CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207924Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102204

MEETING MINUTES

Eli Lilly and Company
Lilly Corporate Center
Drop Code 2543
Indianapolis, IN 46285

Attention: Richard D. Hoffman, MS, RAC
Regulatory Advisor
Global Regulatory Affairs-U.S.

Dear Mr. Hoffman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for baricitinib.

We also refer to the teleconference between representatives of your firm and the FDA on September 2, 2015. The purpose of the meeting was to discuss the content of the initial NDA submission of baricitinib for the treatment of patients with moderately to severely active rheumatoid arthritis. .

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Jessica K. Lee, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: September 2, 2015 at 11:00 am
Meeting Location: via Teleconference

Application Number: IND 102204
Product Name: baricitinib
Indication: Rheumatoid Arthritis
Sponsor Name: Eli Lilly and Company

Meeting Chair: Badrul A. Chowdhury, MD, PhD
Meeting Recorder: Jessica Lee, PharmD

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Associate Director, DPARP
Janet Maynard, MD, Clinical Team Leader, DPARP
Timothy Robison, PhD, Pharmacology/Toxicology Team Leader, DPARP
Matthew Whittaker, PhD, Pharmacology/Toxicology Reviewer, DPARP
Craig Bertha, PhD, CMC Lead, Office of Pharmaceutical Quality (OPQ), Office of New Drug Products (ONDP) Branch IV
Ping Ji, PhD, Clinical Pharmacology, Division of Clinical Pharmacology II
Jianmeng Chen, PhD, Clinical Pharmacology, Division of Clinical Pharmacology II
Gregory Levin, PhD, Mathematical Statistician Team Leader, Division of Biometrics II
Robert Abugov, PhD, Mathematical Statistician, Division of Biometrics II
Jessica Lee, PharmD, Regulatory Project Manager, DPARP
Erin Hachey, PharmD, RPh, Risk Management Analyst, Division of Risk Management
Jamie Wilkins Parker, PharmD, Risk Management Analyst, Acting Team Leader, Division of Risk Management
Teresa McMillan, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis
Michael Sinks, PharmD, Regulatory Project Manager, Office of Surveillance and Epidemiology
Amy Liu, PharmD Candidate, Virginia Commonwealth University, School of Pharmacy

SPONSOR ATTENDEES

William Macias, MD, PhD, Team Leader

Terence Rooney, MD, Medical Director
Scott Beattie, PhD, Sr Research Advisor, Statistics
Richard Hoffman, MS, Director, Global Regulatory Affairs-US
Robin Pitts Wojcieszek, RPh, Sr Director, Global Regulatory Affairs-US
Carl Garner, PhD, Sr Director, Global Regulatory Affairs-US
Isabelle Murray MS, Director, Global Regulatory Affairs-US
Robert Metcalf, PhD, Vice President of Regulatory Affairs and Quality
Bill Willams, MD, VP Exploratory Development (Incyte Corporation)
Neil Wummer, Executive Director of Regulatory Affairs (Incyte Corporation)

1.0 BACKGROUND

In a submission dated, May 15, 2015, Eli Lilly requested a Pre-NDA meeting to discuss the content of the initial NDA submission of baricitinib for the treatment of patients with moderately to severely active rheumatoid arthritis. Baricitinib is a small molecule inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases and Lilly is developing baricitinib for the treatment of moderately to severely active rheumatoid arthritis.

The meeting was granted on May 29, 2015. Lilly's specific questions from the Briefing Document dated, July 21, 2015, are listed below in *italics* and FDA responses are provided in normal font.

In an electronic mail dated, August 28, 2015, Lilly requested that the meeting format be changed to a teleconference from a face-to-face meeting. Therefore, the September 2, 2015 meeting was held as a teleconference. The meeting discussion is provided below in normal font.

FDA sent Preliminary Comments to Eli Lilly on August 27, 2015.

2. DISCUSSION

Question 1:

Does FDA agree that the proposed content, including the proposed content of the 4-Month Safety Update, provides a complete application?

FDA Response to Question 1:

The proposed content, including the proposed content of the 4-Month Safety Update, appears reasonable.

Discussion to Question 1:

No discussion occurred.

Question 2:

Does FDA have any preliminary comments on our approach to address any potential postmarketing risk management actions?

FDA Response to Question 2:

It is difficult to comment on your approach to address any potential postmarketing risk management actions prior to our review of the safety data. The need for a REMS will be a review issue.

Discussion to Question 2:

No discussion occurred.

Question 3:

Does FDA have any preliminary thoughts on whether an Advisory Committee meeting will be scheduled for baricitinib?

FDA Response to Question 3:

The need for an advisory committee meeting for baricitinib will be a review issue.

Discussion to Question 3:

No discussion occurred.

Question 4:

Does FDA have any additional comments regarding the statistical analysis plans (SAPs) for efficacy and safety, in light of the study-level data summarized in this document?

FDA Response to Question 4:

As discussed in in our January 16, 2015, communication, the potential effect of missing data on the reliability of efficacy results will be a review issue. To address the de facto estimand of regulatory interest, for all key efficacy endpoints (including ACR20, mTSS, and HAQ-DI), provide analyses that include all observed data on all subjects regardless of whether they continued or discontinued initially assigned treatment and regardless of use of rescue therapies. In addition, provide tipping point sensitivity analyses that vary assumptions about the missing outcomes on the two treatment arms. The tipping point analyses should be two-dimensional, i.e., should allow assumptions about the missing outcomes on the two arms to vary independently, and should include scenarios where dropouts on baricitinib have worse outcomes than dropouts on control. The goal is to explore the plausibility of missing data assumptions under which the conclusions change, i.e., under which there is no longer evidence of a treatment effect.

Discussion to Question 4:

Lilly provided additional information (refer to the attachment) regarding the planned analyses of efficacy measures prior to the September 2, 2015 meeting. Lilly's plan to collect data after discontinuation of patients was acknowledged by the Agency.

The sponsor's response indicated that tipping point analyses would be conducted by adding a delta score to imputed scores from the baricitinib arm only. The Agency reiterated that tipping point analyses require a two-dimensional array of delta scores, constructed by using all observed data (including data collected after treatment discontinuation and use of ancillary

therapies) and varying the delta score for missing data from the baricitinib and control arms independently. The Agency provided rationale for this request, noting that inference about the treatment effect (and therefore the tipping point) depends not only on the difference between assumed mean outcomes among dropouts on the two treatment arms, but also on the assumed mean outcome among dropouts on the placebo arm. An example was discussed, with different dropout rates on the two arms, to illustrate. The Agency recommended that a grid of deltas from initial imputed values be provided with, for example, deltas for baricitinib on the horizontal axis, and deltas for control on the vertical axis, with associated mean, 95% confidence interval, and p-value for the difference between treatment and control provided using multiple imputation for each pair of deltas.

The sponsor requested that its written response after the meeting be included in the meeting minutes; that response is provided below:

Based on the discussion during the pre-NDA meeting, Lilly agreed to include the following sensitivity analyses utilizing tipping point methodology in the Integrated Summary of Efficacy (ISE) document of the NDA submission:

- *2-dimensional tipping point analyses where the sensitivity parameter (delta) for imputation of data from patients with missing data is allowed to vary independently for the placebo group (or the active control group for studies without placebo) and for the experimental treatment (baricitinib) group.*
- *The tipping point results will be included in a 2-dimensional table that summarizes (for each pair of delta values) the estimated treatment mean difference with 95% confidence interval and associated p-value from the primary analysis method (see example found in Table 4.1). Alternatively, a graphical representation of the tipping point results may be provided in a manner similar to that shown in the references provided by FDA[1].*
- *Efficacy variables to be included in the tipping point sensitivity analyses include ACR20 and the set of continuous endpoints that are included in each study's statistical gatekeeping evaluation. All variables will be assessed at the primary analysis time point for the specific endpoint.*
    - *To conduct the ACR20 tipping point analysis, sensitivity parameters will be converted back to the natural scale (ie, probability of response) for inclusion in the results table.*

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[1] Yan, Xu, Shiowjen Lee, and Ning Li. "Missing data handling methods in medical device clinical trials." *Journal of Biopharmaceutical Statistics* 19.6 (2009): 1085-1098.

