

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761103Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 30, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761103
Product Name and Strength: Ruxience (rituximab-pvvr) Injection
100 mg/mL and 500 mg/mL (10 mg/mL)
Applicant/Sponsor Name: Pfizer, Inc. (Pfizer)
FDA Received Date: May 10, 2019
OSE RCM #: 2018-1602-2
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Ruxience (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant submitted revised container labels and carton labeling received on May 10, 2019 for Ruxience. The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Garrison N. Label and Labeling Review for RUXIENCE (BLA 761103). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 25. RCM No.: 2018-1602-1.

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/s/

NICOLE B GARRISON
05/30/2019 09:30:49 AM

HINA S MEHTA
05/30/2019 11:32:42 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 25, 2019
Requesting Office or Division: Division of Hematology Products (DHP)
Application Type and Number: BLA 761103
Product Name and Strength: Ruxience (rituximab-pvvr) Injection
100 mg/mL and 500 mg/mL (10 mg/mL)
Applicant/Sponsor Name: Pfizer, Inc. (Pfizer)
FDA Received Date: April 11, 2019
OSE RCM #: 2018-1602-1
DMEPA Safety Evaluator: Nicole Garrison, PharmD, BCPS
DMEPA Team Leader: Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

Division of Hematology Products (DHP) requested that we review the revised container labels and carton labeling for Ruxience (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and carton labeling are unacceptable from a medication error perspective. The Medication Guide Statement on the revised container labels and carton labeling do not indicate how the Medication Guide shall be provided to the patient. In addition, the presentation of the nonproprietary name should be revised to the conditionally acceptable nonproprietary name rituximab-pvvr.

3 RECOMMENDATIONS FOR PFIZER

^a Garrison N. Label and Labeling Review for Ruxience (BLA 761103). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 02. RCM No.: 2018-1602-1.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container labels & Carton labeling)

1. Revise the presentation of the nonproprietary name from rituximab-xxxx with the conditionally acceptable nonproprietary name rituximab-pvvr.
2. We continue to reiterate that the Medication Guide Statement does not indicate how the authorized dispenser shall provide the Medication Guide to the patient. Please revise the Medication Guide Statement to include how the Medication Guide is provided (e.g., accompanied, enclosed, or provided separately) in accordance with 21 CFR 208.24(d). Consider if the statement "Provide enclosed Medication Guide to each patient" is appropriate.

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NICOLE B GARRISON
04/25/2019 03:48:51 PM

HINA S MEHTA
04/29/2019 07:50:41 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 10, 2019

To: Ann Farrell, MD
Director
Division of Hematology Products (DHP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

From: Susan Redwood, MPH, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Nisha Patel, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): RUXIENCE (rituximab-xxxx)¹

Dosage Form and Route: Pfizer Ireland Pharmaceutical
c/o Pfizer Inc.

Application Type/Number: BLA

Applicant: 761103

¹ At the time of this review, the proposed non-proprietary name has not been determined, and the proposed proprietary name RUXIENCE has been conditionally accepted, until such time that the application is approved.

1 INTRODUCTION

On July 25, 2018, Pfizer Ireland Pharmaceutical, c/o Pfizer Inc., submitted for the Agency's review an original Biologics License Application (BLA) 761103 for RUXIENCE (rituximab-xxxx) injection. RUXIENCE is a proposed biosimilar to the Reference Product RITUXAN (rituximab) injection (BLA 103705). On September 27, 2018, the Division of Medication Error Prevention and Analysis found the proprietary name RUXIENCE conditionally acceptable; however, the non-proprietary name has not been determined at this time.

The Applicant proposes the following indications for RUXIENCE (rituximab-xxxx):

- Non-Hodgkin's Lymphoma (NHL) 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 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) in combination with fludarabine and cyclophosphamide, for the treatment of adult patients with:
- Previously untreated and previously treated CD20-positive CLL. Rheumatoid Arthritis (RA): in combination with methotrexate for the treatment of adult patients with moderately-to severely-active RA who have had an inadequate response to one or more TNF antagonist therapies.
- Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA): in combination with glucocorticoids for the treatment of adult patients with Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematology Products (DHP) on September 21, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for RUXIENCE (rituximab-xxxx) injection.

2 MATERIAL REVIEWED

- Draft RUXIENCE (rituximab-xxxx) injection MG received on July 25, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 4, 2019.
- Draft RUXIENCE (rituximab-xxxx) injection Prescribing Information (PI) received on July 25, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 4, 2019.

- Approved RITUXAN (rituximab) injection Reference Product labeling dated January 25, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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04/10/2019 11:40:37 AM

SHARON R MILLS
04/10/2019 11:46:54 AM

LASHAWN M GRIFFITHS
04/10/2019 11:48:18 AM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: April 5, 2019

To: Jennifer Lee, Regulatory Project Manager
Division of Hematology Products (DHP)

Virginia Kwitkowski, Associate Director for Labeling, DHP

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for RUXIENCE™ (rituximab-xxxx) injection, for intravenous use

BLA: 761103

In response to DHP's consult request dated September 21, 2018, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for RUXIENCE™ (rituximab-xxxx) injection, for intravenous use (Ruxience).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI emailed to OPDP on April 3, 2019. We have no comments on the draft PI at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

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NISHA PATEL
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 2, 2019
Requesting Office or Division:	Division of Hematology Products (DHP)
Application Type and Number:	BLA 761103
Product Name and Strength:	Ruxience (PF-05280586*) Injection 100 mg/mL and 500 mg/mL (10 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Pfizer
FDA Received Date:	July 25, 2018 and March 5, 2019
OSE RCM #:	2018-1602
DMEPA Safety Evaluator:	Nicole Garrison, PharmD, BCPS
DMEPA Team Leader:	Hina Mehta, PharmD

* PF-05280586 has been developed as a proposed biosimilar to US-licensed Rituxan (rituximab). Since the proper name for PF-05280586 has not yet been determined, the developmental code name, either PF-05280586 or the proposed proprietary name (Ruxience), is used throughout this review to refer to this product. The proposed proprietary name and proposed nonproprietary name (rituximab-xxx) are only conditionally accepted for this product until the application is approved.

