CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207924Orig1s000

CHEMISTRY REVIEW(S)

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

DATE: 06-FEB-2018

TO: N207924 file

FROM: Craig Bertha
CMC Lead
ONDP/DNDP II

THROUGH: Julia Pinto
Acting Branch Chief
ONDP/DNDP II

SUBJECT: Additional CMC data in 04-DEC-2017, Resubmission

SUMMARY and CONCLUSION: The OPQ recommendation for this application at the end of the original review cycle was that the application could be approved, from a CMC perspective. The Agency sent a complete response (CR) action to the applicant. The current 04-DEC-2017, submission is a response to the CR letter.

Although there were no CMC-related comments included in the CR letter, the new submission includes some additional CMC data. Drug product analyses data are provided for an additional 16 new batches (9 at 4 mg and 7 at 2 mg strengths). All of these batches met their specifications. The submission also includes the 18, 24, and 36 month stability data for the primary stability batches of the two strengths. There are also new stability data (up to 18 months with 25°C/60%RH storage and 6 months with 40°C/75%RH storage) for batches of drug product manufactured at the commercial manufacturing facility [Lilly del Caribe, Puerto Rico (PR)]. The applicant will maintain their proposal for a 24 month shelf-life, which was already found acceptable based on the data provided under the previous review cycle. As the updated data show no significant trends for up to 36 months with 30°C/65%RH storage, the 24 month expiry is still acceptable. The new stability data (up to 18 months long term conditions) from the commercial manufacturing site in PR (in bottles and blisters stored at 30°C/65%RH, 30°C/75%RH, and 40°C/75%RH) also demonstrated the drug product to have adequate stability with no significant trending. These data also support the 24 month expiry period when considering the recommendations of ICH Q1E.

The new CMC data submitted with the resubmission does not alter the original recommendation from OPQ to approve the application.

cc:
CDER/OND/DPARP/JLee
CDER/OPQ/ONDP/DNDPII/CBertha
CDER/OPRO/Division I/Branch I/FAisida

CDER/OPQ/ONDP/DNDPII/JPinto

Craig Bertha

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Date: 5/23/2018 06:44:36AM
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Julia Pinto

Digitally signed by Julia Pinto
Date: 5/23/2018 11:03:19AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

Recommendation: Approval

NDA 207924
Review #1

Drug Name/Dosage Form	baricitinib tablets
Strength	2 & 4 mg/tablet
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Eli Lilly and Co.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original	15-JAN-2016	all
Amendment	15-APR-2016	drug product
Amendment	28-APR-2016	laboratory
Amendment	26-MAY-2016	drug substance, drug product, process
Amendment	01-JUN-2016	drug product
Amendment	07-JUN-2016	drug product
Amendment	15-JUN-2016	drug product
Amendment	27-SEP-2016	drug product, process

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Sam Bain	II/Division of New Drug API
Drug Product	Art Shaw	IV/DNDPII
Process	Ted Chang	IV/DPAII
Microbiology	Ted Chang	IV/DPAII
Facility	Rebecca Dombrowski	II/DIA
Biopharmaceutics	Kalpana Paudel	II/DB
Regulatory Business Process Manager	Florence Aisida	I/Division I
Appl. Technical Lead	Craig M. Bertha	IV/DNDPII
Laboratory (OTR)	N/A	
ORA Lead	Paul Perdue, Jr.	ORA/OO/OMPTO/DMPTPO/MDTP
Environmental Analysis	N/A	

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	III	(b) (4)		Not necessary – Sufficient Information in NDA		
	IV					
	III					
	III					
	III					
	III					

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	102204	Lilly's IND for baricitinib

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

I. Recommendations and Conclusion on Approvability

Based on the reviews and recommendations from the drug substance, drug product, biopharmaceutics, process, and facilities teams outlined in the review below, an overall recommendation of **approval** is to be forwarded to the clinical Division (DPARP) from the Office of Pharmaceutical Quality. The amended NDA has provided adequate chemistry, manufacturing and controls information to assure the identity, strength, purity, and quality of the drug product, baricitinib tablets. The applicant has responded adequately to all information requests. Associated manufacturing and testing sites supporting this NDA are deemed acceptable by the Office of Process and Facilities (OPF) as of 24-OCT-2016.

The stability information submitted to the NDA supports a 24 months expiration dating period for the drug product under the labeled storage conditions.

II. Summary of Quality Assessment

A. Product Overview

The current application seeks approval for a solid oral dosage form, baricitinib tablets, for the treatment of rheumatoid arthritis. The synthesis of the new molecular entity, baricitinib, (b) (4) is performed by Lilly in Ireland. The immediate release tablet drug product is manufactured using (b) (4) .

Proposed Indication(s) including Intended Patient Population	Moderate to severe rheumatoid arthritis (RA)
Duration of Treatment	Chronic
Maximum Daily Dose	Recommended daily dose is 2 or 4 mg/day (QD)
Alternative Methods of Administration	No other routes of administration than oral

B. Quality Assessment Overview

Baricitinib is a new molecular entity for the treatment of rheumatoid arthritis. It is synthesized (b) (4) from acceptable starting materials. There is (b) (4) The crystalline achiral drug substance is practically insoluble in water and slightly soluble at lower pH. During

review there were some questions regarding the testing methods, specification acceptance criteria, retest period, commercial storage conditions, and changes to the synthesis process during development, but these issues have been adequately addressed by the applicant.

The immediate release tablet drug product has two strengths, 2 and 4 mg, and these dosage forms are prepared with common compendial grade excipients. Tablet manufacture consists of [redacted] (b) (4) . During review of the drug product and process, there were questions regarding details of the process description that were not outlined in the application, inadequate in-process controls for [redacted] (b) (4), out-of-trend results for microbial data, and [redacted] (b) (4) end product content uniformity. In addition, the applicant provided additional data regarding drug product packaging components and testing of colorants for distinguishing between the two strengths. Based on the evaluation of the applicant's responses to information requests about these issues, the drug product and process review teams have found these aspects of the application to be adequate.

The biopharmaceutics team has found the applicant's dissolution method to be discriminating, and the specification acceptance criterion for dissolution to be acceptable, from a quality control perspective.

The facilities review team has evaluated three sites for the commercial production of the drug product: one drug substance synthesis site (profile class CSN), a drug product production site, and a final packaging site. Based on file review and pre-approval inspections, there are no outstanding facilities issues and all sites are found to be acceptable.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Craig M. Bertha -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
Date: 2016.10.31 12:23:19 -04'00'

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: NDA 207924

Drug Product Name / Strength: Baricitinib (LY3009104) tabs 2 mg and 4 mg

Route of Administration: Oral

Applicant Name: Eli Lilly and Company

Dissolution Method and Acceptance Criteria

The proposed drug products Baricitinib (OLUMIANT™) 2 mg and 4 mg are immediate release (IR) tablets. The Applicant seeks approval of this NDA via the 505(b)(1) regulatory pathway for the treatment of adult patients with moderately to severely active rheumatoid arthritis.

1. Composition of proposed drug product:

The quantitative composition and function of each component of commercial baricitinib (LY3009104) tablets are listed in the Table 1. Both the formulations are proportionally similar.

Table 1: Composition of baricitinib commercial tablets 2 mg and 4 mg (from M.2.3.P)

Ingredient	Quantity (mg/Tablet)		Function
	2 mg	4 mg	
Active Ingredient			
Baricitinib	2.000	4.000	Active Ingredient
			(b) (4)
Mannitol			(b) (4)
Microcrystalline cellulose			
Croscarmellose Sodium			
Magnesium Stearate			
			(b) (4)
Other Ingredient – Film-Coating			
			(b) (4)
Total Finished Tablet Weight	**206.0**	(b) (4)	

2. In vitro dissolution method and acceptance criteria:

The in vitro dissolution method proposed for this NDA is shown below in Table 2:

Table 2: In vitro dissolution method for baricitinib tablets (from M.3.2.P.5)

USP II (Paddles)	Apparatus
75 rpm	Rotation Speed
900 mL	Media Volume
pH 4.5 Acetate Buffer	Media
HPLC with UV Detection at 220 nm	Sample Analysis

The proposed dissolution acceptance criterion is as follows.

