.2.4 Is PK similarity met?

Study B3281001 in patients with active RA

Yes, PK similarity between PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] was demonstrated since the 90% CI of the GMR for the PK endpoints (AUC_{0-inf}, AUC_{0-t}, AUC_{0-2wk}) for each product pairwise comparison was contained within the pre-specified PK similarity acceptance criteria of 80 to 125% (Table 1). Mean serum concentration-time profiles are shown in Figure 2 and descriptive statistics for the PK parameters are presented in Table 3. Among the 220 patients randomized in the study, 22 patients were excluded from the Per Protocol (PP) population (population used for analysis). Of these 22 patients, 6 patients were excluded due to medication noncompliance, 7 patients due to visit schedule deviations, and 9 patients due to enrollment at a clinic site at which the validity of study conduct could not be established.

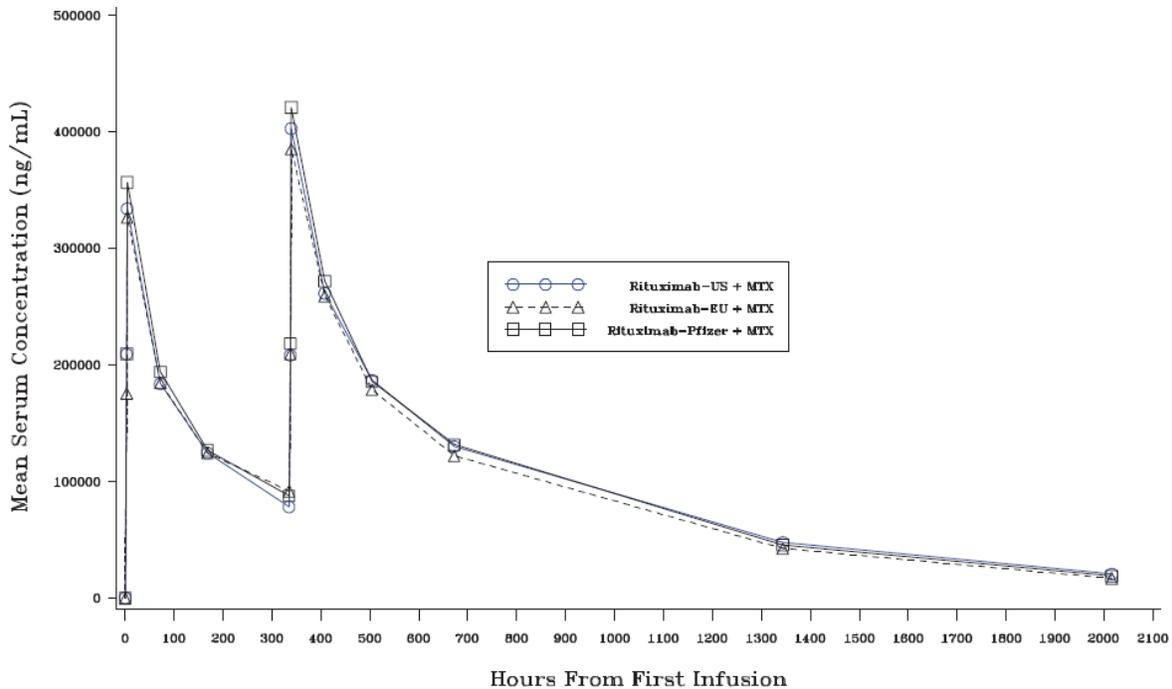


Figure 2: Mean Serum Concentration-Time Profiles for PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] in Patients with Active RA (Study B3281001)

Note: PF-05280586 is reported as rituximab-Pfizer in the Figure

Source: Study B3281001, Clinical Study Report, Figure 14.2.2.1, Page 160

Table 3: Descriptive Statistics for PK Parameter of PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] in Patients with Active RA (Study B3281001)