1 REASON FOR REVIEW

As part of the approval process for BLA 761103 Ruxience (PF-05280586) 100 mg/mL and 500 mg/mL (10 mg/mL), the Division of Hematology Products (DHP) requested that we review the proposed Ruxience Prescribing Information (PI), medication guide, container labels and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

BLA 761103 is a 351(k) BLA and the reference product is US-licensed Rituxan, BLA 103705. US-licensed Rituxan was approved in November 1997 for the treatment of patients with Non-Hodgkin's Lymphoma (NHL). In 2006, Rituxan was approved for the treatment of 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. In 2010, Rituxan was approved for the treatment of Chronic Lymphocytic Leukemia (CLL) and in 2011 it was approved for the treatment of Granulomatosis with Polyangiitis (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids. In 2018, Rituxan was approved for the treatment of adult patients with moderate to severe pemphigus (PV).

3 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters	C- N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E- N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

We performed a risk assessment of the proposed container labels, carton labeling, PI, and medication guide for Ruxience ("PF-05280586") Injection to determine whether there are significant concerns in terms of safety, related to preventable medication errors. We note,

Ruxience has the same dosing, route of administration, strength, dosage form and storage requirements as US-licensed Rituxan (BLA 103705). However, the Applicant is pursuing only five of the six indications (i.e. NHL, RA, CLL, GPA, and MPA) as the sponsor of US-licensed Rituxan has an unexpired orphan-drug status exclusivity for the treatment Pemphigus Vulgaris (PV).

We find the medication guide acceptable from a medication error perspective. We identified areas of the proposed PI, container labels and carton labeling that could be revised to improve clarity and readability of important information. Tables 2 and 3 below includes the identified medication error issues with the submitted PI, container labels and carton labeling our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Hematology Products (DHP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	(b) (4)		
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In Section 2.6 <i>Recommended Dose for Granulomatosis with Polyangiitis (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA)</i> , the dose for methylprednisolone is stated as 1000 mg instead of 1,000 mg.	Numbers greater than or equal to 1000 without a comma may be misinterpreted as hundreds “100” or ten-thousands “10000”.	Consider stating numbers greater than or equal to 1,000 with a comma to prevent the reader from misinterpreting thousands “1000” as hundreds “100” or ten-thousands “10000”.

Table 3. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The finished dosage form is omitted from the principal display panel.	For biological products the dosage form can appear below the proper name.	If space permits, include the finished dosage form on the principal display panel below the proper name as follows: Ruxience (rituximab-xxxx) Injection.

Table 3. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	The route of administration on the side display panel is presented using the abbreviation "IV" instead of "intravenous".	The route of administration should be described without abbreviation to mitigate the risk of product administration errors.	Revise the route of administration on the side display panel from "IV" to "intravenous" to mitigate the risk of product administration errors.
4.	The product is packaged in a vial that contains a solution but requires dilution. However, the cautionary statement informing users of the required dilution is omitted from the principal display (PDP).	The product could be administered incorrectly as an intravenous bolus instead of an intravenous infusion.	Revise the statement, "For Intravenous Use" to "For Intravenous Use after dilution". We recommend this to minimize the risk of administering the drug as an intravenous bolus.
5.	The statement, "NO PRESERVATIVES" is more prominent on the PDP than other important information and also appears on the side display panel.	Having the duplicate statements on the label increases visual clutter.	Delete the duplicate statement, "NO PRESERVATIVES" from the PDP as this information appears on the side display panel. Consider revising the statement, "NO PRESERVATIVES" from appearing in all capital letters to only capitalizing the first letter of each word, "No Preservative". In addition, consider debolding the statement and using a different font color (black) to decrease prominence of this information.
6.	The concentration (10 mg/mL) appears less prominent than route of administration and	Lack of prominence may lead to product preparation errors.	Revise the strength statement to include the total quantity per total volume and the concentration in the colored boxed. For example:

Table 3. Identified Issues and Recommendations for Pfizer (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	package type on the PDP.		500 mg/50 mL (10 mg/mL)
Container Label(s)			
1.	Ruxience is supplied in a single-dose vial, therefore the "Discard Unused Portion" statement should follow the statement, "One Single-Dose Vial."	Having the statement appear as, "One Single-Dose Vial- Discard Unused Portion." may minimize risk of the entire contents of the vial being given as a single dose.	Revise the net quantity statement from, "One Single Dose Vial" to "One Single-Dose Vial- Discard Unused Portion."
2.	The usual dosage statement is lengthy and contains duplicate information from the PDP.	The usual dosage statement is lengthy and increases visual clutter on the side display panel.	Revise the usual dosage statement from, (b) (4) [Redacted] to "Usual Dosage: See prescribing information for dosing and dilution instructions."
Carton Labeling			
1.	The Rx only statement is prominent.	The Rx only statement appears in similar prominence as the route of administration, package type term, and cautionary statements.	Decrease the prominence by debolding the Rx only statement.
2.	The usual dosage statement is lengthy and contains duplicate	The usual dosage statement is lengthy and increases	Revise the usual dosage statement from, (b) (4) [Redacted]

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Ruxience that Pfizer submitted on July 25, 2018, and US-licensed Rituxan.

Table 4. Relevant Product Information for Ruxience and US-licensed Rituxan		
Product Name	Ruxience	US-licensed Rituxan
Initial Approval Date	N/A	November 26, 1997
Active Ingredient	Rituximab-xxxx	Rituximab
Indication	<p>For the treatment of adult patients with:</p> <p>Non-Hodgkin’s Lymphoma (NHL)</p> <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 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) 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. <p>Chronic Lymphocytic Leukemia (CLL)</p>	<p>For the treatment of adult patients with:</p> <ul style="list-style-type: none"> • Non-Hodgkin’s Lymphoma (NHL) • Chronic Lymphocytic Leukemia (CLL) • 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 (GPA) (Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids <ul style="list-style-type: none"> • Pemphigus Vulgaris (PV)