Campbell, Gregory, Gene Pennello, and Lilly Yue. "Missing data in the regulation of medical devices." *Journal of biopharmaceutical statistics* 21.2 (2011): 180-195.

Liublinska, Victoria, and Donald B. Rubin. "Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial." *Statistics in medicine* 33.24 (2014): 4170-4185.

Proposed Tipping Point Example for DAS-28-hsCRP

DAS28-hsCRP: Change from Baseline Using Multiple Imputation and Tipping Point Page x of y
Week 12 hh:mm ddMMMyyyy
Modified Intent-to-Treat Population PDPM
Study I4V-MC-JAD*

	PBO					
BARI 4-mg	**Delta = -2*x**	**Delta = -1*x**	**Delta = 0**	**Delta = 1*x**	**Delta = 2*x**	**Delta = 3*x**
Delta = 0						
LSMD	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx
95% CI	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)
P-value(a)	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
Delta = 1*y						
LSMD	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx
95% CI	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)
P-value(a)	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
Delta = 2*y						
LSMD	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx
95% CI	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)
P-value(a)	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
Delta = 3*y						
LSMD	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx
95% CI	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)
P-value(a)	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx
Delta = 4*y						
LSMD	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx	-x.xx
95% CI	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)	(-x.xx, -x.xx)
P-value(a)	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx

Abbreviations: DAS28 = Disease Activity Score 28 joints; hsCRP = high sensitivity C-reactive protein; LSMD = least squares mean difference.
Delta is the value added to the imputed data after using multiple imputation.
(a) P-value, LSMD, and 95% CI from ANCOVA model: Change=baseline+region+history of bDMARD use (<3,>=3)+treatment group, using imputed datasets from multiple imputation.

FDA Response to Sponsor's Post-Meeting Example for Question 4:

Your approach is reasonable.

Question 5:

Does FDA agree with Lilly's proposal to include, within the appendix of each PRO dossier, the empirical analyses demonstrating the unique contribution of each PRO endpoint?

FDA Response to Question 5:

Your proposal to include, within the appendix of each PRO dossier, the empirical analyses demonstrating the unique contribution of each PRO endpoint, is reasonable.

Discussion to Question 5:

No discussion occurred.

Question 6:

Does FDA have any comments regarding the proposed changes to the types of study reports and studies to be included for the NDA (Section 17.1)?

FDA Response to Question 6:

We do not have any comments regarding the proposed changes to the types of study reports and studies to be included for the NDA.

Discussion to Question 6:

No discussion occurred.

Question 7:

Does FDA have any comment regarding the clarifications to the Data Standards (Section 17.2)?

FDA Response to Question 7:

We do not have any comments regarding the clarification to the Data Standards.

Discussion to Question 7:

No discussion occurred.

Question 8:

Does FDA have any comment regarding the clarifications to the Patient Narratives and information to be supplied within the Table of Significant and Notable Patients (ToSNP) (Section 17.3)?

FDA Response to Question 8:

We do not have any comments regarding the clarifications to the Patient Narratives and information to be supplied within the Table of Significant and Notable Patients (ToSNP).

Discussion to Question 8:

No discussion occurred.

Question 9:

Does FDA have any comment regarding the additional information Lilly plans to supply for the Financial Disclosures and information for the Office of Scientific Investigations (OSI) (Section 17.4 and Section 17.5)?

FDA Response to Question 9:

We do not have any comment regarding the additional information you plan to supply for the Financial Disclosures and information for the Office of Scientific Investigations (OSI).

Discussion to Question 9:

No discussion occurred.

Additional Nonclinical comment:

Provide structures of any impurities and degradants of the drug substance and drug product, respectively, in your NDA submission. Refer to ICH Guidances [ICH Q3A(R2) and ICH Q3B(R2)] for acceptable levels of impurities and degradants of the drug substance and drug product, respectively, and possible qualification requirements. Based upon the proposed chronic administration of your drug product, a 13-week toxicology study in one species would be required for any impurities or degradants that exceed ICH qualification thresholds. Impurities or degradants of active ingredients that are identified as structural alerts should be at or below acceptable qualification thresholds to support an NDA as described in the ICH M7 Guideline, Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk (Step 4 Version dated June 23, 2014).

Discussion to Additional Comments:

No discussion occurred.

3.0

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites including

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential in the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of 42 important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number

b. Principal investigator
c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

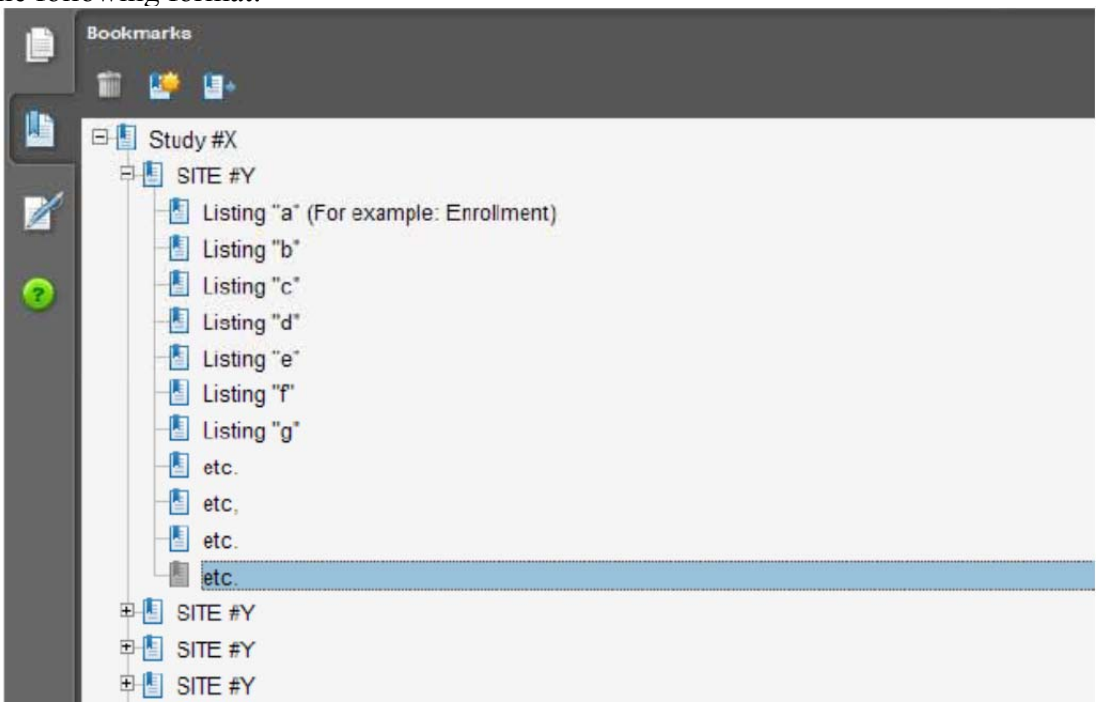
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)

c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

Please refer to the following:

1) Lilly's Regulatory Response: Pre-NDA Preliminary Comments Response
2) Lilly's Regulatory Response: Pre-NDA Meeting Post Meeting Action Item

11 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA K LEE
10/01/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102204

MEETING MINUTES

Eli Lilly and Company
Attention: Dr. Scott Coffey
Director, Global Regulatory Affairs CMC
Lilly Corporate Center
Indianapolis, Indiana 46285

Dear Dr. Coffey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Baricitinib (LY3009104) Capsule.

