CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207924Orig1s000

<u>OTHER REVIEW(S)</u>

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:	May 23, 2018
To:	Sally Seymour, MD Acting Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adewale Adeleye, Pharm.D., MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	OLUMIANT (baricitinib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 207924
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On December 4, 2017 Eli Lilly and Company submitted for the Agency's review a Resubmission of New Drug Application (NDA) 207924 for OLUMIANT (baricitinib) tablets, for oral use. This resubmission was in response to a Complete Response (CR) Letter issued to the Applicant on April 12, 2017 that concluded the overall benefit-risk assessments of baricitinib 2 mg and 4 mg once-daily doses have identified safety concerns that outweigh efficacy observed with the proposed dosing regimen. The 505(b)(2) original NDA for OLUMIANT (baricitinib) tablets, for oral use was submitted for the Agency's review on January 15, 2016.

The proposed indication for OLUMIANT (baricitinib) tablets, for oral use is for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more TNF antagonist therapies.

This collaborative review is written by Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy and Rheumatology Products (DPARP) on January 10, 2018 and January 9, 2018, respectively, for DMPP and OPDP to review the Medication Guide (MG) for OLUMIANT (baricitinib) tablets, for oral use.

2 MATERIAL REVIEWED

- Draft OLUMIANT (baricitinib) tablets, for oral use MG received on December 14, 2017 and received by DMPP and OPDP on May 15, 2018.
- Draft OLUMIANT (baricitinib) tablets, for oral use Prescribing Information (PI) received on December 14, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 15, 2018.

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 have:

- 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)

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/

NYEDRA W BOOKER
05/23/2018

ADEWALE A ADELEYE
05/23/2018

MARCIA B WILLIAMS
05/23/2018

LASHAWN M GRIFFITHS
05/24/2018

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

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

Memorandum

Date: May 24, 2018

To: Raj Nair, M.D.
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Jessica Lee, Pharm.D., Senior Regulatory Project Manager, (DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for OLUMIANT (baricitinib) tablets, for oral use

NDA: 207924

In response to DPARP's consult request dated January 9, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for OLUMIANT (baricitinib) tablets, for oral use (Olumiant).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI and Medication Guide received by electronic mail from DPARP (Jessica Lee) on May 15, 2018, and are provided below. OPDP's comments on the proposed PI are provided directly on the attached copy of the labeling (see below).

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on May 24, 2018.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 18, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
05/24/2018

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 23, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Application Type and Number:	NDA 207924
Product Name and Strength:	Olumiant (baricitinib) 2 mg tablets
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	May 18, 2018
OSE RCM #:	2016-330-2
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

1 PURPOSE OF MEMORANDUM

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that we review the revised container label for Olumiant (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 label for Olumiant is acceptable from a medication error perspective. We have no further recommendations at this time.

[a] McMillan, T. Label and Labeling Review for Olumiant (NDA 207924). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 MAY 09. RCM No.: 2016-330-1.

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APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 18, 2018

Container labels

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/s/

TERESA S MCMILLAN
05/23/2018

SARAH K VEE
05/23/2018

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)

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Date of This Review:	May 9, 2018
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Application Type and Number:	NDA 207924
Product Name and Strength:	Olumiant (baricitinib) 2 mg and 4 mg tablets
Product Type:	Single Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company
FDA Received Date:	December 4, 2017
OSE RCM #:	2016-330-1
DMEPA Safety Evaluator:	Teresa McMillan, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

Reference ID: 4260456

1 REASON FOR REVIEW

Eli Lilly and Company resubmitted NDA 207924 for Olumiant (baricitinib) tablets on December 4, 2017. Thus, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested we evaluate the container labels and prescribing information for areas of vulnerability that could lead to medication errors.

NDA 207924 received a complete response (CR) on April 12, 2017 due to the overall benefit-risk of baricitinib was not favorable given the potential serious risk for thrombosis.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified areas in the labels and labeling that can be improved to increase the readability and prominence of important information and promote the safe use and handling of the product. DMEPA completed a review during the first review cycle[a]. Because the application received a CR, our recommendations were not sent to the Applicant. Thus, we provide recommendations in Section 4.1 for the Applicant to address these deficiencies.

[a] McMillan T. Label, labeling, and packaging Review for Olumiant (NDA 207924). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 4. Panorama No. 2016-330

Reference ID: 4260456

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR ELI LILLY AND COMPANY

We recommend the following be implemented prior to approval of this NDA 207924:

A. General Comments (Container labels & Carton Labeling)
   1. As currently displayed, the font color selection [redacted] (b) (4) of the established name does not afford adequate contrast against the white background and makes this information difficult to read. We recommend revising the font color of the established name to increase readability.
   2. Revise the font color of the proprietary name [redacted] (b) (4)
   3. Relocate the net quantity and Rx only statements away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
   4. To increase the prominence of important information, relocate the strength statement underneath the established name and dosage form statements. In addition, ensure that the first letter of the proprietary name, Olumiant is capitalized. To ensure there is an adequate amount of white space, consider removing the company name, website, or logo. For example:

      Olumiant
      (baricitinib) tablets
      2 mg
   5. Revise dosage statement to “Usual dosage: See Prescribing Information” for consistency with other labels.

Reference ID: 4260456

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Olumiant received on December 4, 2017 from Eli Lilly and Company.

Table 2. Relevant Product Information for Olumiant	
Initial Approval Date	N/A
Active Ingredient	baricitinib
Indication	Treatment of adult patients with moderately to severely active rheumatoid arthritis
Route of Administration	Oral
Dosage Form	Tablets
Strength	2 mg, 4 mg
Dose and Frequency	2 mg once daily. For patients with an inadequate response or intolerance to more than one DMARD, a dose of 4 mg once daily is recommended. Dose tapering to 2 mg once daily may be considered for patients who have achieved sustained control of disease activity with 4 mg once daily
How Supplied	2 mg strength – bottles of 30 tabs (b) (4) (b) (4)
Storage	20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F)

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APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 4, 2018, we searched DMEPA's previous reviews using the terms, Olumiant. Our search identified one previous review [b] and we confirmed that our previous recommendations were considered.

[b] McMillan T. Label, labeling, and packaging Review for Olumiant (NDA 207924). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2017 JAN 4. Panorama No. 2016-330.

Reference ID: 4260456

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Olumiant labels and labeling submitted by Eli Lilly and Company.

- Container label received on December 4, 2017
- Medication Guide (Image not shown) received on December 4, 2017
- Prescribing Information (Image not shown) received on December 4, 2017

G.2 Label and Labeling Images

<u>2 mg container label</u>

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[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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4 mg container label

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TERESA S MCMILLAN
05/09/2018

SARAH K VEE
05/09/2018

MEMORANDUM

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

DATE: April 11, 2018

TO: Jessica Lee, RPM/DPARP

FROM: Saharat Patanavanich, OSE SRPM

SUBJECT: OSE Consult – Hepatotoxicity expert consult

APPLICATION/DRUG: NDA 207924, Olumiant (baricitinib) Tablets

Mark Avigan (OSE hepatotoxicity expert) and Lara Dimick (clinical reviewer in DGIEP) were previously consulted and completed a review dated April 10, 2017, regarding the concern of potential dose-dependent hepatotoxicity with baricitinib. Their recommendations were included as "additional comments" along with other deficiencies in the Complete Response letter to the Applicant dated April 12, 2017. In the resubmission, dated December 8, 2017, the Applicant addressed the deficiencies including the comments related to hepatotoxicity with baricitinib. On February 22, 2018, DPARP consulted OSE to review these hepatotoxicity safety issues from the resubmission.