	<ul style="list-style-type: none"> • Previously untreated and previously treated CD20-positive CLL in combination with fludarabine and cyclophosphamide (FC). • 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 (GPA) (Wegener's Granulomatosis) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids. 	
Route of Administration	Intravenous infusion	Intravenous infusion
Dosage Form	Injection	Injection
Strength	10 mg/mL (500 mg/50 mL and 100 mg/10 mL)	10 mg/mL (500 mg/50 mL and 100 mg/10 mL)
Dose and Frequency	<p>NHL: the dose is 375 mg/m². Depending on severity and/or stage of disease, administration can range from 4 to 16 doses.</p> <p>CLL: 375 mg/m² in the first cycle and 500 mg/m² in cycles 2-6, in combination with FC, administered every 28 days.</p> <p>RA: dose is two-1000 mg intravenous infusions separated by 2 weeks (one course) every 24 hours</p> <p>GPA and MPA: In combination with glucocorticoids, the dose is 375 mg/m² once weekly for 4 weeks.</p>	<p>NHL: the dose is 375 mg/m². Depending on severity and/or stage of disease, administration can range from 4 to 16 doses.</p> <p>CLL: 375 mg/m² in the first cycle and 500 mg/m² in cycles 2-6, in combination with FC, administered every 28 days.</p> <p>RA: dose is two-1000 mg intravenous infusions separated by 2 weeks (one course) every 24 hours</p> <p>GPA and MPA: In combination with glucocorticoids, the dose is 375 mg/m² once weekly for 4 weeks.</p> <p>Component of Zevalin for treatment of NHL: the dose is 250 mg/m²</p>

How Supplied	Ruxience vials are supplied as 100 mg/10 mL and 500 mg/50 mL single-dose vials	Rituxan vials are supplied as 100 mg/10 mL and 500 mg/50 mL single-dose vials
Storage	Store Ruxience vials refrigerated at 2°C - 8°C (36°F-46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake.	Rituxan vials are stable at 2°C - 8°C (36°F-46°F). Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 27, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, Ruxience and PF-05280586. Our search did not identify any previous labeling reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Ruxience labels and labeling submitted by Pfizer.

- Container label(s) received on July 25, 2018
- Carton labeling received on July 25, 2018
- Medication Guide (Image not shown) received on March 5, 2019
- Prescribing Information (Image not shown) received on March 5, 2019

F.2 Label and Labeling Images



^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

NICOLE B GARRISON
04/02/2019 11:18:30 AM

HINA S MEHTA
04/02/2019 03:28:03 PM

MEMORANDUM**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 1, 2019

TO: Ann Farrell, MD
Director
Division of Hematology Products (DHP)
Office of New Drugs

FROM: Gajendiran Mahadevan, Ph.D.
Pharmacologist
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE
OSIS

SUBJECT: Routine inspection of Bluegrass Community Research, Inc., Lexington, KY and Desert Medical Advances, Palm Desert, CA supporting clinical study B3281001 (BLA 761103)

1 Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged an inspection of clinical portion of study B3281001 (BLA 761103) conducted at Bluegrass Community Research, Inc., Lexington, KY and Desert Medical Advances, Palm Desert, CA.

No objectionable conditions were observed, and Form FDA 483 was not issued at the inspection close-out at both clinical sites. The final inspection classification is No Action Indicated (NAI) for both clinical sites. However, the following two inspectional findings need additional consideration.

ORA Investigators verified pharmacokinetic sample collections for all 9 subjects who completed the study at clinical site #1098 (Bluegrass Community Research, Inc., Lexington, KY) and did not find any deviations other than the ones reported to the Agency.

The analytical inspection conducted at [REDACTED] (b) (4) for study B3281001 did not find any issues with the analytical

method used in the PK analysis of subject samples from all clinical sites.

During inspection at Desert Medical Advances, Palm Desert, CA, ORA Investigator found that an adverse event of rosacea associated with Subject (b) (6) in protocol B3281001 and an adverse event of upper respiratory infection associated with Subject (b) (6) in protocol B3281004 were not reported to the Agency.

1.1. Recommendation

After reviewing the inspectional findings, I conclude the clinical data from the audited studies at Bluegrass Community Research, Inc., Lexington, KY and Desert Medical Advances, Palm Desert, CA are reliable to support a regulatory decision. However, the clinical reviewer in the DHP should evaluate the following items.

- **Safety of study subjects from protocols B3281001 & B3281004:**

The adverse event of Subject (b) (6) in protocol B3281001 and an adverse event of upper respiratory infection associated with Subject (b) (6) in protocol B3281004 should be assessed for safety and accounted for the two unreported adverse events (**Attachment-3 & -4**).

- **Pharmacokinetic profiles of subjects from clinical site #1098:**

The clinical inspection found no evidence of clinical conduct process that could explain the questionable PK concentrations. In addition, the analytical inspection for study B3281001 did not find any issues with the analytical method used in the PK analysis of subject samples from all clinical sites.

2 Inspected Studies

BLA 761103

Study Number: B3281001

Study Title: "A randomized, double-blind, study comparing the pharmacokinetics and pharmacodynamics, and assessing the safety of PF-05280586 and Rituximab in subjects with active rheumatoid arthritis on a background of methotrexate who have had inadequate response to one or more TNF antagonist therapies."

Dates of conduct: March 20, 2012-May 7, 2014

Study Number: B3281004

Study Title: "Extension study evaluating treatment with PF-05280586 versus rituximab in subjects with active rheumatoid arthritis who have participated in other PF-05280586 clinical trials."

Dates of conduct: August 16, 2012-March 14, 2016

Clinical site inspection for study B3281001 was conducted at the following two sites;

Clinical site #1098:

Name: Bluegrass Community Research, Inc.
Street Address: 330 Waller Avenue, Suite 100
City & State: Lexington, KY 40504

Clinical site #1125:

Name: Desert Medical Advances
Street Address: 72855 Fred Waring Drive, Suite A-6
City & State: Palm Desert, CA 92260

Name: Advances in Medicine
Street Address: 42362 Bob Hope Drive
City & State: Rancho Mirage, CA

3 Inspectional Findings

1. Bluegrass Community Research, Inc., Lexington, KY (Clinical Site # 1098):

ORA Investigators Marcia Worley (BIMO/DBIMOI) and Kathryn Suttling ((BIMO/DBIMOI) inspected Bluegrass Community Research, Inc., Lexington, KY from December 10-14, 2018. This was the first bioequivalence inspection for this clinical site.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

DHP requested inspection of clinical site #1098 (Bluegrass Community Research, Inc., Lexington, KY) since the sponsor reported in the clinical report that "the majority of individual

PK profiles were contradictory with the known PK characteristics for rituximab and PK sampling procedures were not verified from this site."