Parameters	Mean (CV%)		
	PF-05280586 (n=68)	US-licensed Rituxan [®] (n=63)	EU-approved MabThera [®] (n=67)
C _{max} (µg/mL)	453 (33.7)	430 (37.8)	422 (26.3)
AUC _{0-t} (µg·hr/mL)	198,000 (40.2)	196,000 (40.0)	188,000 (34.2)
AUC _{0-inf} (µg·hr/mL)	213,000 (42.4)	214,000 (44.6) ^a	200,000 (37.2)
AUC _{0-2wk} (µg·hr/mL)	52,100 (34.5)	49,200 (32.4)	49,600 (28.6)
CL (mL/hr/kg)	11.2 (44.0)	11.3 (43.3) ^a	11.4 (39.8)
C _{last,Week 12} ^b (µg/mL)	18.9 (78.8)	20.5 (89.5)	16.9 (78.2)
t _{1/2} (hr)	434 (32.6)	456 (31.9) ^a	424 (29.6)

^a n=62 due to one patient missing multiple samples for whom the terminal phase could not be adequately determined

^b n=64, 59, 65 in the PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] treatment groups, respectively

n=number of patients in the treatment group

Source: Study B3281001, Clinical Study Report, Table 16, Table 14.2.1.1, and Table 14.2.1.4, Page 75, 125-126, and 135

Independent analyses on the PP population analysis set were conducted by the reviewer and the 90% CI of the GMR for AUC_{0-inf}, AUC_{0-t}, AUC_{0-2wk}, and C_{max} were within the pre-specified criteria

of 80 to 125% for the pairwise comparisons among PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®]. In addition, analysis conducted including all patients also met the pre-specified acceptance criteria.

For the additional PK analysis (post-hoc), the exposure parameters up to Week 24 are presented in Table 4. The 90% CI of the GMR for AUC_{t,0-24wk}, AUC_{0-24wk}, and AUC_{0-inf, 24wk} for each product pairwise comparison was within the 80 to 125% interval (Table 5).

Table 4: Descriptive Statistics for PK Parameter of PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] up to Week 24 in Patients with Active RA (Study B3281001)

Parameters	Mean (CV%)		
	PF-05280586 (n=68)	US-licensed Rituxan [®] (n=63)	EU-approved MabThera [®] (n=67)
AUC _{t,0-24wk} (μg·hr/mL)	209,000 (42.1)	209,000 (43.0)	198,000 (35.8)
AUC _{0-24wk} (μg·hr/mL)	212,000 (41.9)	212,000 (43.2)	199,000 (35.9)
AUC _{0-inf, 24wk} (μg·hr/mL)	213,000 (42.1)	214,000 (44.0)	200,000 (36.2)
C _{last, Week 24} ^a (μg/mL)	1.37 (129.2)	1.79 (153)	1.15 (132.8)

n=number of patients in the treatment group

AUC_{t,0-24wk}: AUC from time 0 to the last time point of quantifiable drug concentration; AUC_{0-24wk}: AUC within a 24-week period after Day 1 dosing

^a n=56, 54, 55 in the PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] treatment groups, respectively

Source: Study B3281001, Supplemental Clinical Study Report, Table S3 and 14.2.1.1a, Page 16 and 22, and Study B3281001, Clinical Study Report, Table 14.2.1.4, Page 135

Table 5: Additional PK Analysis (Post-Hoc): Summary of Statistical Comparisons of PK Parameters for PF-05280586, US-licensed Rituxan[®], EU-approved MabThera[®] (Study B3281001)

Comparison	PK Parameter	GMR (90% CI)
PF-05280586 vs. US-licensed Rituxan [®]	AUC _{t,0-24wk}	100.45 (89.46, 112.79)
	AUC _{0-24wk}	100.45 (89.45, 112.81)
	AUC _{0-inf, 24wk}	100.21 (89.12, 112.67)
PF-05280586 vs. EU-approved MabThera [®]	AUC _{t,0-24wk}	103.26 (92.13, 115.73)
	AUC _{0-24wk}	104.22 (92.97, 116.83)
	AUC _{0-inf, 24wk}	104.19 (92.83, 116.93)
EU-approved MabThera [®] vs. US-licensed Rituxan [®]	AUC _{t,0-24wk}	97.28 (86.60, 109.27)
	AUC _{0-24wk}	96.39 (85.79, 108.29)
	AUC _{0-inf, 24wk}	96.18 (85.51, 108.19)