We also refer to the meeting between representatives of your firm and the FDA on October 30, 2013. The purpose of the meeting is to discuss and obtain Agency consensus on planned development activities of baricitinib drug substance and the drug product.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Eric P. Duffy, Ph.D.
Division Director
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, End Of Phase 2 CMC Only
Meeting Category: IND

Meeting Date and Time: October 30, 2013, 1:30 PM to 2:30 PM (ET)
Meeting Location: CDER WO Bldg 22, Room 1419

Application Number: IND 102204
Product Name: Baricitinib Capsule
Indication: Rheumatoid Arthritis
Sponsor/Applicant Name: Eli Lilly and Company

Meeting Chair: Eric P. Duffy
Meeting Recorder: Youbang Liu

FDA ATTENDEES
Eric P. Duffy, Division Director, Division III, ONDQA
Prasad Peri, Branch Chief, Branch VIII, ONDQA
Craig Bertha, CMC Lead, ONDQA
Sharmista Chatterjee, CMC Lead for QbD, ONDQA
Xiaobin Shen, CMC Reviewer, ONDQA
Linda Ng, Senior Policy Advisor. OC
Tara Gooen, Acting Branch Chief, OC
Sarah Yim, Supervisory Medical Officer, DPARP
Youbang Liu, Regulatory Project Manager, ONDQA

ELI LILLY and COMPANY ATTENDEES
Lin-Jau Wu Anderson, Senior Research Scientist, Global Regulatory Affairs CMC
David D MacLaren, Senior Director, Global Regulatory Affairs CMC
D. Scott Coffey, Director, Global Regulatory Affairs CMC
David L Varie, Research Fellow, Process Design and Development
Kevin D Seibert, Senior Engineering Advisor, Process Design and Development
Eric W Crick, Senior Research Scientist, Product and Process Performance
Richard A Berglund, Research Fellow, Process Design and Development
Douglas J Costelle, Advisor, CMC Project Management

1.0 BACKGROUND

IND 102,204 is reviewed under the Division of Pulmonary, Allergy and Rheumatology Products. The IND is active for treatment of patients with rheumatoid arthritis (RA). Information

regarding the chemistry, manufacturing, and controls for baricitinib is included in IND 102,204, with cross-reference to the following INDs:

- (b) (4)
-

The purpose of the meeting is to discuss planned development activities of baricitinib drug substance and the drug product, and obtain Agency consensus.

2.0 DISCUSSION

The FDA Meeting Preliminary Comments were sent to Eli Lilly and Company (Lilly) before the meeting. The meeting discussions were primarily concentrated on the following questions that need clarification or further discussion.

Question 1: *Does the FDA agree with the starting material designation and control strategy proposed for* (b) (4) *used in the synthesis of LY3009104 drug substance?*

Agency Responses:

Your designation of starting materials (b) (4) are acceptable. Their respective control strategies are reasonable. However, their adequacy is a review issue to be determined at time of NDA review.

Your designation of starting material (b) (4) is not acceptable. (b) (4) synthetic pathways should be included as part of the LY3009104 drug substance synthesis, alternatively it can be submitted in a DMF.

Meeting Discussion

Lilly presented the justification for proposing (b) (4) as a starting material and discussed the control strategy.

Lilly noted the control of (b) (4) . In addition, Lilly stated that the analytical method was capable of detecting (b) (4) at expected Genotoxic Impurity (GTI) control levels and that final control strategy would be designed based on (b) (4)

FDA expressed concern over Lilly's ability to (b) (4) , especially

(b) (4)

Based on Lilly's further justification and meeting discussion, the FDA agreed that (b) (4) is acceptable as a starting material.

Question 2:

a) *Does the FDA agree with the Lilly proposed methodology to identify critical and non-critical parameters during the development of the overall process control strategy?*
b) *Does the FDA agree with the methodology of* (b) (4) *?*
c) *In the context of the methodology described within this document, does the agency agree that changes to set points of critical parameters may be made within their proven ranges post-approval without prior notification?*

Agency Responses:

In accordance with ICH Q8(R2) a critical process parameter is one whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. The fact that a risk of failure is mitigated by applying a robust proactive control strategy should not allow for the underestimation of assigning criticality. Additionally, the process parameters that are included in the manufacturing process description should not be restricted to the critical ones; all parameters that have been demonstrated during development as needing to be controlled or monitored during the process to ensure that the product is of the intended quality should be described.

Your approach to (b) (4) appears to be reasonable. However, it is not apparent from the provided information how you would address (b) (4). Clarify your (b) (4) approach in the submission. Additionally, adequacy of proposed ranges would be evaluated during NDA review.

Considering the approach outlined to define proven ranges of critical process parameters, it appears that the intent is to propose a design space. Please confirm. If a design space is proposed and approved then, in concurrence with ICH Q8(R2), no regulatory notification is required for changes to set points within an approved design space. Alternatively, if a design space is not proposed, it is expected that changes with a potential to adversely affect product quality should be notified to the Agency in accordance with 21 CFR 314.70 and related guidance.

Meeting Discussion

Lilly opened the discussion on process parameters, restating Lilly's approach to low risk, medium risk and high risk parameters and its designation of both medium and high risk parameters as critical. Lilly asked if the low risk (non-critical) parameters should be included in the process descriptions located in S.2.2 and P.3.3.

FDA reiterated their expectation that a complete manufacturing process description should be provided in the submission in sections S.2.2 and P.3.3. FDA indicated that the sponsor can use bolding or different colors, etc. to highlight the proposed critical process parameters (CPPs) in sections S.2.2 and P.3.3.

Lilly asked if non-critical parameters were discussed in the process description sections would they be considered commitments.

FDA indicated that changes to all parameters should be carefully monitored under the company's quality system to assess the impact of the change, and the regulatory notification of these changes should be done in accordance with CFR 314.70. FDA indicated that the agency interpreted the wording on page 77 of the briefing document as (b) (4) .

Lilly explained that (b) (4) describes this work in the development history section of the NDA.

FDA acknowledged that design space (b) (4) . The Agency clarified that it does not expect (b) (4) , but expects the sponsor to describe in the NDA how they will assess the risks that (b) (4) FDA indicated that it is our expectation that details of such a plan would be maintained within the firm's quality system, however, it would help in review for the firm to include a high level summary in the application.

Lilly indicated that Lilly conducts all development work with QbD principles, and its approach and data from experiments will be discussed in the development history sections of the submission. Lilly clarified that (b) (4)

FDA indicated that this (b) (4) was acceptable and noted that the design space could be (b) (4)

Question 3: *The process for the production of baricitinib drug substance includes the* (b) (4)

Does the FDA agree with Lilly's approach to batch identification given the manner in which we intend to execute the production of baricitinib drug substance?

Agency Responses:

Based on the information provided, the proposed batch identification approach seems reasonable. Future on-site inspections may evaluate the following:

- (b) (4)

Additionally, clarify the following:

- The proposed approach assumes (b) (4) and if yes, whether this would have any adverse impact on quality of the finished drug substance.

- What controls are in place to [redacted] (b) (4) ?
- It is indicated that for situations when [redacted] (b) (4)

Meeting Discussion

[redacted] (b) (4)

Lilly stated that it would be willing to host FDA personnel at Lilly facilities or at FDA offices for a non-product-specific meeting to discuss its [redacted] (b) (4) and control strategies.