On February 27, 2018, Mark Avigan completed the review of the submitted information related to hepatotoxicity with baricitinib and responded to DPARP via e-mail (see attachment below). Comments from the OSE hepatotoxicity expert's assessment were included in the background document as a part of the Arthritis Advisory Committee (AAC) Meeting for baricitinib. A slide regarding the hepatotoxicity assessment with baricitinib was also provided as a back-up slide for the AAC.

Reference ID: 4252894

Patanavanich, Saharat

From: Avigan, Mark I
Sent: Tuesday, February 27, 2018 4:43 PM
To: Nair, Raj; Dimick, Lara L
Cc: Nikolov, Nikolay; Patanavanich, Saharat
Subject: RE: f/u on baricitinib

Hi Raj and Nikolay,

In follow-up to our Liver Consult to DPARP (Lara Dimick and Mark Avigan) regards baricitinib-related hepatotoxicity in the clinical development program

Your current request pertains to our appraisal of a safety update issued by the sponsor after the liver injury review was completed. The update addresses some of the recommendations made in the original liver consult entered into DARRTs on April 10, 2017. The recommendations in our consult were:

1. Please submit all the data for the study subjects in the phase 2 and 3 trials in an e-DISH format, with narratives complied by someone with expertise in the diagnosis of DILI. See attached document with the requirements for submission of the e-DISH data. See instructions in Appendix A, below.

2. The cases of interest should be reviewed by a panel of expert hepatologists and drug causality and narratives and summary of conclusions provided. Within this expert assessment, distinguish individuals with background/concomitant medications esp. methotrexate. The review of cases should also assess the impact of different doses compared to placebo.

3. Discuss whether there is potential for drug/drug interaction increasing baricitinib's risk of DILI, especially with concurrent exposure to methotrexate. The cumulative exposure to methotrexate should be taken into account.

4. You will also need to identify risks of long-term exposure in RA patients and discuss if there is a potential for adaptation to occur vs. the risk for baricitinib to cause chronic liver injury (e.g., chronic hepatitis, fibrosis etc.).

5. Discuss what monitoring should occur to detect cases of liver injury, and propose an algorithm for response to occurrences of liver enzyme elevations with use of baricitinib.

6. Request a consult from the Divisions of Pharmacovigilance in OPE to interrogate the FAERS database for serious post-marketing adverse events marked by either acute or

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chronic hepatotoxicity, associated with tofacitnib or ruxolitinib.

It appears that the document submitted by the sponsor pertains to Recommendations 1 & 2. The sponsor has provided eDISH plots of ALT vs total bilirubin (Figure 5.38) and of AST vs total bilirubin (Figure 5.40) for patients in the 'All Bari' analysis set. Importantly, all acute liver injury cases of interest in the Hy's law range [right upper quadrant (RUQ)] of the graphic displays marked by elevations of ALT or AST and total bilirubin above 3X ULN and 2X ULN, respectively were individually analyzed by an internal hepatologist and a hepatic and gastrointestinal safety committee regards, their time-related changes in liver test results and their individual narratives describing the corresponding clinical features and diagnostic workups. Of 8 cases in the RUQ, six were associated with baricitinib treatment. From the individual narratives provided in the Appendix (Section 2.5) of the Safety Update Report, plausible alternative diagnostic etiologies have been found and described for each of the cases, leading to a conclusion by the sponsor's analysts that in this dataset there are no cases with biochemical criteria consistent with Hy's law that are causally linked to baricitinib exposure. In my opinion, this conclusion by the sponsor is supported by the clinical and diagnostic data that has been provided in each of the case reports by the sponsor.

It remains to be determined how the other listed recommendations in the April 10, 2017 consult would be addressed either in a pre- or post-market setting.

Thanks,
Mark Avigan

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/s/

SAHARAT PATANAVANICH
04/24/2018

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of Epidemiolocal Study

Date:	February 22, 2018
Reviewer:	Veronica V. Sansing-Foster, PhD, MS Division of Epidemiology 2
Team Leader:	Efe Eworuke, PhD Division of Epidemiology 2
Division Director	Lockwood Taylor, PhD, MPH Division of Epidemiology 2
Subject	Venous Thromboembolism Incidence Rates for Baricitinib
Drug Name(s):	Baricitinib
Application Type/Number:	NDA 207924
Applicant/sponsor:	Eli Lilly and Company
OSE RCM #:	2018-89

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Reference ID: 4224489

EXECUTIVE SUMMARY

The purpose of this epidemiology review is to evaluate the sponsor, Eli Lilly's, claim that the rates of venous thromboembolism (VTE) with baricitinib use within the international clinical studies are comparable to the rates of VTE observed in patients using other approved rheumatoid arthritis (RA) therapies, including disease modifying antirheumatic drugs (DMARDs).

The VTE incidence rate for the all patients exposed to baricitinib in the Phase 2/3 clinical trials (ALL BARI RA) was 0.53 per 100 person years (PY), 0.38 per 100 PY for DVT and 0.24 per 100 PY for PE. The sponsor also conducted an epidemiologic study using FDA Sentinel System (Innovation in Medical Evidence Development and Surveillance [IMEDS] Program) and Truven Marketscan Commercial Claims and Encounters Database (Truven, including Medicare) to provide background rates for VTE observed in patients treated other approved RA therapies. DEPI-II reviewed the methods of the sponsor's epidemiological evaluation and compared them to the ALL BARI RA results. The incidence of VTE per 100 patient years was 1.34 (95% confidence interval [CI] = 1.24 – 1.44) in IMEDS and 1.05 (95% CI=1.01 – 1.09) per 100 PY in Truven. The rate of deep vein thrombosis (DVT) and pulmonary embolism (PE) were also lower in the baricitinib patients as compared to the background rate of DMARD patients.

Based on DEPI-II's review, we cannot conclude that the VTE, DVT, and PE rates within the baricitinib clinical population are comparable to the background rates from the IMEDS/Truven datasets. It is difficult to make a fair comparison between the clinical rates and the background rates for four reasons:

1. The inclusion and exclusion criteria differed between the clinical trials and the observational studies.
2. The absence of a disease severity measure within claims data from the IMEDS/Truven observational study makes it difficult to compare disease severity between the study groups.
3. The US background rates may not be comparable to the international clinical data since the incidence of VTE is higher in Western versus Eastern countries.
4. Data from ALL BARI RA, IMEDS and Truven included patients with current anticoagulant use, potentially for the treatment of a prior VTE.

To help FDA more meaningfully interpret the findings from the study groups, we recommend the sponsor do the following:

1. Provide and compare baseline demographics for ALL BARI RA, IMEDS, and Truven including data regarding cardiovascular (CV) risk factors such as obesity, duration of RA, CV history (including previous VTEs), malignancy history, multiple trauma, number of hospitalizations in the previous year, and concomitant use of drugs with CV risk, including anticoagulant use.
2. Since VTE rates vary by country, please stratify the international clinical data results by U.S. and non-U.S. sites.
3. Please stratify the results by anticoagulant use at baseline.

Reference ID: 4224489

1 INTRODUCTION

The purpose of this epidemiology review is to evaluate the sponsor's (Eli Lilly and Company's (Lilly)) claims that the rates of venous thromboembolism (VTE) with baricitinib use within the clinical studies are comparable to the rates of VTE observed in patients using other approved rheumatoid arthritis (RA) therapies, including conventional and biologic disease modifying antirheumatic drugs (csDMARDs and bDMARDs, respectively). On August 30, 2017, DPARP consulted the Division of Epidemiology II (DEPI-II) to review the epidemiology report by Lilly.