Not less than (b) (4)% (Q) in 30 minutes.

Table 3 shows the representative batches of baricitinib drug product that were evaluated for the dissolution specification proposal.

Table 3: Batches of baricitinib drug product that were evaluated for the dissolution specification proposal

Batch Number	Dose Strength (mg)	Manufacturer	Batch Release Dissolution Results at 30-Minute Time Point (Mean % Released (Range))
C228384[1]	2	Eli Lilly and Company, Indianapolis, IN	(b) (4)
C228385[1]	2		
C292141[1]	2		
C228387[1]	4		
C228388[2]	4		
C228389[1]	4		
CT593690	4	(b) (4)	
CT593520	2		
CT592645	4		
CT591875	2		
CT591873	4		
CT591872	4		
CT591871	4		
CT591825	4		
CT591824	4		
CT589671	4		
CT589670	2		
CT588352	4		
CT585966	4		
CT585965	2		
CT585964	2		
CT585967	4		
CT582873	4		
CT582118	2		
CT581179	2		
CT581178	2		
CT579255	4		
CT579254	4		
CT579253	4		
CT579252	4		
CT578830	2		
CT578829	2		
CT576309	4		
CT576308	4		
CT576307	4		
CT576306	2		
CT576305	2		
CT574503	2		
CT574500	4		
CT574499	4		
CT574498	4		

[1] Dissolution was run in triplicate.
[2] Dissolution was run in quadruplicate.

Figure 1. Dissolution Profiles for 2 mg Commercial Tablet Lots at Release

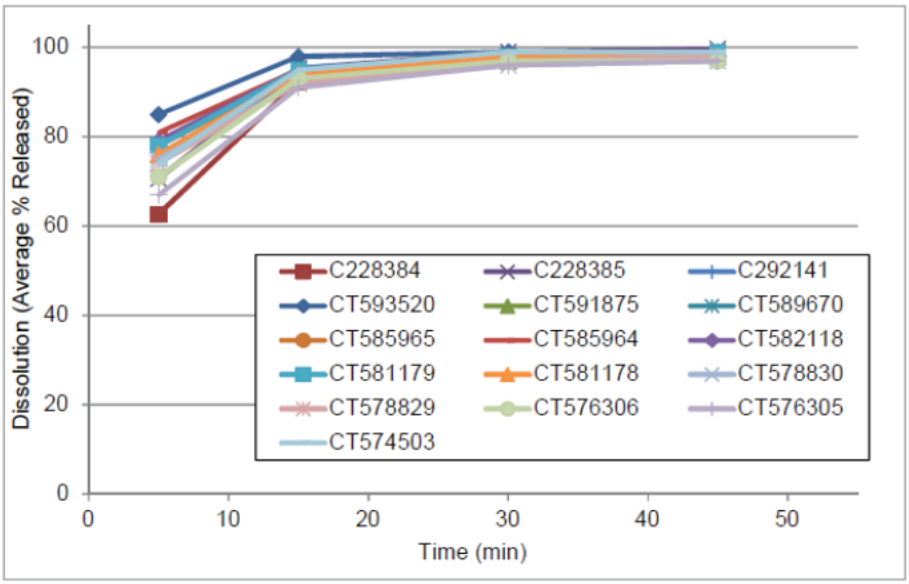

Figure 2. Dissolution Profiles for 4 mg Commercial Tablet Lots at Release

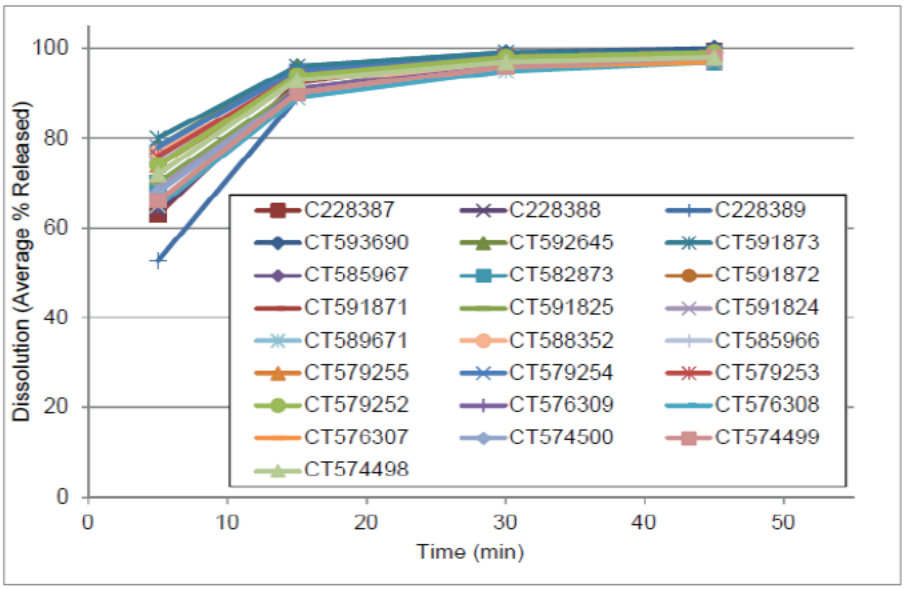

Table APP.2.7.1.4.8. Summary of In Vitro Dissolution Studies. Dissolution Results in pH 4.5 Media

Batch Number	Package Batch	Study ID	Strength (mg)	Dosage Form	Units tested	Apparatus 2 (paddles) at 75 rpm, 900 ml pH 4.5 acetate buffer			
						Dissolution Time (min)			
						5	15	30	45
						Dissolution Result, Average % (range)			
CT565232	CT567281	JDAH	4	Phase 2b Capsule	6	32 (b) (4)	75 (b) (4)	87 (b) (4)	91 (b) (4)
CT566373	CT567282	JDAH	8	Phase 2 Tablet	6	63	86	94	96
	CT591566	JAGO							
CT566374	CT567283	JDAH	8	Phase 2 Tablet	6	54	86	96	97
CT587120	CT591565	JAGO	4	Phase 2 Tablet	6	65	89	94	96
CT588352	CT591564	JAGO	4	Commercial Tablet	6	77	93	96	98
CT578829	CT583308	JAGF	2	Commercial Tablet	6	74	92	97	98
CT574500	CT583279	JAGF	4	Commercial Tablet	6	68	90	96	98
CT576308	CT589824	JAGM	4	Commercial Tablet	6	65	89	95	97
C228384	NA	NA	2	Commercial Tablet	18	63	92	97	99
C228387	NA	NA	4	Commercial Tablet	18	63	92	98	99

Abbreviations: NA = not applicable; rpm = rotations per minute.