Question 4a: *Lilly plans on evaluating the stability of 2-mg and 4-mg baricitinib tablets in a number of different package presentations.* [redacted] (b) (4) *Attached is a copy of the proposed protocol and representative data.*

Does the FDA agree with the proposed protocol design for primary stability testing?

Agency Responses:

Your proposed protocol design appears reasonable.

Question 4b: *Lilly is* [redacted] (b) (4) *Lilly proposes using a bottle for primary stability that is not dimensionally identical to the bottle that will be used for commercial launch. The water vapor transmission rate per tablet for the commercial bottle presentations will be less than or equal to that of the bottle presentations studied in the primary stability study. Attached are stability that demonstrate that the chemical and physical stability of baricitinib tablets are largely unaffected by temperature and humidity.*

Does the FDA agree with the proposed primary stability bottle approach of using a bottle not dimensionally identical, less protective, and made of identical materials as compared to the bottle intended for commercial launch?

Agency Responses:

Your proposed protocol design appears reasonable.

Meeting Discussion

No further discussion at the meeting.

3.0 OTHER DISCUSSION

[redacted] (b) (4)

4.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
None		

5.0 ATTACHMENTS AND HANDOUTS

None.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YOUBANG LIU
11/26/2013

ERIC P DUFFY
11/26/2013

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 102204

MEETING MINUTES

Eli Lilly & Company
Lilly Corporate Center
Indianapolis, Indiana 46285

Attention: Christine A. Phillips, Ph.D., RAC
Director, Global Regulatory Affairs – U.S.

Dear Dr. Phillips:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LY3009104 (baricitinib).

We also refer to the meeting between representatives of your firm and the FDA on June 26, 2012. The purpose of the meeting was to discuss your Phase III development program for the treatment of rheumatoid arthritis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-3420.

Sincerely,

{See appended electronic signature page}

Christine Chung, R.Ph.
CDR, U.S. Public Health Service
Sr. Regulatory Management Officer
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	End of Phase 2
Meeting Date and Time:	June 26, 2012 3:00 – 4:30 P.M.
Meeting Location:	White Oak Building 22 Conference Room 1417
Application Number:	IND 102204
Product Name:	LY3009104 (baricitinib)
Indication:	Rheumatoid arthritis
Sponsor/Applicant Name:	Eli Lilly & Company
Meeting Chair:	Badrul A. Chowdhury, M.D., Ph.D.
Meeting Recorder:	Christine Chung, R.Ph.

FDA ATTENDEES:

Badrul A. Chowdhury, M.D., Ph.D., Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, M.D., Supervisory Associate Director, DPARP
Timothy Robison, Ph.D., Pharmacology/Toxicology Team Leader, DPARP
Mamata De, Ph.D., Pharmacology/Toxicology Reviewer, DPARP
Christine Chung, R.Ph., Senior Regulatory Management Officer, DPARP
Suresh Doddapaneni, Ph.D., Deputy Director, Division of Clinical Pharmacology 2 (DCP2)
Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, DCP2
Lokesh Jain, Ph.D., Clinical Pharmacology Reviewer, DCP2
Thomas Permutt, Ph.D., Director, Division of Biometrics II (DBII)
Robert Abugov, Ph.D., Statistical Reviewer, DBII
Janet Maynard, M.D., Clinical Reviewer, DPARP
Suzette Peng, M.D., Clinical Reviewer, DPARP

SPONSOR ATTENDEES:

William Macias, MD, PhD, Senior Medical Director and Team Leader
Monica Luchi, MD, FACR, Vice President, Inflammatory Disease Development (Incyte)
Steven Zuckerman, Ph.D., Sr. Research Advisor- Translational Science
David Hyslop, MD, Medical Fellow – Global Patient Safety
Scott Beattie, PhD, Research Advisor – Statistics
Mark Carfagna, PhD, DABT, Senior Research Advisor – Toxicology

Ellen Cannady, PharmD, PhD, Sr. Research Scientist, ADME
Lai San Tham, Ph.D., Research Scientist- Pharmacokinetics/Pharmacodynamics
Carol Gaich, Pharm.D., Research Scientist- Global Health Outcomes
Robert Conley, MD, Regulatory Leader – Global Regulatory Affairs-US
Richard Hoffman, M.S., RAC, Manager – Global Regulatory Affairs-US
Christine Phillips, PhD, Director – Global Regulatory Affairs-US
Christopher Payne, M.S., Principal Research Scientist- Clinical Pharmacology

BACKGROUND:

The purpose of the meeting is to discuss Phase 3 development of LY3009104 (baricitinib), a small molecule inhibitor of the Janus kinase (JAK) family of protein tyrosine kinases. Lilly is developing LY3009104 for treatment of inflammatory diseases, including rheumatoid arthritis (RA).

The original meeting was scheduled for May 7, 2012, but at the sponsor's request was rescheduled for June 26, 2012.

After review of the briefing package dated May 22, 2012, the Division provided meeting preliminary comments to Lilly's questions via a letter on June 22, 2012.

Dr. Christine Phillips sent an email on June 25, 2012, stating that they would like further discussion on the following areas:

- Dose Selection (Question 2)
- Rescue Therapy (Question 3a)
- Structure Assessments
- Gatekeeping Strategy for Study JADX (Question 4b)
- Non-inferiority margin for Study JADZ (Question 6)
- Clinical Pharmacology Plans (Question 11)
- Additional Comments provided by FDA: 1 (Study JADY) and 2 (timing of efficacy assessments with respect to dose)

Dr. Phillips also emailed a 2-page document to clarify Lilly's plans for rescue therapy (see Attachment at end of minutes).

The content of the letter is printed below, with Lilly's questions in *italics* and the Division's responses in normal font. Summary of meeting discussions are found in **bold normal** font following the specific questions.

Meeting Minutes

Lilly began the meeting discussing current challenges in conducting RA clinical trials including 1) unacceptability of leaving patients on placebo even in monotherapy trials (treatment switch), rescue therapy, and methotrexate naïve trials and 2) unacceptablility of prolonged wash-out period. These factors are consistent with FDA comments, IRB and consultant recommendations.

FDA Summary Comments

The Division is aware of the increasing difficulty of demonstrating the benefit of an investigational product for structural (i.e., radiographic) outcomes. This has been due to a number of factors:

- Improvements in present background standard of care which have resulted in low amounts of progression in placebo add-on control groups in the typical timeframe of a clinical trial
- The ethical questionability of allowing patients to have uncontrolled disease activity for an extended period of time, which makes it necessary to limit the placebo-controlled period and include provisions for patients to receive rescue therapy by 12 to 16 weeks of assigned study treatment
- As a corollary, the difficulty of drawing conclusions about treatment effect based on comparator results that may be completely extrapolated.
- Concern that treatment effect on radiographic outcomes may be driven by few extreme observations that disproportionately impact the mean change from baseline in the radiographic score (e.g., modified Total Sharp Score).

Because of these issues, it is clear that the approach to demonstrating effect on structural outcomes in RA clinical development programs needs to be changed, but we cannot provide you with definitive guidance at this time. We recommend you consider proceeding first with clinical trials that evaluate core clinical outcomes, such as proportion of patients experiencing remission, ACR Responses, and HAQ-DI. As presently designed, Study JADV is likely to suffer from the same issues as described above, which would make results difficult to interpret. If you have alternative ideas that may address these concerns, we are open to a follow-up proposal.

Discussion:

Lilly stated that it would be ideal to see data at 52 weeks of study, but normally 6 months of data are available with the second 6 months being imputed data. (b) (4) [redacted]

FDA noted a major design problem with (b) (4) [redacted] **This is not acceptable for a primary measure of structural outcomes; linear extrapolation of radiographic progression from weeks 16 to 52 typically creates a disproportionately large number of outliers at week 52. For this reason, radiographic progression should not be imputed.**

Lilly stated that they will send the SAP before finalization and before unblinding.