1.1 BACKGROUND AND REGULATORY HISTORY

- On May 6, 2008, Lilly submitted an initial investigational new drug submission (IND 102204) to seek approval for the use of baricitinib, a janus kinase inhibitor (JAK), for the treatment of adult patients with moderately to severely active RA. RA increases the risk of VTE by 40% as compared to patients without RA.[1]
- In January 2015, FDA issued a Type C written response asking Lilly to pool all four Phase 3 studies, and three Phase 2 studies for a safety analysis.
- On 15 January 2016, Lilly submitted the new drug application (NDA 207924) for baricitinib. During the 24-week randomized placebo-controlled period Phase 2/3 studies, 6 patients treated with baricitinib 4-mg reported VTE events, including deep vein thrombosis (DVT) and pulmonary embolism (PE). No events were reported with the 2-mg dose or placebo during this short period.
- In February 2017, baricitinib was approved as a therapy for RA in Europe under the trade name Olumiant.
- On December 4, 2017 Lilly submitted the updated pooled clinical study reports. The All Baricitinib Rheumatoid Arthritis (All BARI RA) integrated analysis sets contained data on all clinical patients exposed to baricitinib. The VTE incidence rate for the ALL BARI RA set was 0.53 per 100 person years (PY), 0.38 per 100 PY for DVT and 0.24 per 100 PY for PE. The sponsor also submitted data from their epidemiologic study using FDA Sentinel (IMEDS Program) and Truven Marketscan Commercial Claims and Encounters Database (Truven, including Medicare) to provide background rates for VTE observed in patients treated other approved RA therapies.

This review will evaluate the sponsor's epidemiological study of the background rates, as well as the results of the ALL BARI RA analysis. The review will conclude with recommendations to the sponsor.

2 PRODUCT LABELING

The European baricitinib label lists VTE within the Special Warnings and Precautions for Use (Section 4.4). Among the DMARDs studied in the US claims data, only adalimumab (Humira) and methotrexate, tablets and injections, have VTE labeled as an adverse reaction (Section 6). VTE is not labeled on tofacitinib, the only JAK approved for RA therapy in the US.

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2.1 BARICITINIB LABEL – EUROPE

4.4 Venous Thromboembolism
Events of deep venous thrombosis (DVT) and pulmonary embolism (PE) have been reported in patients receiving baricitinib. Olumiant should be used with caution in patients with risk factors for DVT/PE, such as older age, obesity, a medical history of DVT/PE, or patients undergoing surgery and immobilisation. If clinical features of DVT/PE occur, Olumiant treatment should be temporarily interrupted and patients should be evaluated promptly, followed by appropriate treatment.

2.2 ADALIMUMAB (HUMIRA) LABEL - US

6.1 Clinical Studies Experience
Less Common Adverse Reactions in Rheumatoid Arthritis Clinical Studies
Thrombosis: Thrombosis leg

6.2 Postmarketing Experience The following adverse reactions have been identified during post-approval use of HUMIRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to HUMIRA exposure.
Vascular disorders: Systemic vasculitis, deep vein thrombosis

2.3 METHOTREXATE (INJECTION AND TABLETS) LABEL - US

6.2 Other Adverse Reactions Other adverse reactions that have been reported with methotrexate in oncology, RA, pJIA [polyarticular juvenile idiopathic arthritis], and psoriasis patients [from clinical trials] are listed below by organ system.
Cardiovascular: pericarditis, pericardial effusion, hypotension, and thromboembolic events (including arterial thrombosis, cerebral thrombosis, deep vein thrombosis, retinal vein thrombosis, thrombophlebitis, and pulmonary embolus).

3 REVIEW METHODS AND MATERIALS

From the NDA 207924 submission, DEPI-II reviewed the following:

- 2.5.5 Clinical Overview click here
- 2.7.6. Synopses of Individual Studies click here
- 5.3.5.3 Integrated Safety Summary of the ALL BARI RA patients (4-month Safety Update) click here
- 5.3.5.4 Epidemiology Report: Evaluation of Venous Thromboembolism Risk Among Patients Diagnosed and Treated for Rheumatoid Arthritis: A Retrospective Cohort Study Utilizing Select Sentinel and Truven Marketscan Databases click here

4 REVIEW RESULTS

4.1 STUDY OBJECTIVE

The primary objective was to describe the background incidence of VTE with disease modifying antirheumatic drugs (DMARDs), including PE and DVT, among patients diagnosed with and treated for RA in routine clinical care (IMEDS-Sentinel and Truven

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Cohort Study) in relation to the VTE rates in patients treated with baricitinib in randomized clinical trials.

4.2 STUDY METHODS (IMEDS-SENTINEL AND TRUVEN-MEDICARE [IMEDS/TRUVEN] COHORT STUDY)

4.2.1 Design and Setting

This was a retrospective, observational, cohort study conducted using US claims data.

4.3 DATA SOURCES, POPULATION AND TIME PERIOD

IMEDS and Truven Marketscan contain healthcare claims information for enrollees in large employer-sponsored health insurance plans in the US. IMEDS provides access to the FDA Sentinel systems to non-FDA stakeholders. The analyses were done by (b) (4) in collaboration with five Sentinel Data Partners. Data from 10/1/2010 – 9/30/2015 on approximately 75 million patients were included.
Truven, the other data source, is a large commercial claims dataset comprised of Truven Marketscan and Medicare. Data from 1/1/2011 to 12/31/2015 on approximately 115 million patients were included.

Subjects were included in the study if they were diagnosed with RA (defined as at least 2 RA diagnosis codes [ICD-9-CM: 714.0, 714.1, 714.2] within 7-365 days of each other plus the use of any of the listed DMARDS by the index date ± 1 month), age 18 years or older at the date the drug was first dispense (index date), and were continuously enrolled in the health plan with both medical and pharmacy coverage from 12 months prior to the index date through follow-up. Patients were excluded from the cohort if they had a diagnosis for the specified event in any care setting in the 365 days prior to or on their index date.

4.3.1 Exposure

The exposure for cohort inclusion was RA treatments, namely csDMARDs (leflunomide) and biological bDMARDs (abatacept, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, tofacitinib). Exposure to RA treatments was identified using National Drug Codes (NDC) and Healthcare Common Procedure Coding System (HCPCS) codes.

4.3.2 Safety Outcomes

The primary safety outcomes are VTE, DVT and PE. The outcomes were defined as at least two International Classification of Diseases (ICD -9-CM) diagnosis codes 1) in inpatient or emergency department claims; or 2) in ambulatory claims with an outpatient dispensing of anticoagulants within 31 days. For individual outcomes DVT and PE were defined as diagnosis within inpatient, outpatient or ambulatory claims. Anticoagulant use was identified using NDC and HCPCS codes. For the analyses of the individual outcomes, PE and DVT were defined by at least two ICD-9 diagnosis codes within inpatient, emergency room, and ambulatory claims. There was no requirement of anticoagulant use for the ambulatory definition.

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Based on a systematic review of validated methods for identifying VTE in administrative and claims data, the positive predive values (PPV) of the VTE definitions ranged from 42%-93%.[2] The PPV for DVT ranges from 31-97% and the PPV for PE ranges from 24-92%. The PPV for the combination of PE and DVT, regardless of anticoagulant use, was 65%-95%.[2]

4.3.3 Follow-up and Censoring Indicators

Subjects were followed until the event of interest, death, plan disenrollment, or the end the study period: October 2015 in IMEDS and December 2015 in Truven. For treatment-specific incidence rates, patients were also censored when they discontinued the drug of interest or began another medication.