Results based on ANOVA model with treatment as a fixed effect

Source: Study B3281001, Supplemental Clinical Study Report, Table S4, Page 16

Study B3281006 in patients with CD20+ LTB FL

In the comparative clinical study, PK of PF-05280586 and EU-approved MabThera[®] was characterized in patients with CD20+ LTB FL. The primary endpoint of this study was efficacy

and PK was a secondary endpoint. The PK sampling schedule was as follows: Days 1, 8, 15, 22, and Weeks 5, 13, 26, 39, and 52; on days where PF-05280586 or EU-approved MabThera[®] were administered (Days 1, 8, 15, 22) samples were collected prior to dose administration (within 4 hours of start of dosing) and on Days 1 and 22 additional samples were collected within 15 minutes prior to end of infusion. Overall, the range of serum concentrations appeared to be comparable between the PF-05280586 and EU-approved MabThera[®] treatment groups in patients with CD20+ LTB FL (Figure 3).

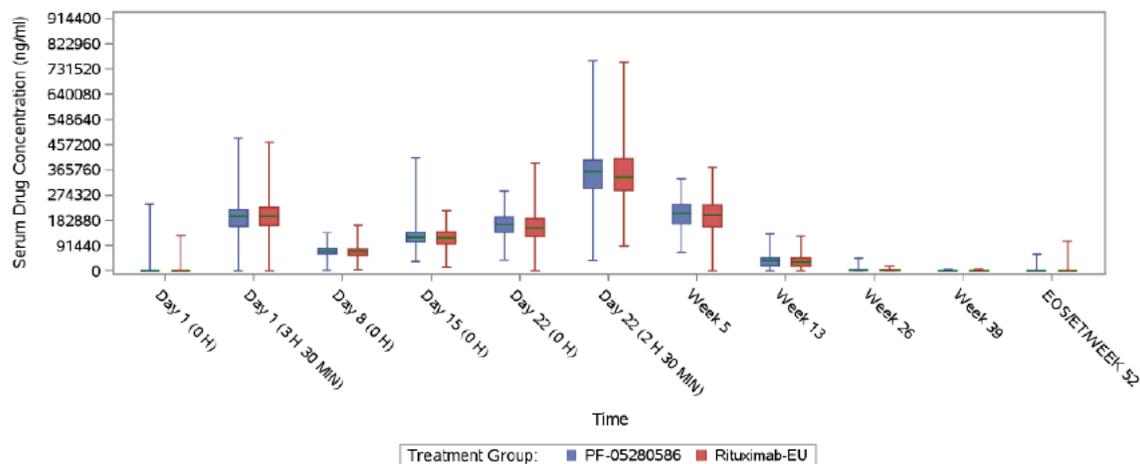


Figure 3: Box Plot of Serum Concentration-Time Profiles for PF-05280586 and EU-approved MabThera[®] in Patients with CD20+ LTB FL (Study B3281006)

Box plot represent median and 25%/75% quartiles

Source: Study B3281006, Clinical Study Report, Figure 8, Page 104

Immunogenicity

3.2.5 Is the immunogenicity assay capable of detecting the antidrug antibodies (ADA) in the presence of concentration of product in the study samples?

Electrochemiluminescence (ECL) assays were used for measurement of ADA in human serum. The Applicant developed two ADA assays, i) ADA against rituximab assay, and ii) ADA against PF-05280586 assay. The ADA assays were adequately validated. Sample analysis of the clinical study samples was performed using the ECL assays with a tiered approach of screening, confirmation, and titer determination. Upon request from the Agency, the clinical study samples from Study B3281006 were reanalyzed using a single ADA assay (anti-PF-05280586 antibody assay). Clinical study samples from Study B3281001 were no longer available, therefore the samples could not be reanalyzed.

For the ADA assay specific for rituximab, the drug tolerance was up to 12.5 µg/mL of dosed product (US-licensed Rituxan[®] or EU-approved MabThera[®]) at 50 ng/mL ADA and up to 50 µg/mL of dosed product (US-licensed Rituxan[®] or EU-approved MabThera[®]) at 400 ng/mL ADA. For the ADA assay specific for PF-05280586, the drug tolerance was up to 25 µg/mL of PF-05280586 at 50 ng/mL ADA and up to 50 µg/mL of PF-05280586 at 400 ng/mL ADA. In Study

B3281006, serum concentrations of PF-05280586 and EU-approved MabThera[®] at Week 26 and 52 (end of study) were below 4 µg/mL and therefore below the drug tolerance of 12.5 µg/mL.