Nine (9) subjects enrolled and completed the study at Bluegrass Community Research, Inc. (Clinical Site # 1098). The subjects were treated per randomization schedule and the intended treatments were confirmed by ORA Investigators (**Attachment-1**). Clinical protocol was followed during pharmacokinetic (PK) sample collections. The protocol deviations for PK sample collections for all 9 subjects were verified during this inspection and the deviations were reported to the Agency (**Attachment-2**).

At the conclusion of the inspection, Investigators Worley and Suttling did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

OSIS Evaluation: During inspection at Bluegrass Community Research, ORA Investigators Worley and Suttling verified PK sample collection, handling, and storage processes for all 9 subjects who completed the study at clinical site #1098. The ORA investigators found no deviations other than the ones reported to the Agency. Thus, there was no evidence to show that a clinical conduct process caused the questionable PK concentrations.

In addition, an analytical inspection associated with study B3281001 was conducted at (b) (4) and an EIR review was uploaded into DARRTS on February 15, 2019. There was no evidence of any issues with the analytical method used in the PK analysis of subject samples from this study. The same analytical method was used analysis of subject samples from all clinical sites. In the absence of any issues with analytical method, there was no evidence to suggest that a problem occurred during PK sample analysis at the analytical site.

2. Desert Medical Advances, Palm Desert, CA & Advances in Medicine, Rancho Mirage, CA (Clinical Site # 1125):

ORA Investigator Julian Hanson (BIMO/DBIMOII) inspected two studies: B3281001 and B3281004 associated with BLA 761103 at Desert Medical Advances, Palm Desert, CA from January 14-18, 2019. This was the first bioequivalence inspection for this clinical site.

ORA intended to inspect the clinical site Advances in Medicine, Rancho Mirage, CA since 23 subjects were randomized under

clinical site #1125. However, during inspection at Desert Medical Advances, Palm Desert, CA, the Principal Investigator of both sites Dr. Maria Greenwald informed ORA Investigator Hanson that the clinical site **Advances in Medicine** (b) (4) facility was used only for X-ray screening of subjects.

The inspection included a thorough examination of study records (paper-based), subject records, informed consent process, protocol compliance, institutional review board approvals, sponsor and monitor correspondence, test article accountability and storage, randomization, adverse events, and case report forms.

At the conclusion of the inspection, Investigator Hanson did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site. However, an adverse event of rosacea associated with Subject (b) (6) in protocol B3281001 (**Attachment-3**) and an adverse event of upper respiratory infection associated with Subject (b) (6) in protocol B3281004 (**Attachment-4**) found during this inspection were not reported to the Agency.

The site's management stated that the electronic case report forms (CRFs) were locked, and they no longer had access to update the adverse event. A "Note to File" was created to document the missing adverse events.

OSIS Evaluation: The adverse events were not reported to the Agency because of access restriction to electronic CRFs; however, these adverse events were documented with source records as a "Note to File." DHP's safety assessment should account for the two unreported adverse events.

4. Conclusion

After reviewing the inspectional findings, I conclude the clinical data from studies B3281001 and B3281004 (BLA 761103) conducted at Bluegrass Community Research, Inc., Lexington, KY and Desert Medical Advances, Palm Desert, CA are reliable to support a regulatory decision. However, the clinical reviewer in the DHP should evaluate the following items.

- **Safety of study subjects from protocols B3281001 & B3281004:**

The adverse event of Subject (b) (6) in protocol B3281001 and an adverse event of upper respiratory infection associated with Subject (b) (6) in protocol B3281004 should be assessed for

safety and accounted for the two unreported adverse events (**Attachment-3 & -4**).

• **Pharmacokinetic profiles of subjects from clinical site #1098:**

The clinical inspection found no evidence of clinical conduct process caused the questionable PK concentrations. In addition, the analytical inspection for study B3281001 did not find any issues with the analytical method used in the PK analysis of subject samples from all clinical sites.

Based on the inspectional findings, clinical data from studies of similar design conducted between start of clinical studies in March 2012 and the end of the current surveillance interval should be considered reliable without an inspection for both clinical sites: Bluegrass Community Research, Inc., Lexington, KY and Desert Medical Advances, Palm Desert, CA

Gajendiran Mahadevan, Ph.D.
Pharmacologist

Final Classification:

Clinical Sites:

NAI: Bluegrass Community Research, Inc., Lexington, KY
FEI#: 3014823865

NAI: Desert Medical Advances, Palm Desert, CA
FEI#: 3003913435

cc:

OTS/OSIS/Kassim/Mitchell/Fenty-Stewart
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Mahadevan
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov
ORABIMOW.Correspondence@fda.hhs.gov

Draft: 02/21/2019, 02/26/2019, 02/28/2019; 03/01/2019

Edits: RCA 02/22/2019, 2/27/2019; 3/1/2019; AD
02/25/2019, 02/28/2019, 3/1/2019

ECMS:

[Bluegrass Community Research, Inc., Lexington, KY/FY19 10-DEC-2018](#)

[Desert Medical Advances, Palm Desert, CA/FY19 14-Jan-2019](#)

Page 7 - Routine inspection of Bluegrass Community Research,
Inc., Lexington, KY and Desert Medical Advances, Palm
Desert, CA

OSIS File #: BE 8249

FACTS: 11884426

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/s/

GAJENDIRAN MAHADEVAN
03/01/2019 03:17:40 PM

RUBEN C AYALA
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ARINDAM DASGUPTA
03/01/2019 04:09:53 PM

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 15, 2019

TO: Dale Conner, Pharm.D.
Director
Office of Bioequivalence
Office of Generic Drugs

Ann Farrell, M.D.
Director
Division of Hematology Products (DHP)
Office of New Drugs

Patricia Keegan, M.D.
Director
Division of Oncology Products 2 (DOP 2)
Office of New Drugs

FROM: Amanda Lewin, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDBE, OSIS

SUBJECT: Surveillance inspection of [REDACTED] (b) (4)

1. Inspection Summary

OSIS and the Office of Regulatory Affairs inspected the analytical portion of B7391001 and B7391003 (BLA 761099, Bevacizumab), B3281001 (BLA 761103, rituximab), and [REDACTED] (b) (4) [REDACTED] (b) (4) conducted at [REDACTED] (b) (4)

We did not observe objectionable conditions and did not issue Form FDA 483 at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

1.1. Recommendation

Based on my review of the inspectional findings, I conclude the data from the audited studies are reliable to support a regulatory decision.