4.3.4 Covariate

The results were stratified by the following covariates: age, calendar year and gender.

4.3.5 Statistical Analysis

For the IMEDS-Sentinel data, incidence rates were calculated as the number of events per 100 patient years (PY) using the modular programs and summary table query tools. Specifically, treatment episode-specific incidence rates were based on the first use of a medication in the record and occurrence of the outcome during the days' supply of the medication or the at-risk window equivalent to 5 half-lives immediately following the end of the treatment episode. No statistical test or direct comparison was conducted, therefore there was no formal power calculation. Incidence rates were stratified by age, gender and calendar year. The sponsor only provided the age-stratified rates in this report. Analyses of the Truven data were conducted using custom program to replicate the analysis of the IMEDS-Sentinel data.

The DEPI-II reviewer calculated the mid-P exact 95% CI's using Open Epi Software in some instances where the sponsor did not provide the 95% CI's.

4.4 STUDY METHODS (ALL BARI RA)

The NDA's clinical safety package included data from international, randomized, placebo-controlled, blinded, clinical studies, including three Phase 2 studies (JADC, JADA, JADN) and four Phase 3 studies (JADV BEAM Study II, JADX BUILD Study III, JADW BEASONG Study IV, JADZ BEGIN Study I), and unblinded data from an ongoing long-term extension study. The RA integrated safety analyses (ALL BARI RA) from the NDA program comprise data from 3464 RA adult patients exposed to baricitinib in the Phase 2/3 studies. The seven Phase 2/3 studies of adult RA patients are described in Figure 1 below and within Appendices A and B.

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a Pati
b Stu
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KEY: ACR20 - American College of Rheumatology score of 20 indicating improvement, cDMARD – conventional synthetic disease modifying antirheumatic drug, IR – insufficient response or failure, MTX – methotrexate, prev – previous, RA – rheumatoid arthritis

Figure 1. Phase 2 and Phase 3 studies of baricitinib in rheumatoid arthritis

5 STUDY RESULTS

The incidence rates of VTE, DVT and PE were lowest in the ALL BARI RA group compared to all the background rates from the observational data, regardless of the sensitivity and specificity of the outcome definitions used.

5.1 VTE

The incidence of VTE per 100 PY was 0.53 (95% CI=0.38 – 0.71) in ALL BARI RA, 1.34 (95% CI= 1.24 – 1.44) in IMEDS and 1.05 (95% CI=1.01 – 1.09) per 100 PY in Truven per definition 2 (Table 1). The incidence of VTE per 100 PY for csDMARDs was 1.49 (95% CI=1.30-1.71) in IMEDS and 1.23 (95% = 1.14 – 1.32) PY in Truven per definition 2. The incidence of VTE per 100 PY for bDMARDs was 0.98 (95% CI = 0.83 – 1.14) in IMEDS and 0.95 (95% CI = 0.89 – 1.02) in Truven per definition 2.

5.2 DVT AND PE

Within ALL BARI RA, the incidence of DVT was 0.38 (95% CI = 0.25 – 0.54) per 100 PY and 0.24 (95% CI = 0.14 – 0.37) per 100 PY for PE. Within IMEDS, the incidence rate of DVT was 1.97 (95% CI=1.85-2.09) per 100 PY, and 0.77 (95% CI=0.70 - 0.84)

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per 100 PY for PE. Within Truven, the incidence rate of DVT per definition 2 was 0.84 (95% CI= 8.00 – 8.72) per 100 PY, and 0.38 (95% CI=0.36 - 0.41) per 100 PY for PE. [1]

The incidence rate of PE was also consistently lower than DVT across drug types and across all data sets.

5.2.1 BY AGE GROUPS AND DRUG

When the results were stratified by age groups, the ALL BARI RA incidence rates remained lower than the background rates with IMEDS/Truven. Age is a risk factor for VTE and, as such, the incidence rates increased with older age groups within ALL BARI RA, Truven and IMEDS (APPENDIX B. Table 3). For example, the VTE incidence rate for the 18-49 year olds ranged from 0.14 – 0.89 events per 100 PY, while the VTE incidence rates for 65 plus age group ranged from 1.09 – 3.15 events per 100 PY.

Within IMEDS/Truven, the incidence rates for VTE, DVT and PE are consistently lowest with adalimumab (range 0.29 – 1.18 per 100 PY) and highest with rituximab (range 2.00 - 5.40 per 100 PY). These differences in incidence rates between specific drug types attenuated when stratified by age.

6 STUDY CONCLUSION

The sponsor concluded that the rates of VTE, DVT and PE within the clinical study population (ALL BARI RA) on baricitinib were lower than or within the lower range of the background rates observed in the underlying RA population treated with DMARDs (IMEDS/Truven). The clinical study rates remained lower than the background rates from the observational studies across all outcome definitions, drug types, and age groups.

Table 1. Study Designs and Results Summary

Author (Year) Design	Exposure (type)	Outcome	Cohort Size (Patients, Patient Years)	Crude Incidence per 100 Patient Years (95% Confidence Intervals)	Comment
Lilly (2016), pooled prospective RCTs	Baricitinib, Placebo/Active Comparator to Baricitinib (Incident use)	VTE, DVT, PE	N=3,492 PY = 7948.6	VTE = 0.53 (95% CI=0.38 – 0.71 DVT = 0.38 (95% CI = 0.25 – 0.54) PE = 0.24 (95% CI = 0.14 – 0.37)	▪ Past DMARD users ▪ Does not exclude patients with history of VTE ▪ Disease severity data available ▪ International study
Lilly (2016), retrospective cohort	DMARDs (Incident User)	VTE, DVT, PE	IMEDS: N=69.095 PY=53,786.0	IMEDS: VTE=1.34 (1.24, 1.44) DVT=1.97 (1.85, 2.09) * PE= 0.77 (0.70, 0.84) *	▪ New DMARD users ▪ Excludes patients with VTE 1 year pre-baseline

[1] The mid-P exact test 95% Confidence intervals calculated by DEPI-II reviewer using Open Epi Software: http://www.openepi.com/Menu/OE_Menu htm

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			Truven: N=205,875 PY=246,360.8	Truven**: VTE= 1.05 (1.01, 1.09) DVT= 0.84 (0.80, 0.87) * PE=0.38 (0.36, 0.41) *	▪ No disease severity data ▪ Claims data retrospectively collected ▪ US only

KEY: CI – confidence interval, DMARDs – disease modifying antirheumatic drugs, IMEDS - Innovation in Medical Evidence Development and Surveillance, PE – pulmonary embolism, PY – patient years, US – United States, RCT – randomized controlled trial, VTE – venous thromboembolism

* The mid-P exact test 95% CIs were calculated by the DEPI-II reviewer using Open Epi Software since they were not provided within the sponsor's report: www.openepi.com.
** The outcome definitions are based on definition (2):

- VTE - an inpatient diagnostic code for venous or pulmonary embolism or phlebitis and thrombophlebitis or (b) an outpatient diagnostic code plus a prescription for an anticoagulant (apixaban, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, rivaroxaban, tinzaparin, warfarin) within 31 days of the VTE diagnostic code.
- DVT - an inpatient diagnostic code for venous embolism or phlebitis and thrombophlebitis or (b) an outpatient diagnostic code plus a prescription for an anticoagulant within 31 days of the DVT diagnostic code.
- PE - an inpatient diagnostic code for pulmonary embolism or (b) an outpatient diagnostic code plus a prescription for an anticoagulant within 31 days of the PE diagnostic code.