Cell-based assays were used for assessment of the neutralizing capacity of the antibodies (neutralizing antibodies (NAb)) in human serum. Similar to the ADA assay, two NAb assays were developed, i) assay measuring NAb against rituximab, ii) assay measuring NAb against PF-05280586. Both NAb assay validation was not adequate due to poor assay sensitivity. Clinical study samples that were ADA+ were analyzed for the presence or absence of NAb using the cell-based assays with a tiered approach of screening, confirmatory and titer determination. For both NAb assays, the drug tolerance was up to 10 µg/mL of dosed product (PF-05280586 or US-licensed Rituxan[®] or EU-approved MabThera[®]) at 59.3 µg/mL NAb.

Refer to the OBP review by Dr. De Silva for detailed information regarding the ADA and NAb assay validation and analysis of clinical study samples.

3.2.6 Is the sampling plan adequate to capture baseline, early onset, and dynamic profile (transient or persistent) of anti-drug antibodies (ADA) formation?

Yes, the sampling schedules for ADA in Studies B3281001 and B3281006 were adequate to capture baseline, early onset, and dynamic profile of ADA formation. In the PK similarity study in patients with active RA (Study B3281001), blood samples for ADA assessment were collected on Days 1, 15 (both at pre-dose), and at Week 5, 9, 13, and 25. In the comparative clinical study in patients with CD20+ LTB FL (Study B321006), blood samples for ADA assessment were collected on Days 1, 15 (both within 4 hours prior to dose administration) and at Week 5, 13, 26, 39, and 52.

3.2.7 What is the incidence of anti-drug antibodies (ADA)?

In Study B3281006, the incidence of ADAs in patients with CD20+ LTB FL following IV infusion of 375 mg/m² of study drug on Days 1, 8, 15, and 22 is summarized in Table 6. The results show a comparable incidence of ADA between the treatment groups at each visit and at the end of the study (Week 52).

Table 6: Summary of ADA Incidence in Patients with CD20+ LTB FL (Safety Population) (Study B3281006)

	Visit	PF-05280586 (N=196) n/N1 (%)	EU-approved MabThera® (n=197) n/N1 (%)
ADA+	Day 1 (Baseline)	14/195 (7.2%)	18/193 (9.3%)
	Day 8 ^a	0/1	NA
	Day 15	1/192 (0.5%)	0/190
	Day 22 ^b	0/3	0/1
	Week 5	0/192	0/191
	Week 13	2/189 (1.1%)	2/190 (1.1%)
	Week 26	10/184 (5.4%)	10/189 (5.3%)
	Week 39	23/174 (13.2%)	33/174 (19.0%)
	Week 52	35/163 (21.5%)	34/167 (20.4%)

^a Day 8 was an unplanned visit

^b Samples collected prior to protocol amendment 1

N = number of patients in the specified analysis population, N1 = number of patients tested who had an observed result at the specified visit, n = number of patients tested at a given visit with a sample that tested ADA+

Source: BLA MidCycle Meeting Follow-up #2 dated March 28th 2019, Table 1, Page 3 and Study B3281006, Clinical Study Report, Summarized data from Table 19, Page 94

In Study B3281001, the incidence of ADAs at Week 25 (end of study) following IV infusion of 1000 mg of study drug on Days 1 and 15 to patients with active RA was overall comparable among the treatment groups (percentage of ADA+ patients was 11.5%, 10.9%, and 13.8% in the PF-05280586, US-licensed Rituxan®, and EU-approved MabThera® treatment group, respectively). However, the reported incidence of immunogenicity should be interpreted with caution since the measurement of ADA in the clinical study samples was not performed adequately. Refer to Section 3.2.5 and the OBP review by Dr. De Silva for further information regarding the analysis of clinical study samples.

3.2.8 Do the anti-drug antibodies (ADA) have neutralizing activity?

In Studies B3281001 and B3281006, ADA+ samples were analyzed for neutralizing activity and the results showed that none of the samples tested positive for neutralizing activity. These results however should be interpreted with caution since the validation of the NAb assays was not adequate. Refer to Section 3.2.5 and the OBP review by Dr. De Silva for further details.

