CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207924Orig1s000

OTHER ACTION LETTERS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 207924

COMPLETE RESPONSE

Eli Lilly and Company
Lilly Corporate Center
Indianapolis, IN 46285

Attention: Richard D. Hoffman, MS, RAC
Regulatory Advisor

Dear Mr. Hoffman:

Please refer to your New Drug Application (NDA) dated January 15, 2016, received January 15, 2016, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for baricitinib.

We acknowledge receipt of your major amendment dated November 23, 2016, which extended the goal date by three months.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL/STATISTICAL

The overall benefit-risk assessments of the baricitinib 2 and 4 mg once-daily doses have identified safety concerns that outweigh efficacy observed with the proposed dosing regimen.

I. Safety

A. Potential Thrombotic Risk

In the pooled analysis of Phase 3 trials (JADV, JADW, JADX, and JADZ) and their extensions (JADY), there was a numeric imbalance in venous thromboembolic events (VTE) not favoring baricitinib. For patients treated with baricitinib, there were 10 pulmonary emboli of which 9 were serious and one was fatal, and 10 deep venous thrombosis of which six were serious. For patients treated with placebo or methotrexate, there was one fatal pulmonary embolus. During the 0-16 week controlled period, the incidence rate of VTEs (per 100 patient years) was 1, 0, and 0, for the baricitinib 4 mg, baricitinib 2 mg, and placebo groups, respectively. Venous thromboembolic events continued to accrue after Week 16 in the baricitinib 4 mg dose group and the limited exposure to baricitinib 2 mg and placebo after Week 16 impedes our ability to determine whether this risk is limited only to the 4 mg dose, is lower in the 2 mg group, or is comparable to background rates. In addition, there was a

pulmonary embolus in a clinical trial in psoriasis and three arterial occlusive events in patients treated with baricitinib.

We acknowledge your arguments regarding potential predisposing or confounding factors, such as obesity or methotrexate use in patients with thrombotic events, but we note that these factors were also present in the comparator arms, including the use of methotrexate as background treatment in JADV, JADX, and JADW.

In your March 3, 2017 submission labeled, "Safety Regulatory Response: Label Rationale," you assert that there is no plausible mechanism of action for an association between baricitinib and venous thrombosis and that a signal has not been observed with other JAK inhibitors. Absence of a mechanism should not form the basis for dismissing a potentially serious safety risk nor should the absence of a similar safety signal in another JAK inhibitor reassure us that the finding in your program is not real. On the contrary, the absence of a signal with other JAK inhibitors should heighten further investigation on whether baricitinib has a differential downstream effect or off-target effects specific for its moiety. We note that baricitinib exposure was associated with a dose-related increase in platelet counts and while these platelet elevations were not clearly associated with thrombotic events, this is a unique finding compared to the JAK-inhibitors approved to date.

B. Inadequate Safety Exposure at Baricitinib 2 mg

Your Phase 3 program emphasized patient exposures to baricitinib 4 mg. During the controlled periods of the Phase 3 trials, patient-years of exposure in the 2 mg group was one-third (122.6) that of the 4 mg group (386.7). By 52 weeks and beyond it was less than one-fifth: 304.8 vs 1694.9 at 0-52 weeks and 210.2 vs 1300.6 at > 52 weeks. You only evaluated the 2 mg dose in two of the four pivotal trials and cross-over in these two trials after Week 16 resulted in low overall and diminishing long-term exposure to baricitinib 2 mg precluding an adequate risk assessment of this dose.

II. Efficacy

A. Efficacy of Baricitinib 4 mg versus 2 mg

Baricitinib 2 and 4 mg doses resulted in statistically significant improvements on the primary composite of ACR20 compared to placebo in JADW and JADX; however, there was not a consistent finding between these two studies to conclude greater efficacy with baricitinib 4 mg over 2 mg. In JADW, there was a numerically greater response with the 4 mg dose whereas in JADX, there was a numerically greater response with the 2 mg dose. Inability to demonstrate consistent efficacy advantages of the 4 mg dose over the 2 mg dose precludes a conclusion that baricitinib 4 mg has a favorable benefit-risk profile given that the majority of thrombotic events occurred at this dose.

Although you showed superiority of baricitinib 4 mg over adalimumab in patients who have not achieved remission on methotrexate in JADV and superiority of baricitinib 4 mg over methotrexate in treatment-naïve patients in JADZ, these two studies did not study the baricitinib 2 mg (or lower) dose. In your March 3, 2017 submission, you presented the

pooled analysis of three trials that enrolled patients who had had an inadequate response to conventional DMARDs. The analysis compared baricitinib 4 mg to 2 mg on achieving low disease activity and showed no difference between these two doses in patients who had previously been treated with methotrexate. Given the results of this pooled analysis and the inconsistent findings of efficacy between these two doses in JADW and JADX, it is conceivable that baricitinib 2 mg could have provided comparable efficacy as the 4 mg dose in JADV and JADZ and such an evaluation might also provide sufficient safety exposure for the 2 mg dose to conduct an adequate benefit-risk assessment.

B. Dose-ranging Considerations

Your Phase 3 program evaluated only baricitinib 2 and 4 mg doses, with emphasis on the 4 mg dose. The Phase 3 data identified dose-related adverse events at the 4 mg dose and inconsistent efficacy results between the 2 and 4 mg doses suggest the need to evaluate lower doses. In fact, Phase 2 dose-ranging studies suggest that a 1 mg dose of baricitinib may be effective. Although thrombocytosis was not directly linked to thrombotic events observed in Phase 3 trials, it was notable that in JADN a significant increase from baseline in platelet counts compared to placebo was observed with the 2 mg dose and higher. Given these observations, it would seem prudent to evaluate the benefit-risk of baricitinib at 1 mg or lower doses.