Question 1 – Nonclinical Studies

Does FDA agree that the nonclinical studies, including the ADME studies, conducted to date together with the additional planned studies will provide sufficient nonclinical safety and disposition information to support registration of LY3009104 for the proposed RA indication (b) (4) [redacted] *?*

FDA Response:
The completed and planned studies, pending review of the data, appear adequate to support an NDA filing.

The teratology findings from the EFD studies should be included in the Investigator's Brochure and Informed consent.

Additional Nonclinical Comments:
During IND development and for a potential NDA, provide structures of impurities and intermediates of the drug substance and drug product. Monitor impurities and degradation products of all active ingredients. Refer to the ICH Guidance for qualification of drug impurities in drug substances [ICH Q3A(R2)] and degradants in drug products [ICH Q3B(R2)]. If applicable, conduct the appropriate toxicity studies to qualify impurities and degradants. Impurities or intermediates that are identified as structural alerts should be at or below acceptable qualification thresholds for genotoxic and carcinogenic impurities as described in the draft FDA Guidance for Industry, "Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches" (December 2008) for assessment of impurities to support clinical studies for an IND and NDA.

Question 2 – Dose Selection for Phase 3 Clinical Trials
As described in Section 6, a single starting dose of 4 mg once daily (QD) LY3009104 will be evaluated in all Phase 3 studies. In three of the Phase 3 studies, a step-down or maintenance dose of 2 mg QD will be evaluated after 24 weeks of treatment in patients who meet criteria for sustained response (described in Section 7.6).
Patients with estimated glomerular filtration rate (eGFR) <50 mL/min/1.73m^2 will receive a 2-mg QD dose, which is expected to produce exposures in the same range as in patients with normal renal function. These patients are not eligible for step-down or maintenance dosing.
(b) (4)

(a) Does FDA agree that the data support selection of a single starting dose of 4 mg QD for all of the Phase 3 studies, with dose adjustment to 2 mg QD for patients with eGFR <50 mL/min/1.73m^2?

FDA Response:
While the available data appear to support the nominal daily 4 mg dose, the dose-ranging data for any given dose are limited, and it would be prudent to take at least two doses (e.g., nominal daily 2 mg and 4 mg dose) into Phase 3 to further characterize the efficacy and safety of a higher vs. lower relative dose. Additionally, you do not have data on a BID dose regimen, which is more consistent with the pharmacokinetic profile of your product. We recommend you evaluate 1 mg BID vs. 4 mg QD in your development program, such as prior to conducting Phase 3 trials. See Additional Clinical Comments below regarding timing of the clinical efficacy assessments with respect to administration of study treatment.

For renal dose adjustment, see response to Question 11a.

Discussion:

Lilly stated that they would have liked to bring 2 doses of baricitinib into phase 3 studies based on two criteria: (1) clear response separation from placebo and between doses and (2) enough separation in PK between doses such that safety can be assigned differentially to high dose vs. low dose. However, in phase 2 studies 8 mg showed no additional benefit over 4 mg (flat part of dose response curve), and 1 and 2 mg once daily doses did not perform well in DAS and remission endpoints. ACR20 for 2 mg showed less than 50% response, whereas 4 and 8 mg doses scored 90% or better. Although 8 mg showed good efficacy, the increase in adverse events is of concern. In terms of PK, both 4 mg and 2 mg doses had overlapping exposures; based on this result, safety may not be differentiated between the two dose levels.

Regarding once-daily versus BID dosing, Lilly stated that simulations based on modeling projected that 1 mg BID dose will have C_{max} values lower than IC_{50} and would not be effective; however, 2 mg BID may show separation from placebo. Once-daily dosing was recommended by their consultant to be similar to a "hormone holiday," in that an "off-time" for JAK inhibition may ameliorate adverse effects such as decreased neutrophils, hemoglobin.

FDA reiterated that baricitinib PK is more consistent with BID dosing. A "drug holiday" concept is hard to support based on the number of patients studied, and in itself, will not be enough to rule out BID dosing until the utility of drug holiday is demonstrated. Although it is Lilly's decision, FDA stated that they have concerns with Lilly's current phase 3 plans, and it is at the sponsor's own risk if they decide to move into phase 3 studies with only one dose. It would be better to sort out once-daily vs. BID dosing by comparing the 1 mg BID and 4 mg QD dosing regimens before going into phase 3. If Lilly decides to go forward with one dose into phase 3, they may be requested based on results to do additional dose ranging at a later, perhaps less desirable, date. FDA suggested that perhaps a phase 3 trial with 3 arms (1 mg BID/2 mg QD/4 mg QD) or 2 doses (1 mg BID and 4 mg QD) as recommended in comments above can be conducted to address the issue of dosing. It would be better to balance efficacy with toxicity as it appears that this drug may have a narrow therapeutic window. A lower dose like 2 mg QD appears to work and should be further explored.

Lilly stated that they will submit data to show that 1 mg BID and 2 mg QD is not effective. They stated that they clearly understand the risk of going into phase 3 with one dose, however, intend to move forward with 4 mg QD while they manufacture the 1 mg dose for further dose ranging studies which will be conducted separately but parallel to the phase 3 studies. The 2 mg QD dose regimen performed suboptimally for endpoints that track with structural benefit, such as DAS28 "remission" (DAS28 <2.6).

FDA stated that DAS improvement does not necessarily correlate to structural improvement. FDA also cautioned the sponsor about overemphasizing phase 2 study efficacy data, which can lead to going into phase 3 with a higher dose and corresponding toxicities.

(b) Does FDA agree that evaluation of a step-down or maintenance dose of 2 mg QD would provide information that would assist physicians as they optimize patient treatment?

FDA Response:
The problem with the proposed evaluation of 2 mg QD as a step-down or maintenance regimen is that there would be no controlled evaluation to characterize the treatment effect size and relative safety profile of this dose regimen. Therefore, it would be preferable to also include 2 mg QD as a dose during the controlled period of the clinical trials. If the lower dose regimen is demonstrated to be safe and efficacious in the controlled period, then this would provide justification for physicians to adjust the dose down as per clinical judgment.

Discussion:
Lilly proposed that in a step-down regimen, blinded study, patients in remission with 4 mg daily would be randomized to either 2 mg or 4 mg daily. If remission is lost based on the Clinical Disease Activity Index (CDAI) criteria, that patient would go back to the 4 mg dose and no permanent harm would be anticipated.

FDA agreed that Lilly's proposal for a step-down regimen with patient monitoring would be unlikely to cause patient harm, however, that is different than providing substantial evidence of efficacy for an alternative treatment regimen. Controlled data would be required, as suggested in the FDA response above.

(c) If yes, does FDA agree with the criteria described for sustained efficacy in Section 7.6 (achieving a Clinical Disease Activity Index [CDAI] remission at Weeks 16 and 24)?

FDA Response:
See response to Question 2b. We recommend you use a remission definition that includes an acute phase reactant because elevation of acute-phase reactants is an important predictor of later radiographic damage. We do not agree that 8 weeks of response would be described as "sustained."

Discussion:
FDA stated that although CDAI is useful in the clinic, where clinicians do not always have inflammatory marker results, disease activity indices that include an inflammatory marker are more desirable in clinical trials as objective confirmation of inflammation control.