3.2.9 What is the impact of anti-drug antibodies (ADA) on the PK, activity, and safety of the therapeutic protein?

Impact on PK

The relationship between ADA status and serum concentrations of PF-05280586 and EU-approved MabThera® at Week 26 in patients with CD20+ LTB FL in Study B3281006 is presented in Figure 4. At Week 26, lower serum concentrations were observed in ADA+ patients when compared to ADA- patients in both treatment groups, however in these ADA+ patients, there was no apparent difference in the PK among the treatment groups.

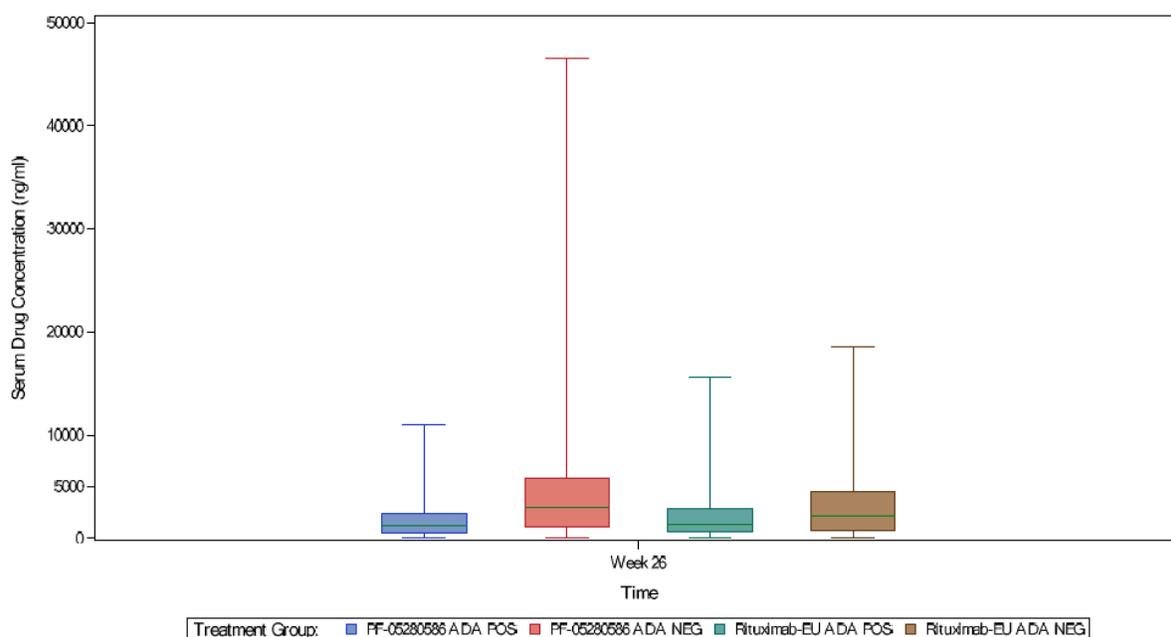


Figure 4: Box plot for serum concentrations of PF-05280586 and EU-approved MabThera® by ADA Status at Week 26 (Study B3281006)

Source: BLA MidCycle Meeting Follow-up #2 dated March 28th 2019, Figure 2, Page 8

Impact on Activity and Safety

The impact of ADA on ORR at Week 26 in patients with CD20+ LTB FL (Study B3281006) is presented in Table 7. No apparent impact of immunogenicity was observed on response rate. However, the impact of immunogenicity on response rate should be interpreted with caution as the number of subjects who developed ADA was low.

Table 7: Summary of ORR at Week 26 by ADA Status (ITT Population; Post-Hoc Subgroup Analysis) (Study B3281006)

	Rituximab-EU (N = 198)	PF-05280586 (N = 196)	Difference (PF-05280586 minus Rituximab-EU)
ADA Pos			
N	8	10	
Overall Response Rate [ORR] (%)	6 (75.0)	9 (90.0)	15.00
95% CI (%)	(34.9, 96.8)	(55.5, 99.7)	(-22.81, 52.84)
ADA Neg			
N	187	185	
Overall Response Rate [ORR] (%)	133 (71.1)	139 (75.1)	4.01
95% CI (%)	(64.1, 77.5)	(68.3, 81.2)	(-5.03, 13.00)

Source: Table 14.2.1.1.5a

Overall Response Rate (ORR) is defined as the proportion of subjects who achieved either complete remission (CR) or partial response (PR).