7 DISCUSSION

7.1 STRENGTHS

IMEDS/Truven provide a large sample size for the background rate. Both IMEDS and Truven cover a large proportion of the US population who are employed and insured, and the Truven data also contains data for patients over the age of 65 enrolled in Medicare. The Medicare data covers elderly RA patients who are retired, disabled, or are too ill to work.

7.2 MAJOR LIMITATIONS

It is difficult to compare incidence rates from the ALL BARI RA clinical trials to the IMEDS/Truven observational data for the following reasons:

First, the inclusion and exclusion criteria differed between the clinical trials and the observational studies. Mainly, the ALL BARI RA clinical trials included patients who were currently using or who failed DMARDs while the IMEDS/Truven background datasets consisted of incident users of DMARDs (APPENDIX A. Table 2). Since the baricitinib patients survived DMARD use, they may be at lower risk of VTE compared to incident users of DMARDs evaluated in the observational data.

Additionally, the IMED/Truven observational studies excluded patients with a VTE event within a year prior to baseline while the ALL BARI RA clinical trials did not. The rates within the clinical trials may include more instances of recurrent VTE than the observational data – though the proportion of recurrent VTE's within the study groups

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would be unknown. A fairer source of VTE background rates would be from the clinical studies of DMARDs with similar exclusion/exclusion criteria, especially tofacitinib (JAK).

Second, the absence of a disease severity measure within claims data from the IMEDS/Truven observational study makes it difficult to compare disease severity between the study groups. RA is a risk factor for VTE. It is unknown if IMEDS/Truven patients had more severe RA, accounting for the higher incidence of RA as compared to the ALL BARI RA patients. Additional data regarding cardiovascular (CV) risk factors such as obesity, duration of RA, CV history (including previous VTE), malignancy history, multiple trauma, number of hospitalizations in previous years, and concomitant use of drugs with CV risk would facilitate comparison of the study groups.[3]

Third, the US observational data may not be comparable to the international clinical data since the incidence of VTE varies by country. While the background rates from the observational data were based on US claims data, between the seven Phase 2/3 studies 26-100% of the ALL BARI RA patients were from international clinical studies, including countries in South America, Europe, and Asia (APPENDIX B. Table 2*).* Eastern countries (i.e. Japan, Korea) have lower VTE rates as compared to Western countries, including the US (APPENDIX C. Table 5).[4,5] For instance the 2018 estimated incidence of VTE ranges from 17 per 100,000 persons in Hong Kong to 143 per 100,000 persons in Norway, and the incidence of PE ranges from 6 per 100,000 in Japan to 69 per 100,000 persons in the US (age adjusted).[5] These global differences could account for the lower rates seen in the international clinical data as compared to the US background rates.

Fourth, both the trial and observational data did not exclude patients with current anticoagulant use for the treatment of prior VTE. Although the All BARI RA and IMEDS/Truven data excluded patients who used the exposure medication or had a recent history of VTE prior to the index date, the studies did not exclude patients who were currently using anticoagulants at baseline. Current anticoagulant use may be indicative of treatment for a previous VTE. A previous VTE is the most important risk factor for predicting recurrence of the condition.[6] Therefore, by including patients currently on anticoagulants, the studies may have captured recurrent VTEs. These events could have inflated the incidence rates across all data sources. However, it is unknown if the proportion of patients on anticoagulants at baseline is different across study groups. A noteworthy difference in this proportion could possibly explain some of the differences in VTE rates between the data sources.

8 CONCLUSIONS

Based on DEPI-II's review, we conclude that the VTE, DVT, and PE rates within the baricitinib clinical population are not comparable to the background rates from the

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DMARDs observational populations. There are limitations which make a fair comparison between the clinical rates and the background rates difficult.

9 RECOMMENDATIONS FOR THE SPONSOR

The current epidemiology report does not provide accurate context for the background rate of VTE, DVT, and PE for the RA patients treated with DMARDS. To help FDA more meaningfully interpret the findings from the study groups, please include the following:

1. Provide and compare baseline demographics for ALL BARI RA, IMEDS, and Truven including data regarding cardiovascular (CV) risk factors such as obesity, duration of RA, CV history (including previous VTEs), malignancy history, multiple trauma, hospitalizations in previous year, and concomitant use of drugs with CV risk, including anticoagulant use.
2. Since VTE rates vary by country, please stratify the international clinical data results by U.S. and non-U.S. sites.
3. Please stratify the results by anticoagulant use at baseline.

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10 REFERENCES

1. Kim SC, Schneeweiss S, Liu J, Solomon DH. Risk of Venous Thromboembolism in Patients With Rheumatoid Arthritis. *Arthritis Care & Research.* 2013;65(10):1600-1607.
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4. Wang K-L, Yap ES, Goto S, Zhang S, Siu C-W, Chiang C-E. The diagnosis and treatment of venous thromboembolism in Asian patients. *Thrombosis Journal.* 2018;16(1):4.
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APPENDIX A.

Table 2.

Relevant Controlled Clinical Studies with Baricitinib in RA

ID Year* *Study*	Study Characteristics† - Patient age - Response to past treatment - Background treatment - Study design; duration	Treatment groups‡	N§	Efficacy Variables¶	Regions and Countries//
Phase 2					
JADC [05/09 to 07/10]	- Over 18 years - Inadequate response to DMARD - DMARD background - Parallel arm, DB, no rescue; 24 weeks	Bar 4 mg QD Bar 7 mg QD Bar 10 mg QD Placebo, up to wk 12	32 32 32 31	1 : ACR 20 at wk 12	US, Europe (74% US)
JADA [11/10 to 02/12 for Part B]	- Over 18 years - Inadequate response to mtx - DMARD background - Parallel arm, DB, no rescue; 12 weeks (Part A), additional 12 weeks (Part B), Open label extension to additional 52 weeks (Part C), and additional 52 weeks (Part D)	Bar 1 mg QD Bar 2 mg QD Bar 4 mg QD Bar 8 mg QD Placebo, up to wk 12 Part B explored BID dosing	49 52 52 50 98	1° :ACR 20 at wk 12	US, Mexico, Europe, India (32% US)
JADN [11/11 to 12/13]	- Over 18 years - Inadequate response to mtx - DMARD background - Parallel arm, DB, 14 weeks (Part A), additional single blind for 52 weeks (Part B)	Bar 1 mg QD Bar 2 mg QD Bar 4 mg QD Bar 8 mg QD Placebo, up to wk 12	24 24 24 24 49	1°:ACR 20 at wk 12	Japan (100%)
Phase 3					
JADV BEAM Study II [10/12 to 09/15]	- Over 18 years - Inadequate response to mtx; no previous biologics - Mtx with sulfalazine or hydroxychloroquine background - Parallel arm, DB, rescue at week 16; 52 weeks	Bar 4 mg QD Adalimumab Placebo, up to wk 24	488 330 487	1°:ACR 20 at wk 12 2°: HAQ-DI at wk 12; mTSS at wk 24	North America, Central and South America, Europe, Asia (30% North America)
JADX BUILD Study III [01/13 to 12/14]	- Over 18 years - Inadequate response to non-biologic DMARDs; no previous biologics - Non-biologic DMARD background - Parallel arm, DB, rescue at week 16; 24 weeks	Bar 2 mg QD Bar 4 mg QD Placebo, up to wk 24	229 227 228	1°: ACR 20 at wk 12 2°: HAQ-DI at wk 12; mTSS at wk 24	North America, Central and South America, Europe, Asia (30% North America)
JADW BEACON Study IV [01/13 to 09/14]	- Over 18 years - Inadequate response to TNF inhibitor biologics - Non-biologic DMARD background - Parallel arm, DB, rescue at week 16; 24 weeks	Bar 2 mg QD Bar 4 mg QD Placebo, up to wk 24	174 177 178	1°: ACR 20 at wk 12 2°: HAQ-DI at wk	North America, Central and South America, Europe, Asia (44% North America)
JADZ BEGIN Study I [01/13 to 08/14]	- Over 18 years - Treatment naïve early RA - None - Parallel arm, DB, rescue at week 24; 52 weeks	Mtx Bar 4 mg QD Mtx + Bar 4 mg QD	213 160 215	1°: ACR 20 at wk 24 2°: HAQ-DI at wk 24; mTSS at wk 24	North America, Central and South America, Europe, Asia (20% North America)
Long-term extension of other studies					
JADY BEYOND [06/13 to ongoing]	Extension of studies JADA, JADZ, JADV, JADX, JADW, and JADS [JADX and JADW (2 mg dose), and other studies (4 mg dose)]	Bar 2 mg QD Bar 4 mg QD	–	Safety	--