3. Dissolution Method Development Report:

A. pH solubility profile of baricitinib

Table 4: Solubility profile of phosphate and salt form of baricitinib

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(b) (4)

[redacted]

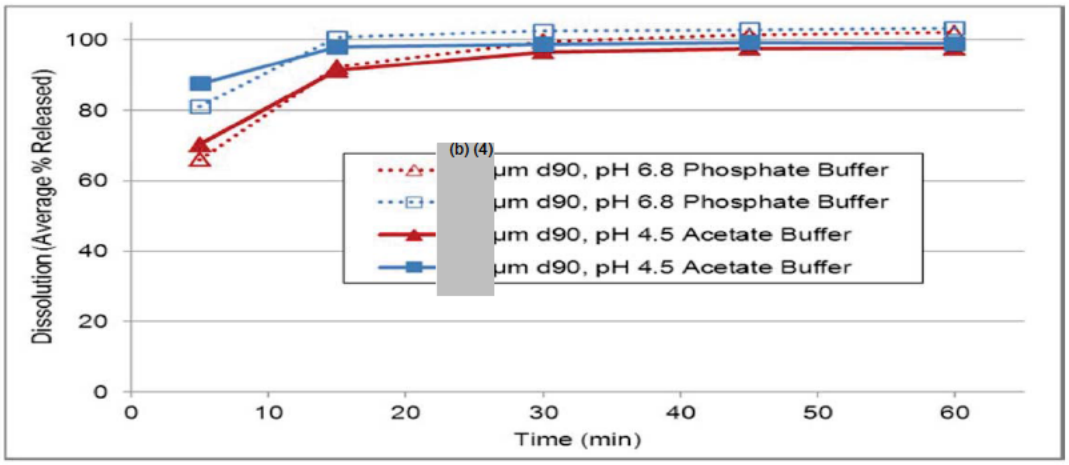
D. Discriminating ability of the *in vitro* dissolution method for baricitinib

The Applicant has evaluated the discriminating capability of the dissolution method with intentional variations in drug substance particle size, manufacturing parameters, and stress stability conditions as shown in the figures and tables below. The Applicant has also carried out dissolution of batches used in in vivo studies.

The dissolution method is sensitive to differences in drug substance particle size and changes in performance due to moisture exposure during storage at accelerated conditions. No significant change in dissolution is observed due to process changes such as (b) (4) [redacted], or tablet coating. No improvement in discrimination was found by changing the dissolution medium pH within the physiological pH range. Significant changes in drug substance form (phosphate salt to free base) and formulation (capsule to tablet) did not result in a change in in vivo exposure.

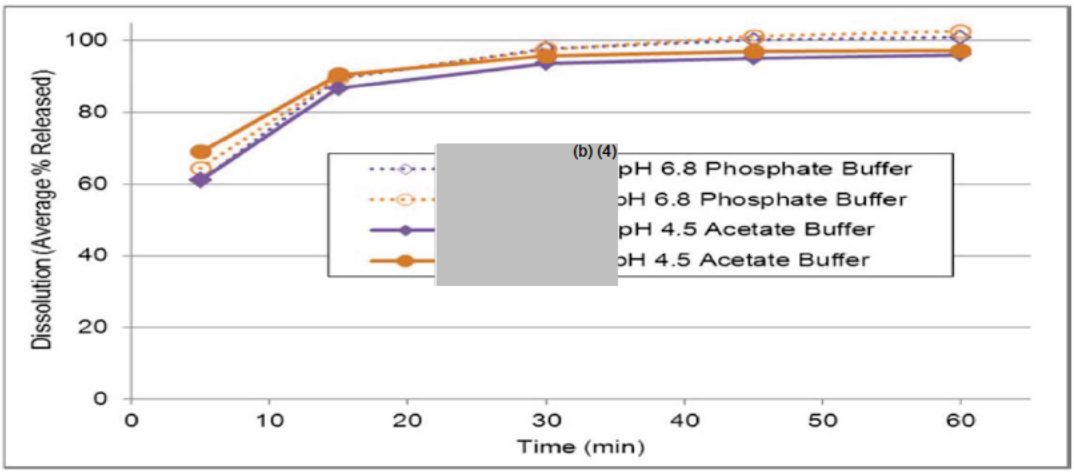
Drug Substance Properties-Particle size variation

Figure 6. Dissolution Profiles for Commercial Tablets Prepared with Low and High Particle Size Drug Substance (Batches EN0202053-020 and EN0202053-021)



Drug Product Process-(b) (4) variation

Figure 7. Dissolution Profiles for Commercial Tablet Cores Prepared with a (b) (4) (Batches EN0202053-016 and EN0202053-018)



Drug Product Process-(b) (4) variation

Figure 8. Dissolution Profiles for 2 mg Commercial Tablets Comparing Uncoated (Core) Tablets with Different (b) (4) and Coated Tablets (Batch DTS24342)

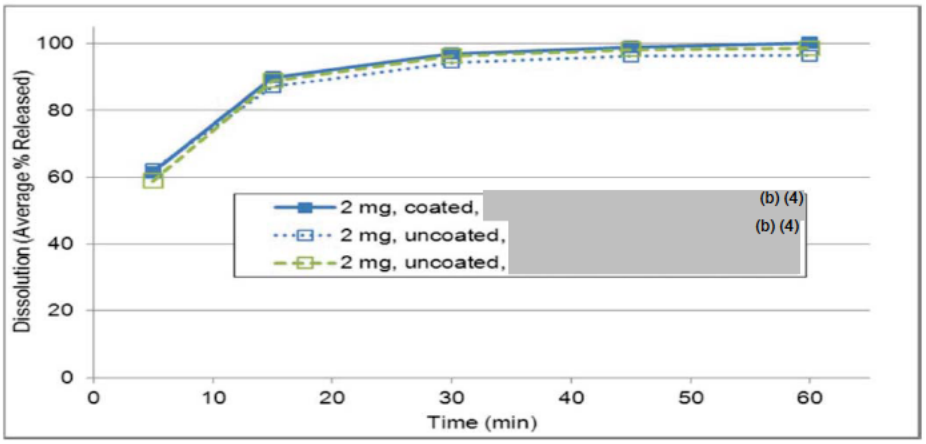
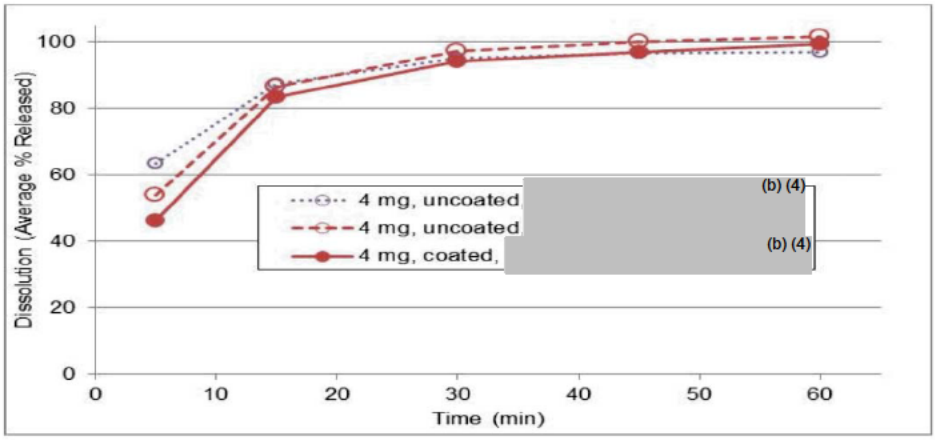


Figure 9. Dissolution Profiles for 4 mg Commercial Tablets Comparing Uncoated (Core) Tablets with Different (b) (4) and Coated Tablets (Batch DTS24345)



Drug Product Stability

Figure 10. Dissolution Profiles for Coated 2 mg Commercial Tablets (Batch DTS24342) Before and After Storage for 6 Months at Accelerated Conditions in (b) (4) Blisters