Lilly summarized major points of discussion thus far:
1) **FDA strongly encourages to go into phase 3 with two doses, and it is at the sponsor's risk to go into phase 3 with only one dose.**

2) **Lilly plans to conduct a separate dose ranging study, in parallel with phase 3 trials, to compare the 1 mg BID, 2 mg QD and 4 mg QD dosing regimens. They will submit the protocol and request a quick turnaround on review.**
3) **The proposed step-down regimen in patients achieving CDAI remission would not be optimal to support the Lilly's proposed labeling.**

Question 3 – Study JADV: Methotrexate-Inadequate Response (MTX-IR) Study
Study I4V-MC-JADV (JADV) is described in Section 7.1 and a protocol worksheet is provided in Appendix 4.
(a) Does FDA agree that the design of Study JADV and analysis plan are adequate to support registration of LY3009104 (administered with MTX) in this patient population, with specific claims for reducing signs and symptoms, improving physical function, and slowing and/or inhibiting structural progression, in adult patients with moderately to severely active RA (b) (4) *?*

FDA Response:
See FDA Summary Comments above. The design of Study JADV appears to be adequate to provide data to evaluate the treatment effect of LY3009104 on signs and symptoms, and physical function.

Based on the protocol synopsis, we have the following comments regarding your analysis plan on signs and symptoms (ACR20), physical function (HAQ-DI), and radiographic (mTSS) endpoints:

For the ACR20 response endpoint at Week 12, the primary analysis proposed (i.e. logistic regression and non-responder imputation for missing data) is acceptable.

For the HAQ-DI endpoint at Week 12, you propose to use analysis of covariance to evaluate treatment effects and apply modified baseline observation carried forward (mBOCF) to handle missing data. It appears that you also plan, as a sensitivity analysis, to apply a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) analysis with an unstructured covariance structure to evaluate treatment differences in HAQ-DI endpoint. The mBOCF approach proposed, assumes that patients who discontinue due to adverse event are treatment failures by assigning the baseline score as a bad outcome. This approach is generally reasonable provided that the reasons for discontinuations are clearly documented to avoid less informative terms such as 'lost to follow-up', 'patient/investigator decision,' 'withdraw consent,' etc. We recommend that you also include two additional sensitivity analyses in the protocol. One sensitivity analysis is to assume that any patients who discontinue treatment or study prior to Week 12 are treatment failures and to apply baseline observation carried forward to these patients' HAQ-DI score at Week 12 in the analysis. Another sensitivity analysis is to conduct a responder analysis using a cut-off of 0.3, and to apply non-responder imputation approach to any patients who discontinue treatment or study. We expect that the results from these sensitivity analyses will support the primary analysis. You may also use MMRM

analysis as a third sensitivity analysis, but note that the estimate (estimand) from this modeling approach will be different from that using mBOCF approach, unless the dropout rate is low.

(b) Rescue therapy will be offered in Studies JADV, I4V-MC- JADX (JADX), and I4V-MC–JADW (JADW). Patients will be assessed for nonresponse at Weeks 14 and 16. Does FDA agree with the strategy of offering LY3009104 as rescue therapy starting at Week 16 to patients who are nonresponders, regardless of their initial randomization arm?

FDA Response:
No, we do not agree. It is not acceptable to leave LY3009104 patients on the same therapy if they have not experienced a response at the Week 16 time point. All patients who have not experienced the pre-specified response criteria at Week 16 should receive a change or step-up in therapy.

Discussion:
See Lilly's document "Proposed Rescue Therapy for baricitinib (LY3009104) Phase 3 Trials" (Attachment at end of meeting minutes).

Lilly clarified that their purpose for offering rescue therapy is to assure patients and investigators that the patients will eventually receive active therapy. If a patient still has not achieved a response within 4 weeks of the initial change in therapy (at week 16), then that patient will be discontinued from the study and treated according to standard of care. Having some patients escape to different treatment will make it more difficult to maintain the blind. For endpoint considerations, once rescued, that patient's data will be counted as missing and imputed accordingly. FDA stated that Lilly should provide their rationale for their rescue therapy plan in their protocol, and include arguments that support their position that up to 20 weeks of uncontrolled disease activity without a change in DMARD therapy is ethical.

(c) Does FDA agree with the statistical method for assessing noninferiority and the choice of the associated noninferiority margin for comparison of LY3009104 with adalimumab in the MTX-IR study?

FDA Response:
We will be relying on the superiority assessment of LY3009104 compared to the placebo-add-on control group in this study for regulatory decision-making. In light of this, we do not believe that a formal noninferiority assessment comparing LY3009104 to adalimumab will be more informative than an annotation of the point estimates and confidence intervals of the LY3009104 and adalimumab groups.

(d) [redacted] (b) (4)

FDA Response:

(b) (4)

(e) Adalimumab will be provided to sites from local sources in accordance with regulations in those countries. Lilly does not expect differences in clinical endpoints as a result of adalimumab being sourced locally and therefore, does not propose any comparability analyses. Does FDA agree?

FDA Response:
It is acceptable to use adalimumab that is sourced locally without comparability analyses. However, you will be expected to provide subgroup analyses by region in the NDA.

(f) Because all patients randomly assigned to receive placebo will be rerandomized to active treatment by Week 24, Lilly plans to use linear extrapolation of mTSS scores to conduct the comparison of structural progression of LY3009104 to placebo at Week 52. Does FDA agree that such a linear extrapolation approach to statistical analysis is appropriate for these data (b) (4) *in this patient population?*

FDA Response:
See FDA Summary Comment.

(g) Lilly proposes to assess the effect of LY3009104 on progression of structural joint damage using (b) (4) *X-rays. The primary endpoint for a structure claim would be based on X-rays at 52 weeks.* (b) (4) *Does FDA have comments on* (b) (4) *? Does FDA agree* (b) (4) *?*

FDA Response:
We encourage you to (b) (4)

(b) (4)

(i) Does FDA agree that the gatekeeping strategy for Study JADV (Figure 7.1) will adequately control the overall type I error rate and that significant results under these testing strategies will support registration of LY3009104 in the MTX-IR patient population?

FDA Response:
Your gatekeeping strategy generally appears to be appropriate and should be able to provide adequate data to evaluate the effect of LY3009104 in the MTX-IR population.

Whether the resulting data will support marketing approval is a review issue and cannot be concluded at this time.

Question 4 – Study JADX: Conventional DMARD-Inadequate Response Study
Study JADX is described in Section 7.2 and a protocol worksheet is provided in Appendix 5.
(a) Does FDA agree that the design of Study JADX and analysis plan are adequate to support registration of LY3009104 (administered alone or in combination with conventional DMARDs (cDMARDs), including MTX) in this patient population, with specific claims for reducing signs and symptoms and improving physical function in adult patients with moderately to severely active RA (b) (4) *?*

FDA Response:
The design of Study JADX appears to be adequate to provide data to evaluate the treatment effect of LY3009104 on signs and symptoms and physical function endpoints in the proposed study population. However, we do not agree with the proposed rescue regimen. It is not acceptable to leave LY3009104 patients on the same therapy if they have not experienced a response at the Week 16 time point. All patients who have not experienced the pre-specified response criteria at Week 16 should receive a change or step-up in therapy. Also, see response to Question 2b and 2c regarding our concerns about the possible step-down maintenance regimen of 2 mg QD.

See FDA Response to Question 3a for comments regarding your analysis plan.

(b) Does FDA agree that the gatekeeping strategy for Study JADX (Figure 7.2) will adequately control the overall type I error rate, and that significant results under these testing strategies will support registration of LY3009104 in the cDMARD-IR patient population?

FDA Response:
Your gatekeeping strategy includes (b) (4) , we disagree with your proposed gatekeeping strategy.