*studies as I, II, III, and IV [month/year study started-completed],
† DMARD = disease modifying anti-rheumatic drugs; Mtx or mtx = methotrexate; DB = double blind
‡ Bar = Baricitinib; In studies JADV, JADX, and JADW, placebo treatment groups and active treatment groups all included background DMARDs with or without methotrexate
§ Intent to treat (ITT); appropriate statistical hierarchy was followed for HAQDI and mTSS
¶ ACR=American College of Rheumatology; HAQ-DI=Health Assessment Questionnaire Disability Index; mTSS=modified Total Sharp Score
// Shows as regions: North America includes USA and Canada

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APPENDIX B.

Table 3. Venous Thromboembolism, Deep Vein Thrombosis, and Pulmonary Embolism Incidence Rates by Age and Study

Source Outcome	Age, Years	Sample Size, N			IR per 100 PY (95 % Confidence Interval)				
		ALL BARI RA	*IMEDS*	*TRUVEN*	*ALL BARI RA*	*IMEDS*	*TRUVEN** ǂ		
							Definition 1	*Definition 2*	*Definition 3*
VTE	All ages	3492	69095	205785	0.53 (0.38, 0.71)	1.34 (1.24, 1.44)	0.68 (0.65, 0.71)	1.05 (1.01, 1.09)	1.63 (1.58, 1.69)
	18-49	1245	16340	62394	0.14 (0.04, 0.35)	0.49 (0.37, 0.63)	0.32	0.50	0.89
	50-59	1121	18151	68260	0.57 (0.32, 0.95)	0.90 (0.75, 1.07)	0.52	0.77	1.27
	60-64	514	9272	33508	0.77 (0.35, 1.47)	1.16 (0.93, 1.43)	0.70	1.05	1.59
	65+	612	25332	41623	1.09 (0.59, 1.83)	2.13 (1.94, 2.33)	1.36	2.16	3.15
DVT	All ages	3492	69483	205785	0.38 (0.25, 0.54)	1.97 (1.85, 2.09)ǂ	0.55 (0.52, 0.58)	0.84 (0.80, 0.87)	1.36 (1.31, 1.40)
	18-49	1245	NR	62394	0.14 (0.04, 0.36)	NR	0.26	0.39	0.75
	50-59	1121		68260	0.46 (0.24, 0.80)		0.42	0.61	1.05
	60-64	514		33508	0.51 (0.19, 1.12)		0.58	0.85	1.32
	65+	612		41623	0.62 (0.27, 1.22)		1.09	1.73	2.61
PE	All ages	3492	70725	205785	0.24 (0.14, 0.37)	0.77 (0.70, 0.84)ǂ	0.26 (0.24, 0.28)	0.38 (0.36, 0.41)	0.46 (0.43, 0.49)
	18-49	1245	NR	62394	0.04 (0.00, 0.19)	NR	0.13	0.18	0.23
	50-59	1121		68260	0.15 (0.04, 0.39)		0.20	0.29	0.35
	60-64	514		33508	0.51 (0.19, 1.12)		0.26	0.39	0.46
	65+	612		41623	0.62 (0.27, 1.22)		0.50	0.76	0.91

KEY: DVT – deep vein thrombosis, DMARDs – disease modifying antirheumatic drugs, IR – incidence rate, NR – not reported, PE – pulmonary embolism, PY – patient years, VTE – venous thromboembolism

* The outcome definitions are based on DEFINITION (1) 1: a diagnostic code plus a prescription for an anticoagulant (apixaban, dabigatran, dalteparin, edoxaban, enoxaparin, fondaparinux, rivaroxaban, tinzaparin, warfarin) within 31 days of the VTE, DVT, PE diagnostic code; DEFINITION 2: (a) an inpatient diagnostic code for venous or pulmonary embolism or phlebitis and thrombophlebitis or DVT or (b) an outpatient diagnostic code plus a prescription for an anticoagulant within 31 days of the VTE diagnostic code; DEFINITION 3: a diagnostic code for venous embolism or phlebitis and thrombophlebitis or DVT in an inpatient, outpatient or emergency department care setting.

ǂ The mid-P exact test 95% confidence intervals for all ages have been calculated by the DEPI-II reviewer using Open Epi Software: http://www.openepi.com/PersonTime1/PersonTime1 htm

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APPENDIX C.

Table 4. Estimated incidence of venous thromboembolism from studies in Western and Asian populations (Wang et al. 2018) [4]

	Western countries			Asian countries				
Incidence[a]	UK	Norway	US (age-adjusted)	Taiwan[b]	Hong Kong	Japan[c]	Korea[c] (age-adjusted)	Singapore[d]
VTE	75	143	117	16	17	NR	14	57
DVT	40	93	48	NR	NR	12	5	NR
PE	34	50	69	NR	NR	6	7	15

[a]First incidence per 100,000 person-years unless indicated otherwise
[b]Crude incidence
[c]Overall incidence
[d]Overall incidence (Chinese, Indian, Malay)
DVT deep vein thrombosis, *NR* not reported, *PE* pulmonary embolism, *VTE* venous thromboembolism

Table 1 from Wang K-L, Yap ES, Goto S, Zhang S, Siu C-W, Chiang C-E. The diagnosis and treatment of venous thromboembolism in Asian patients. Thrombosis Journal. 2018;16(1):4.[4]

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02/22/2018

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

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

Memorandum

Date: April 11, 2017

To: Jessica Lee, Pharm.D., Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: NDA 207924
Baricitinib

OPDP acknowledges receipt of DPARP's March 3, 2016, consult request to review the proposed product labeling (package insert, patient package insert, and carton/container labeling) for Baricitinib. Reference is made to DPARP's email to OPDP on April 4, 2017, conveying that a Complete Response action will be taken. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DPARP submit a new consult request during the subsequent review cycle.

If you have any questions, please contact Adewale Adeleye at 240-402-5039 or adewale.adeleye@fda.hhs.gov.