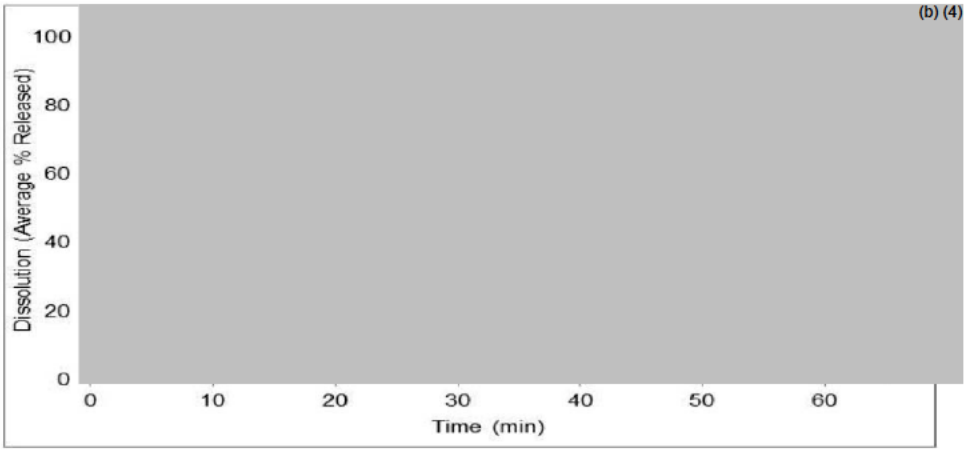
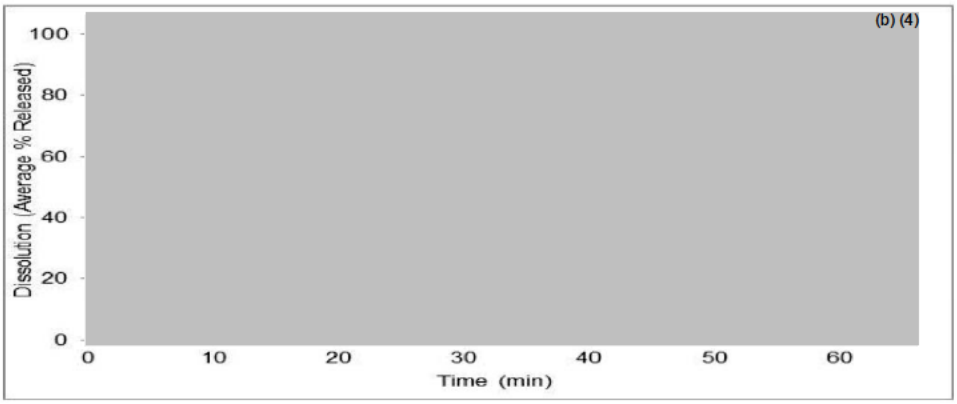


Figure 11. Dissolution Profiles for Coated 4 mg Commercial Tablets (Batch DTS24343) Before and After Storage for 6 Months at Accelerated Conditions in (b) (4) Blisters



4. Dissolution Profile Data Comparisons:

Bridging of Formulations

The Applicant conducted two relative bioavailability studies during the course of baricitinib clinical development which bridge the formulations used in early clinical development to the commercial tablet. The capsule formulation containing the phosphate salt of baricitinib and the Phase 2 tablet formulation containing baricitinib free base were bridged in a relative bioavailability study (Study JADH). This study also investigated the effect of 2 different particle size of baricitinib (free base) on bioavailability and showed that PK parameters were similar for these particle sizes. The Applicant also conducted a relative bioavailability study (Study JAGO) to bridge the Phase 2 tablets and commercial tablets. The in vitro dissolution profiles were also compared between Phase 2 and commercial tablets. The bioavailability and dissolution profiles are similar for Phase 2 tablets and commercial tablets. The commercial tablets were used in the Phase 3 clinical trials.

Figure 12. Dissolution profiles for Clinical Study JADH free base Phase 2 Tablets with two different drug substance particle sizes and phosphate salt capsules

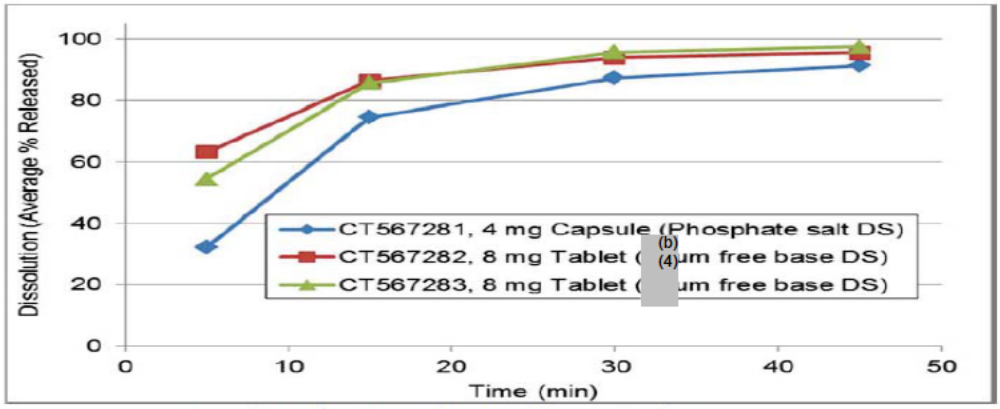


Figure 13. Dissolution profiles for Clinical Study JAGO Phase 2 Tablet formulation and proposed Commercial Tablets (coated)

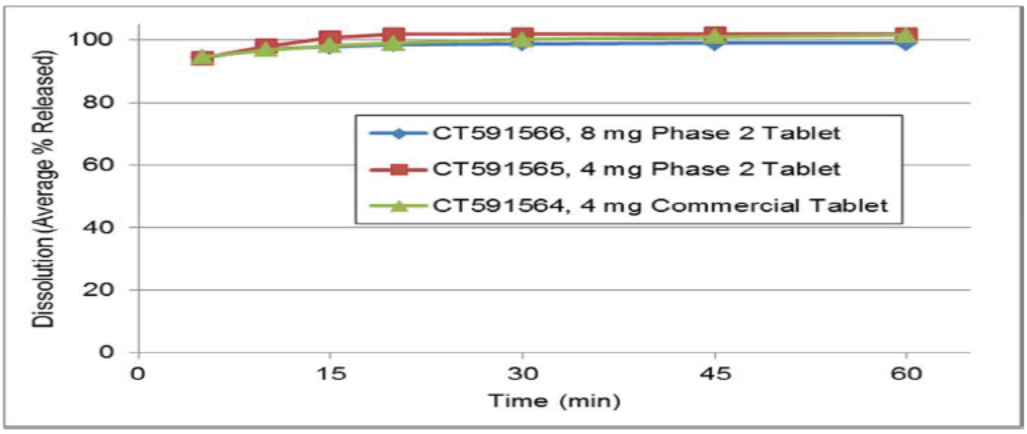


Figure 14. Dissolution profiles for Clinical Study JAGO Phase 2 Tablet formulation and proposed Commercial Tablets (coated)