2. Inspected Studies

B7391001 (BLA 761099)

"Phase 1, Double Blind, Randomized, Parallel-Group, Single-Dose, 3-Arm, Comparative Pharmacokinetic Study of PF-06439535 and Bevacizumab Sourced from US and EU Administered to Healthy Male Volunteers

Sample Analysis Period:

PK: 05/19/2014 - 08/13/2014

ADA: 05/13/2014 - 08/15/2014

NAB: 08/22/14

B7391003 (BLA 761099)

"A Phase 3, Randomized, Double-Blind Study of PF-06439535 Plus Paclitaxel-Carboplatin and Bevacizumab Plus Paclitaxel Carboplatin for the First-Line Treatment of Patients with Advanced Non-Squamous Non-Small Cell Lung Cancer"

Sample Analysis Period:

PK: 05/05/2015 - 06/14/2017

ADA: 02/12/2016 - 06/14/2017

NAB: 06/20/2017 - 06/22/2017

B3281001 (BLA 761103)

"A Randomized, Double-Blind, Study Comparing the Pharmacokinetics and Pharmacodynamics, and Assessing the Safety of PF-05280586 and Rituximab in Subjects with Active Rheumatoid Arthritis on a Background of Methotrexate who have had an Inadequate Response to One or More TNF Antagonist Therapies"

Sample Analysis Period:

PK: 09/19/2012 - 01/13/2014

ADA: 11/19/2012 - 08/13/2013

NAB: 05/21/2013 - 12/05/2013

(b) (4)

3. Scope of Inspection

ORA investigator Joseph Despins, Ph.D. and OSIS scientist Amanda Lewin, Ph.D. audited the analytical portion of the above studies at [REDACTED] (b) (4) from [REDACTED] (b) (4)

The Previous FDA inspection of [REDACTED] (b) (4) was conducted from [REDACTED] (b) (4) [REDACTED] (b) (4). The inspection of [REDACTED] (b) (4) was classified NAI and corrective actions from the previous FDA inspection were not necessary.

The current inspection included a thorough examination of study records, facilities, laboratory equipment, method validation, sample analysis, and interviews with the firm's management and staff and follow up on specific concerns from OND and OGD.

4. Inspectional Findings

At the conclusion of the inspection, we did not observe objectionable conditions. We did not issue Form FDA 483 to [REDACTED] (b) (4) [REDACTED] (b) (4).

4.1 Specific concerns from OND/OGD

(b) (4)



5. Conclusion

After review of the inspectional findings, I conclude that data from the audited studies are reliable. Studies using similar methods conducted between the previous inspection [REDACTED] (b) (4) and the end of the current surveillance interval should be considered reliable without an inspection.

Final Classification:

NAI- [REDACTED] (b) (4)

cc: OTS/OSIS/Kassim/Choe/Kadavil/Mitchell/Fenty-Stewart/Nkah
OTS/OSIS/DNDBE/Bonapace/Dasgupta/Ayala/Biswas/Lewin
OTS/OSIS/DGDBE/Cho/Kadavil/Choi/Skelly/Au
ORA/OMPTO/OBIMO/ORABIMOE.Correspondence@fda.hhs.gov

Draft: AL 02/07/2019

Edit: GB 2/8/2019, 2/14/2019, 2/15/2018; AD 2/14/2019, 2/15/2019

ECMS:

<http://ecmsweb.fda.gov:8080/webtop/drl/objectId/0b0026f881a1c003>

OSIS File #: [REDACTED] (b) (4) (BLA 761099), [REDACTED] (b) (4) (BLA 761103) and [REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

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/s/

AMANDA E LEWIN
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02/15/2019 02:36:13 PM

CLINICAL INSPECTION SUMMARY

Date	February 15, 2019
From	Min Lu, M.D., M.P.H., Medical Officer Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Suzette Peng, M.D., Medical Officer, DPARP Nikolay Nikolov, M.D., Clinical Team Leader, DPARP Jennifer Lee, PharmD, Regulatory Project Manager, DHP
BLA	761103
Applicant	Pfizer Inc.
Drug	Ruxience (PF-05280586), proposed biosimilar to Rituxan (rituximab)
NME	BLA Original for a biosimilar
Therapeutic Classification	CD20-directed cytolytic antibody
Proposed Indication	Treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis
Consultation Request Date	October 1, 2018
Summary Goal Date	June 25, 2019
Action Goal Date	July 25, 2019
BsUFA Date	July 25, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical sites (Drs. Greenwald and Shurmur) were selected for inspections for Protocol B3281001, entitled "A Randomized, Double-Blind, Study Comparing the Pharmacokinetics and Pharmacodynamics, and Assessing the Safety of PF-05280586 and Rituximab in Subjects with Active Rheumatoid Arthritis on a Background of Methotrexate (MTX) who have had an Inadequate Response to One or More Tumor Necrosis Factor (TNF) Antagonist Therapies" and Protocol B3281004, entitled "Extension Study Evaluating Treatment with PF-05280586 versus Rituximab in Subjects with Active Rheumatoid Arthritis Who Have Participated in Other Pf-05280586 Clinical Trials." The study data derived from these clinical sites, based on the inspections, are considered reliable and the studies in support of this application appear to have been conducted adequately.

The final classification for the inspection for Drs. Greenwald's and Shurmur's sites is No Action Indicated (NAI).

2. BACKGROUND

The sponsor submitted this BLA for Ruxience, proposed biosimilar to Rituxan (rituximab) for the indication of treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis.

Ruxience (PF-05280586), a genetically engineered chimeric mouse/human immunoglobulin G1 (IgG1k) monoclonal antibody directed against the CD20 antigen, is developed as a biosimilar product to the reference product US-licensed Rituxan[®]. Rituxan[®] (rituximab) is a CD20-directed cytolytic antibody approved for the treatment of patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), 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 (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids. The reference product was originally approved in the United States (US) in 1997 (BLA 103705) and also approved and marketed under the name MabThera[®] in many other countries including the European Union (EU).