Reference ID: 4082703

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/s/

ADEWALE A ADELEYE
04/11/2017

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:	March 29, 2017
To:	Badrul Chowdhury, MD, Ph.D. Director **Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Twanda Scales, RN, BSN, MSN/Ed. Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
Subject:	Review Deferred: Patient Package Insert (PPI)
Drug Name (established name):	OLUMIANT (baricitinib)
Dosage Form and Route:	tablets
Application Type/Number:	NDA 207924
Applicant:	Eli Lilly and Company

1 INTRODUCTION

On January 15, 2016 Eli Lilly and Company submitted for the Agency's review an original New Drug Application (NDA) 207924 for OLUMIANT (baricitinib) tablets indicated for the treatment of adult patients with moderately to severely active rheumatoid arthiritis. On March 4, 2016 the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Patient Package Insert (PPI) for OLUMIANT (baricitinib) tablets.

This memorandum documents the DMPP review deferral of the Applicant's proposed Patient Package Insert (PPI) for OLUMIANT (baricitinib) tablets.

2 CONCLUSIONS

Due to outstanding clinical deficiencies, DPARP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please let us know if you have any questions.

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/s/

TWANDA D SCALES
03/29/2017

MARCIA B WILLIAMS
03/29/2017

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

PLLR Labeling Memorandum

Date:	January 5, 2017
From:	Tamara Johnson, MD, MS Team Leader, Maternal Health Division of Pediatric and Maternal Health
Through:	Lynne Yao, MD Division Director Division of Pediatric and Maternal Health
To:	Division of Pulmonary, Allergy, Rheumatology Products (DPARP)
Drug:	Olumiant (baricitinib) tablets
NDA:	207924
Applicant:	Eli Lilly
Drug Class:	Janus kinase (JAK) inhibitor
Indication:	Treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate
Subject:	Pregnancy and Lactation Labeling Rule (PLLR) Conversion
Submission Date:	January 15, 2016
Consult Date:	May 17, 2016
Consult Request:	DPARP requests input regarding the PLLR language in the labeling.

Reference ID: 4037220

PURPOSE

The purpose of the memorandum is to acknowledge the input of the Division of Pediatric and Maternal Health (DPMH) on labeling recommendations in order to bring the Olumiant (baricitinib) labeling in compliance with the Pregnancy and Lactation Labeling Rule (PLLR) format and content requirements.

BACKGROUND

The Pregnancy and Lactation Labeling Rule

On June 30, 2015, the "*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*," also known as the Pregnancy and Lactation Labeling Rule (PLLR) went into effect.[1] The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) are removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, 8.3 and 17 of the Olumiant (baricitinib) labeling for compliance with the PLLR. DPMH labeling recommendations were conveyed to DPARP at the September 15, 2016 labeling meeting. DPMH agrees with the PLLR labeling for Olumiant (baricitinib) and refers the reader to the final NDA action for the final labeling.

[1] Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling (79 FR 72063, December 4, 2014).

Reference ID: 4037220

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/s/

TAMARA N JOHNSON
01/05/2017

LYNNE P YAO
01/05/2017

LABLE, LABEING AND PACKAGING 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:	January 4, 2017
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Application Type and Number:	NDA 207924
Product Name and Strength:	Olumiant (baricitinib) 2 mg and 4 mg tablets
Product Type:	Single-ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Eli Lilly and Company
Submission Date:	January 15, 2016 and February 10, 2016
OSE RCM #:	2016-330
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (Acting):	Mishale Mistry, PharmD, MPH

Reference ID: 4029893

1 REASON FOR REVIEW

Eli Lilly and Company submitted NDA 207924 for Olumiant (baricitinib) tablets on January 15, 2016. Thus, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested we evaluate the container labels and prescribing information for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material 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
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We performed a risk assessment of the proposed container labels and prescribing information to identify deficiencies that may lead to medication errors and other areas of improvement. DMEPA identified areas in the labels and labeling that can be improved to increase the readability and prominence of important information and promote the safe use and handling of the product. We provide recommendations in Section 4.1 for the Applicant to address these deficiencies.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels and labeling can be improved to promote the safe use of the product.

Reference ID: 4029893

4.1 RECOMMENDATIONS FOR THE ELI LILLY AND COMPANY

We recommend the following be implemented prior to approval of this NDA 207924:

A. Container Label

1. As currently displayed, the font color selection (b) (4) of the established name does not afford adequate contrast against the white background and makes this information difficult to read. We recommend revising the font color of the established name to increase readability.
2. Revise the font color of the proprietary name (b) (4)
3. Relocate the net quantity and Rx only statements away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
4. To increase the prominence of important information, relocate the strength statement underneath the established name and dosage form statements. In addition, ensure that the first letter of the proprietary name, Olumiant is capitalized. To ensure there is an adequate amount of white space, consider removing the company name, website, or logo. For example:

   Olumiant
   (baricitinib) tablets
   2 mg
5. Revise dosage statement to "Usual dosage: See Prescribing Information" for consistency with other labels.

Reference ID: 4029893

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Olumiant (baricitinib) that Eli Lilly and Company submitted on January 15, 2016.

Table 2. Relevant Product Information for Olumiant (baricitinib)	
Initial Approval Date	Pending
Active Ingredient	baricitinib
Indication	Treatment of adult patients with moderately to severely active rheumatoid arthritis
Route of Administration	Oral
Dosage Form	Tablets
Strength	2 mg and 4 mg
Dose and Frequency	4 mg once daily (some patients require 2 mg once daily)
How Supplied	2 mg strength – bottles of 30 tabs (b) (4) (b) (4)
Storage	20˚C - 25˚C (68˚F - 77˚F); excursions permitted to 15˚C - 30˚C (59˚F - 86˚F)

Reference ID: 4029893

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following Olumiant (baricitinib) labels and labeling submitted by Eli Lilly and Company on January 15, 2016 and February 10, 2016.

- Container Label

G.2 Label and Labeling Images

Container Label

(b) (4)

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

Reference ID: 4029893

(b) (4)

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/s/

TERESA S MCMILLAN
01/04/2017

MISHALE P MISTRY
01/04/2017

CLINICAL INSPECTION SUMMARY

Date	July 20, 2016
From	Anthony Orencia M.D., F.A.C.P., GCPAB Medical Officer Susan D. Thompson, M.D. Team Leader for Janice Pohlman M.D., M.P.H., GCPAB Team Leader Kassa Ayalew, M.D., M.P.H., GCPAB Branch Chief
To	Raj Nair M.D., Medical Officer Janet Maynard, M.D., Clinical Team Leader Jessica Lee, Pharm.D., Regulatory Project Manager
NDA	207924
Applicant	Eli Lilly
Drug	baricitinib
NME	Yes
Therapeutic Classification	NME
Proposed Indication	Rheumatoid Arthritis
Consultation Request Date	April 5, 2016
Summary Goal Date	October 15, 2016
Action Goal Date	January 17, 2017
PDUFA Date	January 15, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

For NDA 207924, four clinical sites (Drs. Fleischmann, Greenwald, Ludivico and Surbeck) were selected for audit and inspection. The sponsor (Eli Lilly) was also inspected. Based on results of the inspections, the data submitted by the sponsor in support of the requested indication appear acceptable and the studies appear to have been conducted adequately.

The final classification for the inspection of Drs. Fleischmann, Surbeck and Ludivico is No Action Indicated (NAI). The preliminary classification for the inspections of the sponsor (Eli Lilly) and Dr. Greenwald is No Action Indicated (NAI) based on communications with the field investigator.

2. BACKGROUND

JAK kinases are intimately involved in signal transduction by various cytokine receptors. Given the role of cytokines in various phases of active autoimmune arthritis, their inhibition with JAK inhibitors (e.g., baricitinib) is thought to provide a clinical benefit, by dampening a set of inflammatory processes found disease conditions, such as active rheumatoid arthritis. Baricitinib is a JAK inhibitor with specificity for JAK1/2.