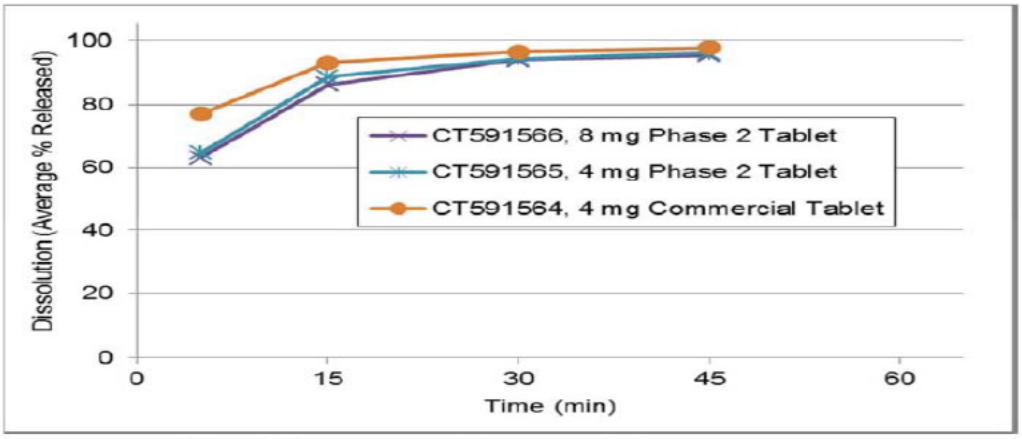
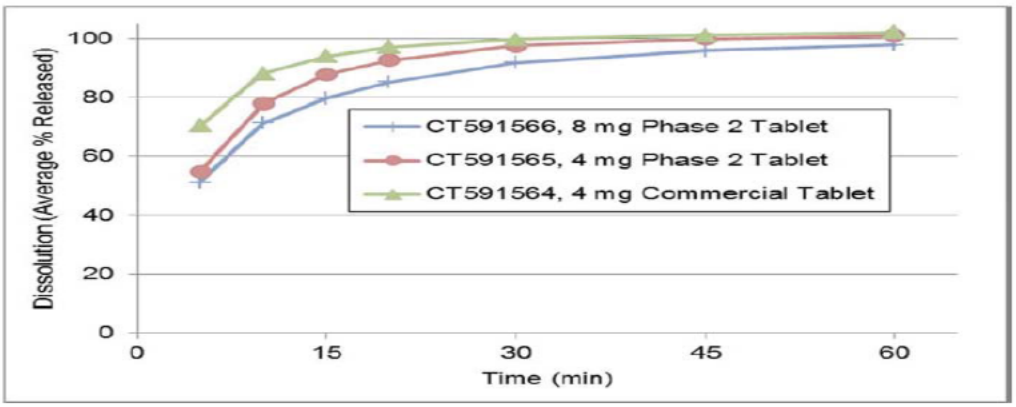


Figure 15. Dissolution profiles for Clinical Study JAGO Phase 2 Tablet formulation and proposed Commercial Tablets (coated)



5. Analytical Method and Its Validation:

In vitro dissolution analytical method validation report for Baricitinib IR tablets (Validation code B13225) was submitted in M.3.2.P.5.3, which were validated in terms of specificity, linearity, precision, accuracy, solution stability, and robustness, and is summarized below in Table 5.

Table 5: Summary of Method Validation for Dissolution of Baricitinib tablets (from M.3.2.P.5.3)

CHARACTERISTIC	EXPERIMENT	RESULT	ACCEPTANCE CRITERIA	CONCLUSION

Specificity	• The following samples were analyzed (n=1 each)
	• Media
	• Placebos (0.5-mg, 4-mg, 12-mg) in medium
	• 900 mL of medium was placed into each of four dissolution vessels equipped with paddles (apparatus II).
	• Each placebo was added to a separate vessel. One vessel contained only media. Heat was applied to the vessels to 37 °C and stirred at 150 rpm for 30 minutes.
	• The following clarification techniques were applied on each vessel (medium and placebo, n=1)
	  ◦ Pall Acrodisc 0.45µm nylon p/n 4502
	  ◦ Centrifuge (at a minimum 5 minutes at min 4000rmp or until clarified)
	• Also analyzed (n=1) baricitinib reference standard in medium at a concentration of approximately equivalent to the lowest strength
	• Compared the chromatography to evaluate any interference from medium, filter, and excipients in media.
	• Quantitated any interference against the response of the lowest standard.
		• No interfering peaks were observed in the components of the media, placebo or extractables.
		• See Figure 1 for example chromatograms.
			• No significant interference with the LY3009104 peak from components of the media, placebo or extractables.
			• If peaks are observed, the total response (as calculated by the method) contributes not more than 2% error vs. the response of the reference standard in media.
				Specificity is acceptable.

<table>
<tr><th>CHARACTERISTIC</th><th>EXPERIMENT</th><th>RESULT</th><th>ACCEPTANCE CRITERIA</th><th>CONCLUSION</th></tr>
<tr>
<td>Linearity</td>
<td>
• Evaluated linearity using six solutions of baricitinib at concentrations ranging from 40% of the lowest strength (0.5mg/tablet); 40%, 70%, 100% and 130% of the 4.0 mg/tablet; and 120% of the highest strength (12 mg/tablet).
• Compared the peak response versus the theoretical concentration of each standard solution (mg/mL)
• Calculated the correlation coefficient (r), y-intercept, 95% confidence interval of the y-intercept and slope.
• Calculated the residuals of the theoretical concentrations from the linear curve and evaluate the results for any trending.
• Calculated the residual sum of squares.
</td>
<td>
Linearity Results:
<table>
<tr><th>Parameter</th><th>Result</th></tr>
<tr><td>r value</td><td>1.000</td></tr>
<tr><td>y-intercept (Area Units)</td><td>461</td></tr>
<tr><td>Slope (AU*mL/mg)</td><td>55828576</td></tr>
<tr><td>y-Intercept p-value</td><td>0.6850</td></tr>
<tr><td>Residual sum of squares</td><td>13946746.8</td></tr>
</table>
<table>
<tr><th>Concentration</th><th>Residuals (%)</th></tr>
<tr><td>40% of the 0.5 mg/tablet</td><td>-0.5</td></tr>
<tr><td>40% of the 4 mg/tablet</td><td>-0.5</td></tr>
<tr><td>70% of the 4 mg/tablet</td><td>0.4</td></tr>
<tr><td>100% of the 4 mg/tablet</td><td>-0.1</td></tr>
<tr><td>130% of the 4 mg/tablet</td><td>1.1</td></tr>
<tr><td>120% of the 12 mg/tablet</td><td>-0.4</td></tr>
</table>
See Figure 2.
</td>
<td>
Perform linear regression of peak area versus theoretical concentration.)
Correlation coefficient (r) must be NLT 0.997.
The y-intercept is either
a) not statistically significantly different from zero (p-value must be >0.0500), or
b) ≤ 4.0% of the response corresponding to 100% of the 4-mg/tablet strength
All residuals are ≤ 5% of the response for the nominal strength (nearest to 100%) standard.
</td>
<td>
The correlation coefficient meets the acceptance criterion.
The y-intercept is not statistically different from zero. The p-value was greater than 0.05 and is not statistically significant.
Linearity is acceptable over a range of 0.0002 – 0.0180 mg/mL (See Figure 2 for results.)
.
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</table>