Question 5- Study JADW: Tumor Necrosis Factor Inhibitor-Inadequate Response (TNFIR) study
Study JADW is described in Section 7.3 and a protocol worksheet is provided in Appendix 6.
(a) Does FDA agree that the design of Study JADW and analysis plan are adequate to support registration of LY3009104 (administered with cDMARDs, including MTX) in this patient population, with specific claims for reducing signs and symptoms and improving physical function in adult patients with moderately to severely active RA (b) (4) ?

FDA Response:
The design of Study JADW appears to be adequate to provide data to evaluate the treatment effect of LY3009104 on signs and symptoms and physical function endpoints in the proposed study population. However, we have concerns that the rescue regimen is not appropriate for patients who are randomized to LY3009104 and require rescue. See responses to Question 3b and 4a. See FDA Response to Question 3a for comments regarding your analysis plan.

(b) Does FDA agree that the gatekeeping strategy for Study JADW (Figure 7.3) will adequately control the overall type I error rate and that significant results under these testing strategies will support registration of LY3009104 in the tumor-necrosis factor inadequate response (TNF-IR) patient population?

FDA Response:
Your gatekeeping strategy generally appears to be appropriate and should be able to provide adequate data to evaluate the effect of LY3009104 in the TNF-IR population. Whether the resulting data will support marketing approval is a review issue and cannot be concluded at this time.

Question 6 – Study JADZ: Early RA/DMARD-Naïve Study
Study JADZ is described in Section 7.4 and a protocol worksheet is provided in Appendix 7.
(a) Does FDA agree that the design of Study JADZ and analysis plan are adequate to support registration of LY3009104 (administered alone or in combination with MTX) in this patient population, with specific claims for reducing signs and symptoms and improving physical function in adult patients with moderately to severely active RA (b) (4) ?

FDA Response:
The design of Study JADZ appears to be adequate to provide data to evaluate the treatment effect of LY3009104 on signs and symptoms and physical function endpoints in the proposed study population. We note that this is a non-inferiority trial design compared to MTX. This is acceptable as long as there will also be evidence of efficacy in RA clinical trials designed to show superiority of LY3009104 compared to a control group. However, we do not agree with the lack of a rescue option during the entire study period for patients experiencing uncontrolled disease activity. Because of the titration period and the study population, it is reasonable to not incorporate an escape option during the first 6 months of the study. However, patients should be evaluated at Week 24, 32, and 40, with the intention of escalating or changing therapy if disease activity is uncontrolled at these visits.

In terms of the analysis plan, you propose to conduct your primary analysis (for non-inferiority) on the modified intent-to-treat population (mITT). We have limited information on how protocol violations (e.g. non-adherence, patient switching treatment, misclassification of primary endpoint, or measurement errors) or patient discontinuation (i.e. missing data imputation) may affect the efficacy analysis on the mITT population or possibly on the per-protocol (PP) population. The Division's assessment of efficacy will evaluate the results from the analyses using these two populations (i.e. mITT and PP) and differences in results will need close examination. Furthermore, to minimize bias due to patient discontinuation or protocol violation, we recommend that you minimize or avoid missing data due to patient discontinuation and protocol violations (e.g. non-adherence, and misclassification of the primary endpoint) by carefully planning your study design and by continually monitoring the conduct of your trial.

Discussion
Lilly asked if their proposal of noninferiority margin of 12% would be appropriate for this study. FDA responded that the proposed margin appeared to be reasonable.

(b) Does FDA agree that it is appropriate to include patients who have received less than 4 doses of MTX?

FDA Response:
It is acceptable to include patients who have received less than 4 doses of MTX.

(c) Does FDA agree that the gatekeeping strategy for Study JADZ will adequately control the overall type I error rate, and that significant results under these testing strategies will support registration of LY3009104 in the Early RA/DMARD-Naïve patient population?

FDA Response:
Your gatekeeping strategy generally appears to be appropriate and should be able to provide adequate data to evaluate the effect of LY3009104 in the DMARD-IR population. Whether the resulting data will support marketing approval is a review issue and cannot be concluded at this time.

(b) (4)

FDA Response:
See response to Question 3g.

Question 7 – Patient-Reported Outcomes: Morning Joint Stiffness, Tiredness, and Pain
In Study JADV and Study JADX, patient diaries will be used to collect information on patient reported outcomes of morning joint stiffness, tiredness, and pain. Patients will answer 7 questions every day for 12 weeks. To ensure that the most appropriate questions are being asked and to establish content validity of the draft questions to measure duration and severity of morning joint stiffness, a series of open-ended qualitative patient interviews is planned. To establish reliability, construct validity, and ability to detect change, a quantitative validation study will be conducted in parallel to the Phase 3 studies and in accordance with the FDA's PRO Guidance (2009). (b) (4)

these measures are included in the gatekeeping strategies for Study JADV (Figure 7.1). Lilly intends to use analyses from Study JADX as supportive evidence to the findings from JADV.
(a) Does FDA agree that the proposed diary questions are appropriate (b) (4) *If not, can FDA please comment on suitable alternatives?*

FDA Response:
The endpoints you are proposing represent overlapping and ancillary benefits with respect to the core outcome measures currently used to support RA labeling claims. For example, patient pain is already a component of the ACR response criteria, and it is not clear that "weariness/tiredness" or morning stiffness represent benefits distinct from the benefit seen with control of disease activity in RA, which is already captured by ACR response criteria. (b) (4)

The inclusion of these outcome measures will be a review issue.

(b) Does FDA agree that the proposed diary questions are appropriate to support claims regarding severity of tiredness? If not, can FDA please comment on suitable alternatives?

FDA Response:
See response to Question 7a.

(c) Does FDA agree that the proposed diary questions are appropriate to support claims regarding pain severity? If not, can FDA please comment on suitable alternatives?

FDA Response:
See response to Question 7a.

(d) Does FDA agree that the gatekeeping strategy for patient-reported outcome (PRO) measures in Study JADV, with supportive data from Study JADX, is sufficient to support claims regarding the PRO measures?

FDA Response:
See response to Question 7a.

Question 8 – Safety Monitoring Plans
Safety monitoring plans are described in Section 9.

(b) Does FDA agree that the proposed safety monitoring plans in totality will be adequate to characterize any early safety signals prior to the initial NDA submission and together with additional plans to address longer-term safety will support registration in the treatment of moderately to severely active RA?

FDA Response:
Your proposed safety monitoring and risk management plans appear reasonable given what is known about LY3009104 and other JAK inhibitors to date. If unexpected safety signals arise during your Phase 3 trials, it is possible that additional data or monitoring could be required.

(c) Does FDA agree that the recommendations for initiation and discontinuation of dosing in response to safety monitoring are appropriate for this clinical development program (b) (4) *?*

FDA Response:
Based on the currently available data, these recommendations appear to be reasonable. However it is possible that with larger numbers of patients and greater exposure in the Phase 3 program that other safety monitoring may be needed, e.g., lymphocyte counts.

Question 9 – Impact of LY3009104 on (b) (4)

(b) (4)

Question 10 – Anticipated Patient Exposures
Does FDA agree that the proposed number of patient exposures (from Phase 2 and 3 studies in RA, along with exposures from the Phase 2 studies in plaque psoriasis and diabetic nephropathy) for the duration specified in Table 10.1 is adequate to support registration of LY3009104 for the treatment of adult patients with moderately to severely active RA?

FDA Response:
The anticipated safety database for your planned NDA includes 1790 patients treated with LY3009104 for at least 1 year, and 2537 patients treated with LY3009104 for at least 24 weeks. This appears adequate, barring unexpected safety signals that might arise during your Phase 3 trials and require further characterization.