Inspections were requested for the three randomized clinical trials that were submitted in support of the applicant's NDA for the treatment of adult patients with moderately to severely active rheumatoid arthritis, who have had an inadequate response or intolerance to modifying anti-rheumatic drugs (DMARDs) in various rheumatoid arthritis-treated patient subgroup scenarios.

For this NDA under the PDUFA V program review, for baricitinib, CDER DPARP requested four domestic sites for inspection. These sites principally enrolled large numbers of patients and were considered to have other study risk considerations by CDER DPARP. Inspection of the sponsor is being done to assess oversight and conduct of studies submitted to support approval of this NME NDA.

Protocol I4V-MC-JADV

Study I4V-MC-JADV (JADV) was a 52-week, Phase 3, multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled, parallel-group, outpatient study comparing the efficacy of baricitinib versus placebo on signs and symptoms, function, remission, and structural progression in patients with moderately to severely active rheumatoid arthritis who had an insufficient response to MTX and who had never been treated with a biologic DMARD (i.e., MTX-IR patients).

The objective of the study was to determine whether baricitinib is superior to placebo in the treatment of patients with moderately to severely active rheumatoid arthritis despite methotrexate (MTX) treatment (that is, inadequate response to methotrexate [MTX-IR]), as assessed by the proportion of patients achieving a 20% treatment response improvement in American College of Rheumatology criteria (ACR20) at Week 12. The primary efficacy endpoint was ACR20 response.

The study was conducted in 281 study centers in 26 countries. There were 1280 subjects planned to be enrolled in this clinical investigation; 1307 subjects were randomized. The first patient was enrolled on October 23, 2012 and the last patient completed on September 29, 2015.

Protocol I4V-MC-JADW

Study JADW was a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo controlled, outpatient study comparing the efficacy of 4-mg and 2-mg QD doses of baricitinib versus placebo on signs and symptoms of rheumatoid arthritis. Eligible patients had moderately to severely active rheumatoid arthritis, had an insufficient response to or were intolerant to at least one biologic Tumor Necrosis Factor (TNF) inhibitor therapy (TNF-IR patients), and were taking background DMARD therapy (with or without methotrexate [MTX]).

The primary objective of the study was to determine whether baricitinib 4-mg daily (QD) is superior to placebo in the treatment of patients with moderately to severely active rheumatoid arthritis who had an inadequate response to a TNF inhibitor, despite ongoing treatment with conventional DMARDs, as assessed by the proportion of patients achieving a 20% treatment response improvement in American College of Rheumatology criteria (ACR20) at Week 12. The primary efficacy endpoint was ACR20 response.

The study was conducted in 140 study centers in 20 countries. There were 735 subjects planned to be enrolled in this clinical investigation; 525 subjects were randomized. The first subject enrolled on January 23, 2013, and the last subject completed on September 2, 2014.

Protocol I4V-MC-JADX

Study JADX was a Phase 3, multicenter, randomized, double-blind, double-dummy, placebo controlled, outpatient study comparing the efficacy of 4-mg and 2-mg QD doses of oral baricitinib with placebo, in combination with a DMARD (including methotrexate [MTX]) on signs and symptoms and function during a 24-week treatment period.

The primary objective of the study was to determine whether baricitinib 4-mg once daily was superior to placebo in the treatment of patients with moderately to severely active rheumatoid arthritis who had an inadequate response to or were intolerant to at least one conventional DMARD (DMARD-IR [inadequate response] patients) and who had not received a biologic disease-modifying anti-rheumatic drug, as assessed by the proportion of patients achieving a 20% treatment response improvement in American College of Rheumatology criteria (ACR20) at Week 12. The primary efficacy endpoint was ACR20 response.

This study was conducted at 182 study centers in 22 countries. There were 220 subjects planned to be enrolled in this clinical investigation; 228 subjects were randomized. The first subject enrolled on January 10, 2013, and the last subject completed on December 19, 2014.

3. RESULTS (by site):

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
Roy Fleischmann, M.D. 8144 Walnut Hill Lane Dallas, TX 75231	Site 907 I4V-MC-JADX 8 enrolled subjects	June 8-14, 2016	NAI
Maria Greenwald, M.D. 72855 Fred Waring Drive Palm Desert, CA 92260	Site 913 I4V-MC-JADV 14 enrolled	June 1-13, 2016	Pending: Preliminary NAI
Charles Ludivico, M.D. 701 Ostrum St. Bethlehem, PA 18015	Site 968 I4V-MC-JADW 15 enrolled	April 25-27, 2016	NAI

Name of CI, Address	Site #, Protocol #, and # of Subjects	Inspection Date	Classification
William Surbeck, M.D. 4619 S Harvard Tulsa, OK 74135	Site 958 I4V-MC-JADW 11 enrolled	May 2-6, 2016	NAI
Eli Lilly and Company Lilly Corporate Center Indianapolis, IN 46285	Sponsor for: IV-MC-JADX 228 randomized IV-MC-JADV 1307 randomized IV-MC-JADW 525 randomized	June 6-10, 2016	Pending: Preliminary NAI

Key to Compliance Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

Clinical Study Site Investigator

1. **Roy Fleischmann, M.D./Study Protocol JADX Site 907**
   Dallas, TX 75231

The inspection was conducted from June 8 to14, 2016. Under Study JADX, a total of 18 subjects were screened, and 8 subjects enrolled and were randomized. Two patients discontinued (#(b) (6) due to herpes zoster and #(b) (6) died). Six subjects completed the study. An audit, of all eight enrolled plus screened subjects' records, was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. 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 or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

2. Maria Greenwald, M.D./Study Protocol JADV/Site 913
Palm Desert, CA 92260

The inspection was conducted from June 1 to June 13, 2016. Under Study JADV, a total of 27 subjects were screened and 14 subjects enrolled. One subject discontinued from the study after enrollment. Thirteen subjects completed the study. An audit of 14 enrolled and randomized subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. 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 or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Charles Ludivico, M.D./ Study Protocol JADW/ Site 968
Bethlehem, PA 18015

The inspection was conducted from April 25 to 27, 2016. Under Study JADW, a total of 25 subjects were screened and 15 enrolled. Two subjects (Subject # (b) (6) and Subject # (b) (6)) discontinued due to adverse events. Thirteen subjects completed the study. An audit of 15 enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. 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 or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

4. William Surbeck, M.D./ Study Protocol JADW/Site 958
Tulsa, OK 74135

The inspection was conducted from May 2 to 6, 2016. Under Study JADW, a total of 30 subjects were screened and 11 enrolled. One subject (Subject # (b) (6)) withdrew from the study. Ten subjects completed the study. An audit of 11 enrolled subjects' records was conducted.

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. 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 or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued at the conclusion of the inspection.

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR-CRO

5. Eli Lilly and Company
Indianapolis, IN 46285

This inspection was conducted from June 6 to 10, 2016. This sponsor inspection was needed to ensure that there were no monitoring concerns for this biosimilar application. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, training of staff and site monitors; review of controls and security of electronic systems; and data collection and handling procedures; adequacy of monitoring and corrective actions taken by the sponsor/monitor for the studies; clinical site study personnel training in GCP, and memorandum documents and reporting updates to clinical site investigators regarding serious unexpected adverse events.

In general, this site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 was not issued at the end of the sponsor inspection. No monitoring problems were found during the sponsor inspection. There was no underreporting of serious adverse events noted. Data submitted by this sponsor appear acceptable in support of the requested indication.

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Anthony Orencia, M.D.
Good Clinical Practice Assessment Branch
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