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<tr><th>CHARACTERISTIC</th><th>EXPERIMENT</th><th>RESULT</th><th>ACCEPTANCE CRITERIA</th><th>CONCLUSION</th></tr>
<tr>
<td>Accuracy (including filter recovery)</td>
<td>
• Evaluated accuracy by preparing one solution of baricitinib at each of three concentration levels: 40% of the 0.5-mg strength spiked into 0.5-mg placebo (85F), 100% of 4 mg strength spiked into 4-mg (85G) placebo and 120% of the 12-mg strength spiked into 12-mg placebo (85G). Add 900mL of solution to each dissolution vessel, allowed solutions to equilibrate to 37°C, add placebo (85F or 85G) and mix at 150 rpm to generate a homogeneous sample.
• After 30 min, acquire triplicate samples for each concentration level and sampling technique described in the method.
• Sample each vessel (n=3) and use the following filter/techniques:
• Manual sampling
o Pall Acrodisc 0.45µm Nylon p/n 4502
o Centrifugation (at a minimum 5 minutes at min 4000rpm or until clarified)
• Analyzed each of the 18 solutions per the method
• Remove a portion of the highest and lowest level solutions (n=3) clarified using both techniques and store at room temperature and under refrigerated conditions (5°C) in HPLC vials for solution stability.
• Calculated % of theory for average, SD, and RSD.
• Calculated the 95% confidence intervals (upper and lower) on the standard error.
</td>
<td>
<table>
<tr><th rowspan="2">Level</th><th rowspan="2">Parameter</th><th colspan="2">Recovery (%)</th></tr>
<tr><th>Filtration</th><th>Centrifugation</th></tr>
<tr><td colspan="2"></td><td>(b) (4)</td><td></td></tr>
<tr><td rowspan="7">40% of 0.5 mg</td><td>Mean (n=3)</td><td>99.5</td><td>101.5</td></tr>
<tr><td>Std Dev</td><td>1.2</td><td>0.4</td></tr>
<tr><td>%RSD</td><td>1.2</td><td>0.4</td></tr>
<tr><td>Lower 95% SD</td><td>0.6</td><td>0.2</td></tr>
<tr><td>Upper 95% SD</td><td>7.3</td><td>2.8</td></tr>
<tr><td>Filter Bias</td><td>98.0</td><td></td></tr>
<tr><td rowspan="7">100% of 4 mg</td><td>Mean (n=3)</td><td>99.1</td><td>101.0</td></tr>
<tr><td>Std Dev</td><td>1.4</td><td>0.2</td></tr>
<tr><td>%RSD</td><td>1.4</td><td>0.2</td></tr>
<tr><td>Lower 95% SD</td><td>0.7</td><td>0.1</td></tr>
<tr><td>Upper 95% SD</td><td>8.9</td><td>1.4</td></tr>
<tr><td>Filter Bias</td><td>98.1</td><td></td></tr>
<tr><td rowspan="7">120% of 12 mg</td><td>Mean (n=3)</td><td>98.8</td><td>100.7</td></tr>
<tr><td>Std Dev</td><td>0.5</td><td>0.7</td></tr>
<tr><td>%RSD</td><td>0.5</td><td>0.7</td></tr>
<tr><td>Lower 95% SD</td><td>0.3</td><td>0.3</td></tr>
<tr><td>Upper 95% SD</td><td>3.1</td><td>4.2</td></tr>
<tr><td>Filter Bias</td><td>98.1</td><td></td></tr>
<tr><td colspan="4">Lilly</td></tr>
<tr><td rowspan="7">40% of 0.5 mg</td><td>Mean (n=3)</td><td>99.1</td><td>99.1</td></tr>
<tr><td>Std Dev</td><td>0.7</td><td>0.3</td></tr>
<tr><td>%RSD</td><td>0.7</td><td>0.3</td></tr>
<tr><td>Lower 95% SD</td><td>0.4</td><td>0.2</td></tr>
<tr><td>Upper 95% SD</td><td>4.6</td><td>2.1</td></tr>
<tr><td>Filter Bias</td><td>100.0</td><td></td></tr>
<tr><td rowspan="7">100% of 4 mg</td><td>Mean (n=3)</td><td>100.2</td><td>100.0</td></tr>
<tr><td>Std Dev</td><td>0.3</td><td>0.1</td></tr>
<tr><td>%RSD</td><td>0.2</td><td>0.1</td></tr>
<tr><td>Lower 95% SD</td><td>0.1</td><td>0.0</td></tr>
<tr><td>Upper 95% SD</td><td>1.6</td><td>0.4</td></tr>
<tr><td>Filter Bias</td><td>100.2</td><td></td></tr>
<tr><td rowspan="7">120% of 12 mg</td><td>Mean (n=3)</td><td>99.0</td><td>99.2</td></tr>
<tr><td>Std Dev</td><td>0.2</td><td>0.1</td></tr>
<tr><td>%RSD</td><td>0.2</td><td>0.1</td></tr>
<tr><td>Lower 95% SD</td><td>0.1</td><td>0.0</td></tr>
<tr><td>Upper 95% SD</td><td>1.0</td><td>0.4</td></tr>
<tr><td>Filter Bias</td><td>99.8</td><td></td></tr>
</table>
</td>
<td>
• The average recovery (n=3) of baricitinib from placebo at each level (sample/filter/technique combination) must be within 98.0% to 102.0% of the theoretical response when analyzed against the 40% (0.5 mg tablet strength), 100% of 4 mg strength and 120% of the 12-mg strength lacking the placebo matrix.
• Report the filter bias at each concentration level as the average recovery at each level relative to the centrifuged samples is 98.0-102.0%
</td>
<td>
The accuracy results meet the criterion for recovery and filter bias, measured by relative recovery. Therefore, the method is accurate and suitable for the intended use.
</td>
</tr>
<tr>
<td>Range (analyte and</td>
<td>• Established from accuracy precision</td>
<td>• Linearity, accuracy, and precision results met the</td>
<td>• Linearity,</td>
<td>Range is</td>
</tr>
</table>

<table>
<tr><th>CHARACTERISTIC</th><th>EXPERIMENT</th><th>RESULT</th><th>ACCEPTANCE CRITERIA</th><th>CONCLUSION</th></tr>
<tr><td>sample preparation)</td><td>and linearity data</td><td>acceptance criteria.
• See Linearity and Accuracy</td><td>accuracy, and precision results must meet the acceptance criteria
• Report range.</td><td>established from 40% of a 0.5 mg dose to 120% of a 12 mg dose (0.0002 0.0180 mg/mL) in 900 mL of media.</td></tr>
<tr><td>Robustness (Standard Solution Stability)</td><td>• Prepared a stock standard and a working standard per the method and assess stability using the standard for the 0.5 mg tablet strength.
• Tested the aged working standard solutions against fresh duplicate standard solutions:
o For at least 3 days and 7 days for solutions stored at room temperature
o For at least 3 days and 7 days for solutions stored at refrigerated conditions (5°C)
• Calculated the average % recovery</td><td><table><tr><th>Condition</th><th>Interval</th><th>Average Percent Recovery Relative to Day 0</th></tr><tr><td rowspan="5">Ambient (Room Temperature)</td><td>Day 0</td><td>Not applicable</td></tr><tr><td>Day 1</td><td>99.5</td></tr><tr><td>Day 3</td><td>101.5</td></tr><tr><td>Day 5</td><td>101.0</td></tr><tr><td>Day 7</td><td>99.1</td></tr><tr><td rowspan="5">Refrigerated (5 °C ± 3 °C)</td><td>Day 0</td><td>Not applicable</td></tr><tr><td>Day 1</td><td>100.4</td></tr><tr><td>Day 3</td><td>99.2</td></tr><tr><td>Day 5</td><td>99.3</td></tr><tr><td>Day 7</td><td>99.0</td></tr></table></td><td>• Average percent recovery for aged standards must be 98.0% to 102.0% (relative) of the average result obtained immediately after preparation.</td><td>Standard solutions are stable for 7 days at ambient and refrigerated conditions.</td></tr>
<tr><td>Robustness (Mobile Phase and buffer medium solution stability)</td><td>• Mobile phase was prepared per the method and stored at ambient conditions. Freshly prepared system suitability solutions were analyzed using the stored mobile phase at 7 and 14 days.
• The dissolution medium was prepared per the method and stored at ambient conditions. Using the stored dissolution medium, the 4 mg working standards was prepared and analyzed per the method at 7 and 14 days.</td><td><table><tr><th>Parameter</th><th>14 Days</th><th>Method Criteria</th></tr><tr><td>Precision (%RSD)</td><td>0.2</td><td>NMT 2.0</td></tr><tr><td>Tailing Factor</td><td>1.3</td><td>NMT 2.0</td></tr><tr><td>Response Factor (%RSD)</td><td>0.3</td><td>NMT 2.0</td></tr></table></td><td>• System suitability must meet all method criteria for stored solutions.</td><td>Mobile phase was shown to be stable for 14 days at ambient conditions. Dissolution medium was shown to be stable for 14 days at ambient conditions.</td></tr>
</table>