The Miettinen and Nurminen method (unstratified) is used to obtain the asymptotic 95% confidence interval of the estimated difference (PF-05280586 minus Rituximab-EU).

An ADA Positive subject is one who had at least one positive ADA result (titer ≥ 1.88) post baseline up to and including any sample taken on or before their week 26 visit. Otherwise the subject is considered ADA Negative.

Source: BLA MidCycle Meeting Follow-up #2 dated March 28th 2019, Table 3, Page 10

The impact of ADA on clinical safety in patients with CD20+ LTB FL (Study B3281006) is summarized in Table 8. In ADA+ patients, the incidence of infusion related reactions (IRR) was comparable between the PF-05280586 and EU-approved MabThera® treatment groups. No clinically meaningful differences were observed in IRR between ADA+ versus ADA- patients. The results should be interpreted with caution due to limited number of subjects who developed ADA in the study. Refer to the Clinical review by Dr. Kasamon for further details.

Table 8: Summary of ADA and Infusion Related Reactions (Safety Population) (Study B3281006)

	Infusion Related Reactions	PF-05280586 (N=196) n/N1 (%)	EU-approved MabThera® (N=197) n/N1 (%)
	Total IRR reported	49/196 (25.0%)	59/197 (29.9%)
ADA+		43/195 (22.1%)	45/196 (23.0%)
	IRR reported	11/43 (25.6%)	12/45 (26.7%)
ADA-		152/195 (77.9%)	151/196 (77.0%)
	IRR reported	36/152 (23.7%)	45/151 (29.8%)

N= Number of patients in the specified analysis population; N1 = number of patients in the analysis population (and within the ADA status subgroup where applicable) for the study; n = corresponding number of those patients represented in each denominator with at least 1 specified event during the study

Source: BLA MidCycle Meeting Follow-up #2 dated March 28th 2019, Table 4, Page 12

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 Pharmacokinetics

4.1.1.1 How are the concentrations of the pharmacologically active moieties (parent and/or any relevant catabolites) measured in the plasma and other matrices in the clinical pharmacology studies?

Serum concentrations of rituximab and PF-05280586 were measured using a validated enzyme-linked immunosorbent assay (ELISA) method. The ELISA method for quantification of PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] in human serum was validated at (b) (4) (Original: Pfizer Validation Study No. B3289001, (b) (4) Project No. 15-1132; Addendums: Pfizer Validation Study No. B3289003, (b) (4) Project No. 15-1132 Addendum 1, 2, 3, 4, 5). In brief, the ELISA method procedures are as follows:

In this single ELISA method, licensed rituximab or PF-05280586 is captured onto a microtiter plate coated with a rat anti-rituximab. The bound licensed rituximab or PF-05280586 is detected with the enzyme conjugate, goat anti-human horseradish peroxidase (HRP). TMB (3,3',5,5'-tetramethylbenzidine) is utilized as a substrate for signal generation and colorimetric readout.

A summary of the method performance for the ELISA assay used to measure PF-05280586, US-licensed Rituxan[®], and EU-approved MabThera[®] in human serum is presented in Table 9, and acceptance criteria were met.

Office of Study Integrity and Surveillance (OSIS) inspection was requested for the bioanalytical site and clinical sites for the PK similarity study, Study B3281001. For the bioanalytical site (b) (4), OSIS concluded that the data from Study B3281001 was reliable for further Agency review (refer to OSIS memorandum by Dr. Lewin dated February 15, 2019). For the clinical sites, OSIS concluded that the clinical data from the audited studies are reliable for further Agency review (refer OSIS memorandum by Dr. Mahadevan dated March 1, 2019).

Analysis of the PK samples from Studies B3281001 and B3281006 were performed using four quality control (QC) samples; the accuracy and precision of the QC samples in both studies were within the acceptance criteria. Pharmacokinetic samples from Studies B321001 and B3281006 were re-analyzed as part of the incurred sample reproducibility assessment, and results of the incurred sample reanalysis met the acceptance criteria. All PK samples for Studies B3281001 and B3261006 were analyzed within the established stability periods.