In this application, the sponsor proposes PF-05280586 as a biosimilar product to the US-licensed Rituxan[®] reference product under section 351(k) of the Public Health Service Act (PHS Act) for all indications for which US-licensed Rituxan is currently approved with the same dosage form, route of administration, and dosing regimen.

The sponsor's clinical development program for PF-05280586 for rheumatoid arthritis (RA) included a Phase 1/2 pharmacokinetic (PK) and safety study (Protocol B3281001) followed by a Phase 2 extension safety and efficacy study (Protocol B3281004) in subjects with active rheumatoid arthritis on a background of methotrexate (MTX) treatment who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies.

Protocol B3281001

Protocol Title: A Randomized, Double-Blind, Study Comparing the Pharmacokinetics and Pharmacodynamics, and Assessing the Safety of PF-05280586 and Rituximab in Subjects with Active Rheumatoid Arthritis on a Background of Methotrexate (MTX) who have had an Inadequate Response to One or More Tumor Necrosis Factor (TNF) Antagonist Therapies

This was a multinational, randomized, double-blind, controlled trial in subjects with active RA on a background of methotrexate who had an inadequate response to 1 or more TNF antagonist therapies to evaluate the PK/PD similarity, safety (including immunogenicity), and clinical response of rituximab-Pfizer, rituximab-EU, and rituximab-US.

The primary objective of the study was to demonstrate the pharmacokinetic (PK) similarity of rituximab-Pfizer, rituximab-Europe (EU), and rituximab-United States (US) in subjects with active

rheumatoid arthritis (RA) on a background of methotrexate who had an inadequate response to 1 or more tumor necrosis factor (TNF) antagonist therapies. The secondary objectives of the study were: to utilize population PK/pharmacodynamic (PD) modeling approaches to integrate PK and PD data for the purpose of detecting potential differences in PK/PD profiles among rituximab-Pfizer, rituximab-EU, and rituximab-US; to assess additional clinical response endpoints of rituximab-Pfizer, rituximab-EU, and rituximab-US; to evaluate the overall safety, tolerability and immunogenicity of rituximab-Pfizer, rituximab-EU, and rituximab-US; and to evaluate health outcomes using Health Assessment Questionnaire – Disability Index (HAQ-DI) in subjects receiving rituximab-Pfizer, rituximab-EU, and rituximab-US.

The primary PK endpoints were maximum plasma concentration [C_{max}] and area under the serum versus concentration-time profile time zero extrapolated to infinite time [AUC 0-∞]. The PD parameter included circulating CD19 + B-cell counts (surrogate marker for CD20+ B-cells) and serum IgM.

Clinical efficacy endpoints include composite endpoints of Disease Activity Score in 28 joints-C-reactive protein (DAS28-CRP), and American College of Rheumatology assessment (ACR) for improvement (ACR20, ACR 50, and ACR 70). These clinical endpoints were assessed during the treatment and at the end of study (Week 25). The components of the DAS28-CRP assessment included tender/painful joint count for the 28 joints assessed, swollen joint count for the 28 joints assessed, high-sensitivity C-reactive protein (hsCRP) from the central laboratory, and patient's Global Assessment of Arthritis, Visual Analog Scale (VAS), with a scale from 0 to 100 mm. The components of ACR assessments included tender/Painful Joint Count (68 joints assessed), swollen Joint Count (66 joints assessed), patient's Assessment of Arthritis Pain, VAS, with a scale of 0 to 100 mm, patient's Global Assessment of Arthritis, VAS, with a scale of 0 to 100 mm, physician's Global Assessment of Arthritis, with a scale of 0 to 100 mm, hsCRP from central laboratory, and Health Assessment Questionnaire – Disability Index (HAQ-DI).

The study main inclusion criteria included subjects 18 years or older who had a confirmed diagnosis of RA based on 2010 American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria for RA; met Class I, II, or III of ACR Revised Criteria for Global Functional Status in RA; RA seropositivity as documented by screening assessment for RF and/or anti-cyclic citrullinated peptide antibodies (anti-CCP); active disease as defined by ≥6 tender/painful joints (of 68 assessed) at Screening and Baseline, ≥6 swollen joints (of 66 assessed) at Screening and Baseline, hsCRP greater than the upper limit of normal (>ULN) at Screening, performed by central laboratory or Patient's Global Assessment of Arthritis score ≥50, and Screening Disease Activity Score in 28 joints, C-reactive protein (DAS28-CRP) >3.2; stable dose of oral or parenteral methotrexate 10-25 mg per week and received for at least 3 months and received a stable dose for at least 4 week prior to the first dose of study drug; inadequate response in the opinion of the investigator to 1 or more approved TNF antagonist therapies; discontinued prior therapies for RA and/or were taking only those therapies allowed during the study in specified regimens.

Study subjects were randomized in a 1:1:1 ratio to 1 of 3 treatment groups: rituximab-Pfizer, rituximab-Europe (EU), and rituximab-United States (US). Rituximab was administered at a dose of 1000 mg/500 mL on study Days 1 and 15. PK/PD parameters, clinical endpoints, and safety response

were assessed during the treatment and at the study visits to Week 25. Subjects who completed this clinical trial were offered access to further treatment in an extension study (Protocol B3281004).

The study randomized 220 subjects from 60 centers in 10 countries (Australia, Canada, Colombia, Germany, Israel, Mexico, Russia, South Africa, United Kingdom [UK] and United States [US]). The study screened the first subject on March 20, 2012 and the last subject completed the last visit on May 7, 2014.

Protocol B3281004

Protocol Title: Extension Study Evaluating Treatment with PF-05280586 versus Rituximab in Subjects with Active Rheumatoid Arthritis Who Have Participated in Other Pf-05280586 Clinical Trials

This was an extension study for subjects with active rheumatoid arthritis who had participated for at least 16 weeks in protocol B3281001 and had not received intervening treatment with investigational agents or other biologics (including Rituxan and MabThera).

The primary objective of the study was to provide continued treatment access to subjects with active rheumatoid arthritis (RA) who have participated for at least 16 weeks in other protocols in the PF-05280586 program, to evaluate the overall safety, tolerability and immunogenicity of PF-05280586 occurring after transition from a licensed rituximab product to PF-05280586, and to continue follow-up of biomarker and efficacy endpoints of interest in the previous B3281001 Study.