Question 11 – Clinical Pharmacology Plan
Lilly proposes a clinical pharmacology plan tailored to support registration and labeling for LY3009104. Based on human metabolism data that showed LY3009104 is predominantly excreted unchanged in the urine (Section 5.2.4), along with in vitro CYP inhibition and available transporter data, a study in hepatically impaired patients, a warfarin interaction study, studies

evaluating LY3009104 as substrates of the organic cation transporters (OCT) or anion transporters (OAT) OCT1, OCT2, OAT1, and OATP1B1, and studies evaluating LY3009104 as inhibitors of the transporters OCT1, OCT2, OAT1, OAT3, and OATP1B1 ***are not planned****. The population pharmacokinetic (PK) analysis is described in Section 11.5.*

Discussion:
Lilly stated that they will conduct dedicated hepatic impairment studies (mild and moderate groups). Lilly also requested confirmation that it is acceptable not to conduct an in vivo warfarin interaction study.

FDA stated that their proposal appears to be reasonable based on the in vitro summary data presented in this meeting package.

(a) Does FDA agree that the clinical pharmacology package proposed is comprehensive and will support the registration of LY3009104 for the treatment of adult patients with moderately to severely active RA (b) (4)

FDA Response:
In general, the types of data you are proposing seem reasonable to support the filing of an NDA.

For transporter related issues, we refer you to current FDA Draft Guidance for Industry: "Drug Interaction Studies –Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (January 2012)" for Agency's current thinking.

We recommend that you classify patients with impaired renal function based on estimated GFR (eGFR) as recommended in the FDA Draft Guidance for Industry: "Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling (March 2010)." That is, for mild and moderate renally impaired patients, the eGFR should be within the range of 60-89 mL/min/1.73m^2 and 30-59 mL/min/1.73m^2, respectively. Thus, the renal dose for Phase 3 clinical trials is 2 mg QD when eGFR is between 40 and 60 mL/min/1.73m^2.

Discussion:
Lilly stated that they agree with renal impairment classification recommendations.

In addition, you will need to identify the formulations (capsules and tablets) used in different studies in the clinical development program and provide appropriate information linking them to the to-be-marketed formulation.

Discussion:
Lilly stated that their Phase 3 formulation is the to-be-marketed formulation.

FDA responded that if the formulation is changed, Lilly needs to conduct appropriate studies to link them to the to-be-marketed formulation.

(b) Does FDA agree with the population PK analysis plan to assess specific populations and drug interactions?

FDA Response:
If you plan to assess the impact of specific populations and drug interactions on drug exposure using population PK analysis, we recommend that you prospectively develop a plan and submit that for FDA review. In general, you will have to consider the following for your analysis plan:

- Appropriate recording of the doses and duration of coadministered drugs
- Demonstration that subjects were on stable doses of coadministered drugs for sufficiently long duration to allow evaluation of drug-drug interaction
- *A priori* or *post-hoc* demonstration that analysis had sufficient power to detect the differences in metrics of interest based on evaluated covariate

In addition, to characterize the effects of varying hepatic function on pharmacokinetics of LY3009104, we recommend that you classify patients based on Child-Pugh status as stated in the FDA guidance titled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling."

Please submit all the datasets and corresponding codes for these analyses. We encourage you to refer to the following pharmacometric data and models submission guidelines:

All datasets used for model development and validation should be submitted as SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.,: myfile_ctl.txt, myfile_out.txt). Provide a model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

Additional Clinical Comments

1) Regarding Study JADY:

- A 5-year long-term extension does not appear to be adequately justified given that the effect of LY3009104 is not yet well characterized. We recommend you limit the duration of the extension (e.g. to 2 years) and amend the protocol if desired at a later

time when additional data are available to justify continued treatment in a long-term extension.

- We recommend you consider continuing a lower dose regimen (i.e., 2 mg nominal daily dose) and your active comparator (i.e., Humira) into the long-term extension to provide groups for comparison, which would make Study JADY more informative.

2) Regarding timing of the efficacy assessments with respect to dose:

- We recommend that you perform the clinical efficacy assessments prior to administering study medication, at what would be pharmacokinetic trough level of the drug. If clinical efficacy assessments are obtained after LY3009104 is administered for that day, this raises a question of whether efficacy results would have been negatively impacted by the once daily administration of the product and resulting "drug holiday."

Discussion:

Lilly agreed to revise the duration of the long-term extension to a more limited time frame.

Regarding timing of the efficacy assessments with respect to dose, Lilly stated that they are not sure when pharmacodynamic effects are at peak. (b) (4) **may use patient diaries for recording symptoms during the day. Perhaps they can perform an analysis of timing of dosing through to the next day.**

FDA stated that there are concerns with using patient diaries for efficacy assessments and that it would optimal to perform efficacy assessments at PK trough, and to include an active comparator to increase reliability of data by having a known effective drug for benchmarking.

FDA added that although clinical trials are designed to show efficacy, safety assessment is another important aspect to address.

Lilly noted that some patients may still be on 2 mg QD during the extension periods, but they are not planning on continuing Humira.

The Division strongly recommended they continue to include an active comparator as a benchmark for safety comparisons. The Division also noted that the safety assessment becomes more complicated the more patients are crossing over to different treatments, such as if a step-down regimen is included in the extensions. Lilly will need to keep in mind how adverse events will be attributed. Additionally, Lilly should keep in mind that the safety data to support the 4 mg dose may not end up being adequate if patients are stepping down to the 2 mg dose.

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ACTION ITEMS

There were no follow-up action items.

ATTACHMENTS (at end of meeting minutes)

Lilly's document "Proposed Rescue Therapy for baricitinib (LY3009104) Phase 3 Trials"

Proposed Rescue Therapy for baricitinib (LY3009104) Phase 3 Trials

- The purpose of offering rescue therapy is to assure patients and investigators that participants will eventually receive an active therapy.
- The rescue scheme must maintain the study blind.
- Rescue Criteria at week 16 = patients who have not experienced an improvement in tender joint count (TJC), swollen joint count (SJC) and hsCRP of >20% from baseline. Rescue treatment will be assigned automatically by the IVRS based on the change from baseline data above.
- Rescue Criteria after week 16 = patients who have not experienced an improvement in tender joint count (TJC) and swollen joint count (SJC) of >20% from baseline; along with investigator judgment
- Once patients are rescued, the investigators may titrate analgesics and anti-inflammatory therapies as needed
- Patients will continue to be assessed at each visit (4-8 weeks apart); patients can come in for unscheduled visits if they believe they are not responding adequately to therapy
- Patients can only be rescued once; after rescue, if patient again meets rescue criteria, they will be discontinued from the study after appropriate follow-up so that they can receive standard of care

Study JADZ (Early RA/cDMARD-naïve)

Treatment Groups	At Week 16 or After, Rescued to
MTX Monotherapy	LY + MTX (added LY)
LY Monotherapy	LY + MTX (added MTX)
LY + MTX	LY + MTX (no change)

Study JADX (cDMARD-IR)

Treatment Groups	At Week 16 or After, Rescued to
PL + cDMARD	LY + cDMARD (added LY)
LY + cDMARD	LY + cDMARD (no change)
LY Monotherapy	LY + MTX (added MTX)
PL + MTX	LY + MTX (added LY)
LY + MTX	LY + MTX (no change)

Study JADW (TNF-IR)

Treatment Groups	At Week 16 or After, Rescued to
PL + cDMARD	LY + cDMARD (added LY)
LY + cDMARD	LY + cDMARD (no change)

Study JADV (MTX-IR)

Treatment Groups	At Week 16 or After, Rescued to
PL + MTX	LY + MTX (after Week 24, all patients go to LY + MTX)
ADA + MTX	LY + MTX (change ADA to LY)
LY + MTX	LY + MTX (no change)

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/s/

CHRISTINE H CHUNG
07/22/2012