Table 9: Summary of method performance for the ELISA assay used to measure rituximab and PF-05280586 in human serum

Bioanalytical method validation report and amendments	The Validation of an Enzyme-Linked Immunosorbent Assay Method for the Determination of Rituximab and Rituximab-Pfizer (PF-05280586) in Human Serum (B3289001, Addendum 1 and 2 issued under B3289003)		
Method description	In this single PK ELISA method, licensed rituximab or PF-05280586 is captured onto a microtiter plate coated with a rat anti-rituximab. The bound licensed rituximab or PF-05280586 is detected with the enzyme conjugate, goat anti-human horseradish peroxidase (HRP). TMB (3,3',5,5'-tetramethylbenzidine) is utilized as a substrate for signal generation and colorimetric readout. Sample concentrations are determined by interpolation from a calibration curve that has been fit using a 4-parameter logistic regression with the weighting factor as 1.		
Materials used for calibration curve & concentration	MabThera [®] (Rituximab-EU)		
Validated assay range	LLOQ 100 ng/mL to ULOQ 5000 ng/mL		
Material used for QCs & concentration	Rituximab-EU (MabThera [®]), Lot #: H0029B01, 10.0 mg/mL Rituximab-US (Rituxan [®]), Lot#: 911829, 10.0 mg/mL Rituximab-Pfizer (PF-05280586), Lot #: 87201, 110.2 mg/mL		
Minimum required dilutions (MRDs)	1:200		
Source & lot of reagents (LBA)	Capture Reagent: Rat Anti-Rituximab, Lot # 140711, Concentration ~0.5 µg/mL Sourced from (b) (4) Detecting Reagent : Goat anti-Human IgG HRP, monkey adsorbed Lot # A80-319P-14, Dilution factor used in the assay~1:50,000, Sourced from (b) (4)		
Regression model & weighting	4-parameter logistic regression with the weighting factor as 1		
Validation parameters	Method validation summary		Source location
Calibration curve performance during accuracy & precision Per BMV, At least 75% and minimum of 6 non-zero calibrators without anchor points and LBA: ±20% bias (±25% at LLOQ), ≤20%CV	No of standard calibrators from LLOQ to ULOQ	8	Table 3A/3B of B3289001
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-2.9 to 3.50 %	Table 3A/3B of B3289001
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ 7.4%	Table 3A/3B of B3289001

QCs performance during accuracy & precision for Rituximab-EU Per BMV, LBA QCs: $\pm 20\%$ bias ($\pm 25\%$ at LLOQ), $\leq 20\%$ CV and $\leq 30\%$ total	EU Cumulative accuracy (%bias) in 5 QCs VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	-8.8 to -1.6 %	Table 4A of B3289001
	Inter-batch %CV QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 9.5\%$	Table 4A of B3289001
	Total error QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 14.7\%$	Table 4A of B3289001
QCs performance during accuracy & precision for Rituximab-US Per BMV, LBA QCs: $\pm 20\%$ bias ($\pm 25\%$ at LLOQ), $\leq 20\%$ CV and $\leq 30\%$ total	US-Cumulative accuracy (%bias) in 5 QCs VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	-5.3 to 5.6 %	Table 4A of B3289001
	Inter-batch %CV QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 10.7\%$	Table 4A of B3289001
	Total error QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 16.3\%$	Table 4A of B3289001
error ($\leq 40\%$ at LLOQ)	Total error QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 16.3\%$	Table 4A of B3289001
QCs performance during accuracy & precision for PF-05280586 Per BMV, LBA QCs: $\pm 20\%$ bias ($\pm 25\%$ at LLOQ), $\leq 20\%$ CV and $\leq 30\%$ total error ($\leq 40\%$ at LLOQ)	PF-05280586-Cumulative accuracy (%bias) in 5 QCs VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	-16.3 to -9.0%	Table 4B of B3289001
	Inter-batch %CV QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 11.9\%$	Table 4B of B3289001
	Total error QCs: VSLLOQ 100 ng/mL, VSL 300 ng/mL, VSM 1500 ng/mL, VSH 4000 ng/mL and VSULOQ 5000 ng/mL	$\leq 25.8\%$	Table 4B of B3289001