The safety endpoints included incidence of anti-drug antibodies (ADA) and adverse event reporting. Clinical efficacy endpoints including DAS28-CRP and ACR assessments.

The study main inclusion criteria included subjects with active RA who have had participated for at least 16 weeks in Study B3281001 and who were receiving background therapy with methotrexate and had an inadequate response to 1 or more tumor necrosis factor (TNF) antagonist therapies.

Subjects assigned to PF-05280586 (rituximab-Pfizer) in Study B3281001 continued to receive PF-05280586 throughout this study. Subjects who were assigned to licensed product (rituximab-EU or rituximab-US) in Study B3281001 were assigned in a blinded manner (1:1) to receive either the previously assigned licensed product or PF-05280586 for the first course of treatment. In subsequent treatment courses, all subjects were assigned to receive PF-05280586. All subjects were offered up to 3 courses (6 doses) of study treatment. A course was defined as 2 intravenous (IV) infusions of 1000 mg of study treatment, each administered on Days 1 and 15 of a 24-week (± 8 week) course. Courses were administered based on clinical evaluation and in accordance with local and/or regional regulation, but no sooner than 16 weeks after the initiation of the previous course. The total length of study participation could be between 48 and 96 weeks depending on when courses were delivered. The immunogenicity, safety, and efficacy endpoints were evaluated during the treatment at study visits.

The study enrolled 185 subjects of the 220 subjects treated in the Study B3281001. The study screened the first subject on August 16, 2012 and the last subject completed the last visit on March 14, 2016.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Enrolled Subjects	Inspection Date	Classification
Maria W. Greenwald, M.D. Desert Medical Advances 72855 Fred Waring Dr, Ste A-6 Palm Desert, CA 92260	Protocols B3281001 and B3281004 Site# 1125 Subjects= 23	January 14-18, 2019	NAI
Robert W. Shurmur, M.D. Bronson Internal Medicine and Rheumatology 2845 Capital Ave SW, Ste 302 Battle Creek, MI 49015	Protocol B3281001 and B3281004 Site# 1055 Subjects= 15	January 16-18, 22-23, 2019	NAI

Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

* Pending = Preliminary classification based on information in the EIR. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigators**1. Maria W. Greenwald, M.D. (Site #1125, Palm Desert, CA)**

The site screened 28 subjects and enrolled 23 subjects in Study Protocols B3281001 and B3281004. An audit of all 23 enrolled subjects' records was conducted. All 23 enrolled subjects completed both Study Protocols B3281001 and B3281004.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and correspondence with the ethics committee, monitors, and sponsor were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site.

The following findings were identified and discussed at the end of the inspection:

- 1) Under-reporting of non-serious adverse events:
 - Subject (b) (6) (receiving PF-05280586) in protocol B3281001 had an adverse event of rosacea reported during the study in the source documents but it was not reported in the case report form.
 - Subject (b) (6) (receiving PF-05280586 in the treatment course) in protocol B3281004 had an adverse event of upper respiratory infection reported during the study in the source documents but it was not reported in the case report form.

During the inspection the clinical investigator provided note to files about the missing adverse events and confirmed that as the electronic case report forms had been locked and they no longer had access and could not update the forms.

- 2) PK sampling outside of the specified window:

The protocol stated that the end of infusion sample can be drawn up to 15 minutes prior to the end of the infusion; however, on multiple occasions the end of infusion sample was drawn after the end of the infusion. These have been reported as protocol deviations in the clinical study reports.
- 3) Correction to some source documents were initialed but not dated, or an entry was overwritten instead of being initialed and dated.

The clinical investigator should have conducted the study in accordance to the investigational plan. The findings noted above appear to be clinically insignificant and, they are unlikely to impact data reliability, nor did it compromise the rights, safety and welfare of subjects in the study. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Robert W. Shurmur, M.D. (Site #1055, Battle Creek, MI)

The site screened 19 subjects and enrolled 15 subjects in Study Protocol B3281001 and 13 in Study Protocol B3281004. An audit of all enrolled subjects' records was conducted. All 15 enrolled subjects in Study Protocol B3281001 completed the study. Among the 13 enrolled subjects in Study Protocol B3281004, 12 subjects completed the study and one subject (Subject (b) (6)) discontinued due to an adverse event (arthritic bacterial/right septic elbow). The discontinuation data listing provided in the BLA were verified by review of source documents.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and correspondence with the ethics committee, monitors, and sponsor were also inspected. Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and BLA subject line listings. There were no limitations during conduct of the clinical site inspection.

Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events was noted.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. No significant observations were identified. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this specific indication.

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Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H.
Branch Chief, Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:

Central Doc. Rm.
Review Division /Medical Team Leader/ Nikolay Nikolov
Review Division/Medical Officer/ Suzette Peng
Review Division /Project Manager/ Jennifer Lee
OSI/DCCE/ Division Director/Ni Khin
OSI/DCCE/Branch Chief/Kassa Ayalew
OSI/DCCE/GCP Reviewer/Min Lu
OSI/ GCP Program Analyst/Yolanda Patague

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/s/

MIN LU
02/15/2019 11:05:13 AM

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02/15/2019 11:38:48 AM

CLINICAL INSPECTION SUMMARY

Date	February 13, 2019
From	Min Lu, M.D., M.P.H., Medical Officer Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Yvette Kasamon, M.D., Medical Officer Angelo de Claro, M.D., Clinical Team Leader Jennifer Lee, PharmD, Regulatory Project Manager Division of Hematology Products (DHP)
BLA	761103
Applicant	Pfizer Inc.
Drug	Ruxience (PF-05280586), proposed biosimilar to Rituxan (rituximab)
NME	BLA Original for a biosimilar
Therapeutic Classification	CD20-directed cytolytic antibody
Proposed Indication	Treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis
Consultation Request Date	October 3, 2018
Summary Goal Date	March 5, 2019
Action Goal Date	July 25, 2019
BsUFA Date	July 25, 2019

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The sponsor's site was selected for inspection for Protocol B3281006, entitled "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". In general, the sponsor maintained adequate oversight of the clinical trial and appeared to be in compliance with Good Clinical Practices.

The final classification for the inspection for the sponsor's site is No Action Indicated (NAI).

2. BACKGROUND

The sponsor submitted this BLA for Ruxience, proposed biosimilar to Rituxan (rituximab) for the indication of treatment of non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's Granulomatosis) and microscopic polyangiitis.