<table>
<tr><th>CHARACTERISTIC</th><th>EXPERIMENT</th><th>RESULT</th><th>ACCEPTANCE CRITERIA</th><th>CONCLUSION</th></tr>
<tr><td>Robustness (Sample Solution Stability)</td><td>• Analyzed the low and high level accuracy solution samples (n=3 preps at each level) for each filter technique against fresh duplicate standard solutions:
- immediately after preparation (this analysis can be taken from the accuracy results).
- For at least 3 and 7 days stored at room temperature
- For at least 3 and 7 days stored at refrigerated conditions (5°C).
• Compared the results obtained from stored solutions to results from samples analyzed immediately after preparation.</td><td><table><tr><th>Accuracy Solution</th><th>Storage Condition</th><th>Clarification Technique</th><th>7 day Average Recovery (%)</th></tr><tr><td rowspan="4">40% of the 0.5 mg/tablet</td><td rowspan="2">Ambient</td><td>0.45 µm Nylon Acrodisc</td><td>102.2</td></tr><tr><td>Centrifugation</td><td>99.5</td></tr><tr><td rowspan="2">Refrigerated</td><td>0.45 µm Nylon Acrodisc</td><td>102.4</td></tr><tr><td>Centrifugation</td><td>99.4</td></tr><tr><td rowspan="4">120% of the 12 mg/tablet</td><td rowspan="2">Ambient</td><td>0.45 µm Nylon Acrodisc</td><td>102.0</td></tr><tr><td>Centrifugation</td><td>99.8</td></tr><tr><td rowspan="2">Refrigerated</td><td>0.45 µm Nylon Acrodisc</td><td>101.9</td></tr><tr><td>Centrifugation</td><td>100.1</td></tr></table></td><td>• Average aged result at each concentration level must be 97.0% to 103.0% (relative) of the average result obtained immediately after preparation.</td><td>Sample solutions are stable for 7 days at ambient conditions and refrigerated conditions.</td></tr>
</table>

<table>
<tr><th>CHARACTERISTIC</th><th>EXPERIMENT</th><th>RESULT</th><th>ACCEPTANCE CRITERIA</th><th>CONCLUSION</th></tr>
<tr>
<td>Precision (Intermediate Precision, Repeatability)</td>
<td>

0.5, 1, 4, and 12- mg tablets were tested by two analysts. (b) (4) executed the precision test on the 0.5-mg and 4-mg preparations and Lilly executed the precision test on the 1-mg and 12-mg preparations.
Repeatability: Determined the within run standard deviation of each of four runs (n=6 vessels) at 15 and 45 min for each strength; and then calculated the pooled within run SD for each timepoint by strength (n=24).
Intermediate Precision: For each tablet strength, determined the run averages (n=4) at both 15 and 45 min, and the SD of the 4 run averages.
Calculated the 90% confidence intervals for the mean for each timepoint (15 and 45 min) for each strength (upper and lower)

</td>
<td>
<table>
<tr><th>Dose, Time Point</th><th>Method Repeatability SD (%)</th><th>Intermediate Precision SD (%)</th></tr>
<tr><td>0.5-mg, 15 min</td><td>2.52</td><td>2.40</td></tr>
<tr><td>0.5-mg, 45 min</td><td>1.80</td><td>2.36</td></tr>
<tr><td>1-mg, 15 min</td><td>1.30</td><td>0.94</td></tr>
<tr><td>1-mg, 45 min</td><td>1.68</td><td>1.00</td></tr>
<tr><td>4-mg, 15 min</td><td>1.58</td><td>0.66</td></tr>
<tr><td>4-mg, 45 min</td><td>1.22</td><td>0.62</td></tr>
<tr><td>12-mg, 15 min</td><td>0.92</td><td>1.00</td></tr>
<tr><td>12-mg, 45 min</td><td>1.37</td><td>1.12</td></tr>
</table>
<table>
<tr><th>Dose, Time Point</th><th>Mean (n=4)</th><th>90% Lower CI</th><th>90% Upper CI</th></tr>
<tr><td>0.5-mg, 15 min</td><td>98.64</td><td>95.81</td><td>101.46</td></tr>
<tr><td>0.5-mg, 45 min</td><td>101.57</td><td>98.79</td><td>104.35</td></tr>
<tr><td>1-mg, 15 min</td><td>91.83</td><td>90.73</td><td>92.93</td></tr>
<tr><td>1-mg, 45 min</td><td>98.97</td><td>97.79</td><td>100.14</td></tr>
<tr><td>4-mg, 15 min</td><td>87.48</td><td>86.70</td><td>88.26</td></tr>
<tr><td>4-mg, 45 min</td><td>96.13</td><td>95.63</td><td>96.63</td></tr>
<tr><td>12-mg, 15 min</td><td>84.81</td><td>83.64</td><td>85.99</td></tr>
<tr><td>12-mg, 45 min</td><td>96.89</td><td>95.57</td><td>98.20</td></tr>
</table>
</td>
<td>

Repeatability: For each strength at 15 and 45 minutes the pooled within run SD must be ≤3.5%
Intermediate Precision: for each strength at 15 and 45 min, the standard deviation (n=4) of the run averages for each timepoint must be ≤4.0%

</td>
<td>Both repeatability and intermediate precision met the acceptance criteria. Therefore, the precision is acceptable for its intended use.</td>
</tr>
<tr>
<td>Robustness (analyst/setup)</td>
<td>

For each lot, the overall run average (n=6) result was calculated.

</td>
<td>
<table>
<tr><th rowspan="2">Time (min), Strength (mg)</th><th colspan="2">Difference</th></tr>
<tr><th>Analyst (%)</th><th>HPLC (%)</th></tr>
<tr><td>15 min, 0.5</td><td>3.84</td><td>0.53</td></tr>
<tr><td>45 min, 0.5</td><td>3.78</td><td>1.38</td></tr>
<tr><td>15 min, 1</td><td>1.59</td><td>0.2</td></tr>
<tr><td>45 min, 1</td><td>1.47</td><td>0.6</td></tr>
<tr><td>15 min, 4</td><td>0.63</td><td>0.78</td></tr>
<tr><td>45 min, 4</td><td>0.59</td><td>0.38</td></tr>
<tr><td>15 min, 12</td><td>1.37</td><td>0.91</td></tr>
<tr><td>45 min, 12</td><td>1.19</td><td>1.34</td></tr>
</table>
</td>
<td>

For each strength, at 15 and 45 min., the estimated difference between analysts (main effect estimate) must be ≤5.0% (absolute).
For each strength, at 15 and 45 min., the estimated difference between HPLC instruments (main effect estimate) must be ≤5.0% (absolute).

</td>
<td>The main effects met the acceptance criteria; therefore, the method is robust.</td>
</tr>
</table>

<table>
<tr><th>CHARACTERISTIC</th><th>EXPERIMENT</th><th>RESULT</th><th>ACCEPTANCE CRITERIA</th><th>CONCLUSION</th></tr>
<tr><td>Robustness (Chromatographic conditions and dissolution settings)</td><td>Twelve factors were investigated in a sixteen-run split-plot study augmented with four center points.</td><td>The robustness of the chromatographic conditions and dissolution settings was evaluated using a sixteen-run split-plot study augmentd with four center points. Twelve factors were examined to determine the effects of small changes in the method parameters on the dissolution (% released at 15 and 30 minutes) and system suitability results.