In conclusion, the overall benefit-risk assessment of baricitinib 2 mg and 4 mg for rheumatoid arthritis is not favorable given the potential serious risk for thrombosis.

To support approval of baricitinib in rheumatoid arthritis, additional clinical data will be necessary to identify a safe and effective dose(s). Your resubmission should include sufficient safety data to evaluate the risk of thrombosis. Exploration of 1 mg or lower doses of baricitinib may be critical to adequately evaluate the dose-response curve for baricitinib and to identify an appropriate dose. We strongly encourage that you request an End-of-Review meeting to discuss potential paths forward for your program.

ADDITIONAL CLINICAL ISSUES

More patients receiving baricitinib 4 mg (n=10) were permanently discontinued due to liver related abnormalities than baricitinib 2 mg (n=2), adalimumab (n=2), or placebo (n=1). Five of these discontinuations were considered drug-related, four on baricitinib 4 mg and one on adalimumab. There were no cases meeting the criteria for Hy's Law; however, some cases had symptoms and laboratory findings consistent with drug-induced liver injury but definitive association with baricitinib treatment could not be established given data presentation.

Your resubmission should also include data for study subjects in Phase 2 and 3 trials in e-DISH format and patient narratives for subjects with ALT or AST > 3xULN and TBL > 2xULN (See Appendix A).

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the prescribing information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

PROPRIETARY NAME

Please refer to correspondence dated, May 3, 2016, which addresses the proposed proprietary name, Olumiant. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(*b*). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
    - Present tabulations of the new safety data combined with the original application data.
    - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
    - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.

4. Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.

6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).

7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.

8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products," March 2015 at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm437431.pdf.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Mary T. Thanh Hai, MD
Deputy Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

Appendix A

Format of Standard Narrative Data

Requirement	Standard Variable	The variable means...	Variable-type
1. **Required**	STUDYID	**Unique identifier for a study within the submission**	Char
2. **Required**	USUBJID	**Unique subject identifier within the submission**	Char
3. **Required**	NARRAT1* (Required): Clinical Narrative, first part (Char, length<=200) NARRAT2* (Required): Clinical Narrative, continued (Char, length<=200) NARRAT3* (Required): Clinical Narrative, continued (Char, length<=200) ... NARRATn* (Required): Clinical Narrative, last part (Char, l ength<=200)	**Clinical Narrative***	Char

*** Requirements for Variables NARRATI1-NARRATIn - To the medical writer:**

Please be aware that we wish to use eDISH to assess the likelihood that your new compound causes liver toxicity and identifying potential "Hys Law" cases of elevated ALT or AST > 3xULN and TBL > 2xULN (or more in Gilbert syndrome) is just the first step. The next two steps are: 1) looking at all the liver test data for patients of interest over the time of observation, to appreciate the time-related elevations and which of the tests rises first, and then 2) evaluating the narrative data gathered to adjudicate the probable cause of the abnormal findings. This may require additional questions, tests, examinations to search for the cause, and only after ruling out other causes can a presumptive diagnosis of probable drug- related liver injury (DILI) be made. Liver biopsy is not definitive, and there is no single test or finding that proves DILI. For the adjudication to be successful, your investigators must search actively for the cause of all cases of elevated ALT or AST >3xULN and TBL > 2xULN. Finding a probable, very likely, or definite cause of the liver injury other than the drug is very important. The eDISH system, as used by medical reviewers at CDER, includes the capability to create time-course graphs for each subject, and to read the narrative summaries, helping them in drawing their own conclusions as to

whether the drug may have caused the abnormal findings. We will want to review the data independently. Estimation of the likelihood that the liver injury was caused by the drug being studied is frequently difficult and requires information to rule out or rule in other possible causes.

Therefore, we recommend that the narratives should be written by physicians or other medical personnel skilled in medical differential diagnosis. Pertinent negative findings should be included in any narrative. The data that needs to be gathered by the investigator are those that can establish or rule out other causes, such as acute viral hepatitis A or B (less often C or E), biliary disease such as stones or tumors, cardiac failure or shock, acute alcoholic or autoimmune hepatitis.

It is not necessary to include all subjects in this patient narrative data set. However, make sure to include narratives for subjects with ALT or AST >3xULN and TBL > 2xULN.

The narratives should include information described in the following points:

1. Indication
2. Subject's medical history and concomitant medications
3. Dates and laboratory values of diagnostic tests done to evaluate liver disease including X-ray, ultrasound, or liver biopsy
4. Time course of any signs or symptoms of liver disease, including jaundice
5. Differential diagnosis and final diagnosis of liver disease
6. The study site investigator and the sponsor's assessment of relationship of study drug to abnormal hepatobiliary lab results or adverse events
7. Clinical course of liver-related adverse events including treatment and outcome
8. Complete information about the resolution, or progression, of increased ALT or total bilirubin in each of these study subjects, including time to complete resolution of all hepatobiliary lab results, or most current available patient status for any cases in which the events had not resolved at the time of report preparation.
9. It is also helpful to include in the narrative:
   - Dose and duration of study therapy in weeks
   - Laboratory values for ALT, AST, ALP, TBL and corresponding dates of measurements.

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/s/

MARY T THANH HAI
04/12/2017