Ruxience (PF-05280586), a genetically engineered chimeric mouse/human immunoglobulin G1 (IgG1k) monoclonal antibody directed against the CD20 antigen, is developed as a biosimilar product to the reference product US-licensed Rituxan[®]. Rituxan[®] (rituximab) is a CD20-directed cytolytic antibody approved for the treatment of patients with non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), 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 (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA) in adult patients in combination with glucocorticoids. The reference product was originally approved in the United States (US) in 1997 (BLA 103705) and also approved and marketed under the name MabThera[®] in many other countries including the European Union (EU).

In this application, the sponsor proposes PF-05280586 as a biosimilar product to the US-licensed Rituxan[®] reference product under section 351(k) of the Public Health Service Act (PHS Act) for all indications for which US-licensed Rituxan is currently approved with the same dosage form, route of administration, and dosing regimen.

The sponsor's clinical development program for PF-05280586 included a Phase 3 clinical efficacy, safety, pharmacokinetics (PK), and immunogenicity study comparing PF-05280586 with EU-marketed MabThera in subjects with CD20-positive, low tumor burden follicular lymphoma (LTB FL) in the first-line treatment setting (Protocol B3281006).

Protocol B3281006

This was a Phase 3, multi-center, randomized, double-blind, active-controlled, parallel group study to compare the efficacy, safety and pharmacokinetics and immunogenicity of PF-05280586 with rituximab-EU (MabThera) in subjects with CD20-positive, low tumor burden follicular lymphoma in the first-line treatment setting.

The primary objective of the study was to compare the efficacy of PF-05280586 to rituximab-EU when administered as a first-line treatment to subjects with CD20-positive, LTB FL. The secondary objectives were to evaluate the safety of PF-05280586 and immunogenicity of PF-05280586.

The primary efficacy endpoint of the study was the overall response rate (ORR) at Week 26 of PF-05280586 versus rituximab-EU based on central review which included radiographic assessment and review of clinical data (B-cell depletion and bone marrow biopsy results) based on Cheson et al, 2007

criteria. The secondary endpoints included time to treatment failure (TTF), progression-free survival (PFS), complete response at week 26, Duration of response (DOR), and overall survival (OS).

The study main inclusion criteria included patients 18 years or older with histologically confirmed, Grade 1-3a, CD20-positive FL (containing no elements of diffuse large B-cell lymphoma); Ann Arbor classification stage II, III or IV; at least 1 measurable disease lesion identifiable by imaging; low tumor burden follicular lymphoma; and Eastern Cooperative Oncology Group performance status of 0 to 1.

Study subjects were randomized into two study treatment arms to receive either PF-05280586 or rituximab-EU. Randomization was stratified by low, medium, and high-risk subjects using the Follicular Lymphoma International Prognostic Index 2 (FLIPI2). During the study, subjects received 4 weekly doses of PF-05280586 or rituximab-EU administered via intravenous infusion. The dose of PF-05280586 or rituximab-EU was 375 mg/m² of body surface area (BSA). All subjects were to be followed up for 52 weeks. Central review was performed for all disease assessments and continued through the End of Study (Week 52).

The study enrolled 394 subjects (196 subjects in the PF-05280586 group and 198 subjects in the rituximab-EU group) from the 160 clinical sites in 29 countries (Austria, Belarus, Belgium, Brazil, Croatia, France, Georgia, Germany, Greece, India, Italy, Japan, Republic of Korea, Lebanon, Mexico, Peru, Poland, Portugal, Puerto Rico, Romania, Russian Federation, South Africa, Spain, Switzerland, Thailand, Turkey, Ukraine, the United Kingdom, and the United States). The study screened the first subject on September 30, 2014 and the last subject completed the last visit on April 19, 2018.

3. RESULTS (by site):

Sponsor Inspection	Site #, Protocol #, and # of Enrolled Subjects	Inspection Date	Classification
Sponsor - Pfizer Inc. Trial master file location: 558 Eastern Point Road Groton, CT 06340	Protocol B3281006 N=394 subjects	October 29- November 2, 2018	NAI

Key to Compliance Classifications

NAI (No Action Indicated) = No deviation from regulations.

VAI (Voluntary Action Indicated) = Deviation(s) from regulations.

OAI (Official Action Indicated) = Significant deviations from regulations. Data unreliable.

* Pending = Preliminary classification based on information in the EIR. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Sponsor Site- Pfizer Inc. (Groton, CT)

This inspection evaluated compliance with sponsor responsibilities concerning the conduct of Protocol B3281006. The sponsor's inspection covered the following area: protocol and amendments, organization and personnel, FDA Forms-1572 investigator agreements and financial disclosure forms, patient protection/institutional review board (IRB) communications, investigator/sponsor/CRO correspondence, training records, monitoring procedures and activities, site monitoring visit reports, quality assurance, site correspondence, test article integrity and accountability, data collection and handling, primary efficacy assessment, and adverse event reporting.

The sponsor employed (b) (4), an outside monitoring firm, to conduct their monitoring activities for this trial. Monitoring activities across 16 of the 160 clinical sites participating in the Protocol B3281006 trial were selected at random and reviewed during this inspection.

At the end of the inspection, the following items were identified and discussed with the sponsor's site management team:

1. Blood sampling time for additional pharmacokinetics (PK) in the protocol was translated incorrectly for two countries, Brazil and Greece. In Greece, the error was caught before any of the sites had enrolled any subjects. In Brazil, however, one site had enrolled three subjects before the error was caught. The protocol translation in error asked for taking the PK blood sampling within 15 minutes after the end of the test drug infusion. However, it was stated within 15 minutes prior to the end of the infusion in the protocol. These were reported as protocol deviations in the clinical study report.
2. Eleven of the 13 clinical investigators that were placed on enrollment holds did not attend an Investigator's Meeting for study specific training. These investigators were given study specific training by the CRAs when the CRAs conducted their Site Initiation Visits, or during early Interim Monitoring Visits. These clinical investigators may not have had enough training.

In general, the sponsor maintained adequate oversight of the clinical trial. The monitoring of investigator sites was adequate. The primary study endpoint data were verifiable. No under-reporting of adverse events or serious adverse events was noted. The sponsor site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued.

{See appended electronic signature page}

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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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