The following factors and ranges were evaluated.
<table>
<tr><th>Factor</th><th>Low Level</th><th>Mid Level</th><th>High Level</th></tr>
<tr><td>Paddle Speed (rpm)</td><td>72</td><td>75</td><td>78</td></tr>
<tr><td>Bath Temperature (°C)</td><td>35</td><td>37</td><td>39</td></tr>
<tr><td>Paddle Height (mm)</td><td>23</td><td>25</td><td>27</td></tr>
<tr><td>Dose (mg)</td><td>1</td><td>-</td><td>12</td></tr>
<tr><td>De-aeration of media</td><td>No</td><td>-</td><td>Yes</td></tr>
<tr><td>Buffer salt amount in media (g) per 6 L</td><td>16.11</td><td>17.9</td><td>19.69</td></tr>
<tr><td>Column Age</td><td>Old</td><td>-</td><td>New</td></tr>
<tr><td>Mobile phase % Organic</td><td>18</td><td>20</td><td>22</td></tr>
<tr><td>Flow rate (mL/min)</td><td>2.7</td><td>3</td><td>3.3</td></tr>
<tr><td>Injection volume (µL)</td><td>45</td><td>50</td><td>55</td></tr>
<tr><td>Column Temperature (°C)</td><td>36</td><td>40</td><td>44</td></tr>
<tr><td>Detector Wavelength (nm)</td><td>218</td><td>220</td><td>222</td></tr>
</table>
While a number of statistically significant effects were observed, the absolute magnitude of those effects were small and not of practical significance. Furthermore, all of the individual experimental results are well within acceptable ranges that meet system suitability criteria indicated in the method. There was no appreciable impact to the dissolution release or HPLC system performance attributable to the dissolution or HPLC parameters examined in this study. The tablet dosage was found to have an effect on the % released at the 15 minute and 30 minute time points; however, the effect is not method related and is a function of the drug product formulation.</td><td>N/A</td><td>Method demonstrates acceptable robustness over the factor ranges evaluated.</td></tr>
</table>

Reviewer's Assessment:

{Assess method development, method robustness, and criteria; modeling approach}

- The Applicant's dissolution method development report and the proposed dissolution method is acceptable.

- Applicant's proposed dissolution acceptance criteria is, *Not less than* (b)(4) *% (Q) in 30 minutes*. The proposed dissolution acceptance criterion is acceptable.

- The Applicant reported that the dissolution method was able to discriminate differences in drug substance particle size and changes in performance due to moisture exposure during storage at accelerated conditions.

- The comparative dissolution profile data for the clinical study JAGO Phase 2 Tablet formulation and proposed Commercial Tablets are reviewed and considered acceptable. Both Phase 2 Tablets and proposed Commercial Tablets release more than (b)(4)% of drug at 15 minutes and have similar dissolution profiles. No f2 values were calculated as the product is rapidly dissolving.

- The analytical method validation report for baricitinib are reviewed and considered acceptable. The linearity was demonstrated with concentrations ranging from 40% of a

0.5 mg dose to 120% of a 12 mg dose (0.0002 – 0.0180 mg/mL) of baricitinib. There were some concentrations lower than 40% at 5 minutes sampling point for 4 mg phase 2b capsule (see figure 12, batch#CT567281 used in JADH study) which were not covered in this range. However, this is acceptable because the commercial baricitinib tablets have concentrations above 40% at 5 minute time point (figures 13-15).

- A dose proportionality study was conducted which showed that the PK of baricitinib are dose proportional up to 30 mg. Section 2.7.2.3.1.8 contains a complete description of the dose proportionality assessments for baricitinib.

List of Deficiencies:

From the Biopharmaceutics perspective, this NDA is recommended for approval.

Primary Biopharmaceutics Reviewer Name and Date: **Kalpana Paudel, 05/24/2016**

Secondary Reviewer Name and Date (and Secondary Summary, as needed): **Haritha Mandula, 09/20/2016**

Haritha Mandula

Digitally signed by Haritha Mandula
Date: 10/06/2016 11:48:48AM
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Kalpana Paudel

Digitally signed by Kalpana Paudel
Date: 10/06/2016 11:47:13AM
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Attachment I – Final Risk Assessment – NDA 207924

DP attribute/ CQA	Factors that can impact the CQA	O[1]	S[1, 2]	D[1]	FMECA RPN #	Comment & considerations
Description	• (b) (4)	1	3	3	9	(b) (4)
Identification	• incorrect drugs formulated • no drug formulated • incorrect crystalline form of API	1	3	2	6	
Potency(assay) /Purity	• input purity of APIs • input purity of excipients • incorrect amounts of API formulated • impurity formation due to interaction of drugs with excipients or catalyzed by excipients • degradation of drug substances due to moisture and oxidation (protection from environment) • presence of (b) (4) • (b) (4)	1	3	2	6	

[1] O = Probability of Occurrence; S = Severity of Effect; D = Detectability
[2] Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs.

	[redacted]					[redacted]
Release (dissolution)	• [redacted] • changes in input excipients and APIs • API particle size change • [redacted] particle size • [redacted] • tablet hardness	2	3	3	18	

Content uniformity	• (b) (4) • particle size of API	2	3	3	18	(b) (4)
Microbial limits[3]	• microbial load of input materials for formulation • microbial contamination during processing (e.g., during tablet coating) • microbial growth during shelf life	1	3	3	9	

Craig M. Bertha -S

Digitally signed by Craig M. Bertha -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300103470, cn=Craig M. Bertha -S
Date: 2016.10.31 11:11:27 -04'00'

[3] See process review chapter for details.

Craig
Bertha

Digitally signed by Craig Bertha
Date: 11/01/2016 05 23:44AM
GUID: 50841a65000098a9383c817879a6a84d

DEPARTMENT OF HEALTH & HUMAN SERVICES
Food and Drug Administration

Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis
645 South Newstead Ave
St. Louis, Missouri 63110
Telephone (314) 539-3822
FAX (314) 539-2113

Date: June 20, 2016

To: Arthur B. Shaw, CMC Reviewer DNDPII/NDPBIV
Craig Bertha, CMC Lead
Florence Aisida, MVP Manager

Through: Michael Trehy, Ph.D., CDER/OPQ/OTR/DPA, Lab Chief, Branch II

From: Jeffrey T. Woodruff, Chemist, CDER/OPQ/OTR/DPA

Subject: Method Verification for NDA-207924: Olumiant Baricitinib Tablets 2mg, 4 mg

The following methods were verified and are acceptable for quality control and regulatory purposes:

- Analytical Procedure – Assay and Uniformity of Dosage Units (HPLC – Potency – Method Code B13320)
- Analytical Procedure – Purity (HPLC – Potency – Method Code B13319)
- Analytical Procedure – Assay (HPLC – Method Code G1749) for Drug Substance
- Analytical Procedure – Impurities (HPLC – Method Code G1750) for Drug Substance

Analyst worksheets can be viewed through ECMS:
http://ecmsweb.fda.gov:8080/webtop/drl/objectId/090026f880d255e8

Reference ID: 3948419

SUMMARY OF RESULTS:

Assay (HPLC)
(Drug Substance)

Assay (%)
99.5
99.3

Limit: (b) (4)%

Impurities (HPLC)
(Drug Substance)

Impurity	Sample 1 %Impurity	Sample 2 %Impurity
(b) (4)		

Limit: Any Unspecified NMT (b) (4)%. Total NMT (b) (4)%

Identity (Drug Product)

Identity						
Std Peak Retention Time (min)	2mg Tablet Peak Retention Time (min)	2mg Tablet Relative Retention	Pass/Fail	4mg Tablet Peak Retention Time (min)	4mg Tablet Relative Retention	Pass/Fail
1.38699	1.385	1.00	Pass	1.381	1.00	Pass

Limit: Relative Retention (b) (4)

Reference ID: 3948419

Assay (Drug Product)

	2mg Tablet	4mg Tablet
	%Assay	%Assay
Sample 1	95.4	102.5
Sample 2	96.9	98.1
Sample 3	97.1	99.6

Limit: (b) (4) %

Uniformity (Drug Product)

2mg Tablet	4mg Tablet
Acceptance Value	Acceptance Value
4	5

Limit: Acceptance value NMT (b) (4)

Purity (Drug Product)

	Total %Impurity
2mg Tablet	(b) (4)
4mg Tablet	

Reference ID: 3948419

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

/s/

LAURA POGUE
06/20/2016

MICHAEL L TREHY
06/20/2016