Selectivity & matrix effect	<p>Matrix Effect/Selectivity Evaluation: All met criteria</p> <p>10 lots Normal human Serum: 10/10 passed for EU (83.3-119.3%), 10/10 passed for US (86.3-113.3%) and 8/10 passed for PF-05280586 (83.5-113.3%)</p> <p>10 lots of Solid Tumor 10/10 passed for EU (90.3-115.7%), 10/10 passed for US (81.3-115.0%) and 10/10 passed PF-05280586 (88.0-111.0%)</p> <p>20 lots of Rheumatoid Arthritis: 17/20 passed for EU (87.7-115.7%), 19/20 passed for US (81.8-118.7%) and 19/20 passed for PF-05280586 (80.7-112.3.0%)</p>	Table 6A/6B of B3289001
Interference & specificity	<p>Interference of ADA tested using Positive Control (PC), an affinity purified rabbit anti- Rituximab polyclonal antibody, tested at 0. 05, 1, 2.5, 5 and 10 ug/mL of PC levels</p> <p>No ADA interference was observed for VSH 4000 ng/mL of EU, US and PF-05280586</p> <p>Interference to VSL 300 ng/mL was not observed in Rituximab-EU: up to 0.5 µg/mL of PC Rituximab-US: up to 1.0 µg/mL of PC PF-05280586: up to 1.0 µg/mL of PC</p>	Table 8A/8B of B3289001
Hemolysis effect	<p>6 lots of Hemolysis matrix (2 low, 2 medium and 2 high level of hemoglobin levels) tested: 6/6 passed for EU (% difference ranged -11.0 to 15.5%) 6/6 passed for PF-05280586 (% difference ranged -11.0 to 7.8%)</p>	Table 3 of B3289003, Addendum 2
Lipemic effect	<p>6 lots of hyperLipemic matrix (2 low, 2 medium and 2 high level of lipid levels) tested: 3/6 passed for EU (% difference ranged -9.3 to 19.3%), one lot from each level observed over-recovery 4/6 passed for PF-05280586 (% difference ranged -7.0 to 10.8%), one lot observed over recovery at LQC level, one lot Not reportable</p>	Table 3 of B3289003, Addendum 2
Dilution linearity & hook effect	<p>Rituximab-EU, Rituximab-US and PF-05280586 tested dilution linearity 1x and 10x dilution tested with ALQ shown no Hook Effect Linearity shown at 125x, 500 x and 2000x dilution</p>	Table 7 of B3289001
Bench-top/process stability	<p>18 hour Ambient Temperature Matrix Stability for Rituximab-EU and PF-05280586</p>	Table 9 of B3289001
Freeze-Thaw stability	<p>At least 5 Cycles at -20 °C for Rituximab-EU and PF-05280586 At least 5 Cycles at -70 °C for Rituximab-EU and PF-05280586</p>	Table 10 of B3289001
Long-term storage	<p>Rituximab-EU: 741 days at -20 °C / at -70 °C PF-05280586: 741 days at -20 °C / at -70 °C</p>	Table 2 of B3289003, Addendum 2
Parallelism	<p>Parallelism is currently planned at bioanalytical lab and results will be shared with the agency by Dec 21st 2018 or earlier.</p>	
Carry over	<p>NA</p>	

Abbreviations: ADA = anti-drug antibody; ALQ= Above Limit of Quantification); CV = coefficient of variation; ELISA = Enzyme-Linked Immunosorbent Assay; EU = European Union; IgG = immunoglobulin G; LLOQ = lower limit of quantification; PC = Positive Control; US = United States, ULOQ =Upper limit of quantification, VS = Validation sample; VSL = Validation Sample; VSLLOQ = Validation sample lower limit of quantification; VSH = Validation sample High; VSM = Validation sample Medium; VSULOQ= Validation samples upper limit of quantification

Additional validation runs:

- **Selectivity & Matrix Effect:** 10 lots of non-Hodgkin's lymphoma human serum: 8/10 passed for PF-05280586 (91.0-108.3%)
- **Bench-Top/Process Stability:** 18 hours at room temperature matrix stability for rituximab-US
- **Freeze-Thaw Stability:** At least 5 cycles at -20°C for rituximab-US and at least 5 cycles at -70°C for rituximab-US
- **Parallelism:** Parallelism established, all tested incurred samples met acceptance criteria

Note: For 'Interference & Specificity' it should read "tested at 0, 0.5, 1, 2.5, 5, 10 µg/mL of PC levels".

Source: Response to the FDA Information Request dated 20 November 2018, Table 1, Page 1-4

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