CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216059Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA Executive Summary

1. Application/Product Information

NDA Number.	216059		
Applicant Name	Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company		
Drug Product Name	JAYPIRCATM (pirtobrutinib) tablets		
Dosage Form.	Tablet		
Proposed Strength(s)	50 mg and 100 mg		
Route of Administration	Oral		
Maximum Daily Dose	200 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	For the treatment of adult patients with mantle cell lymphoma (MCL) who have previously been treated with a covalent BTK inhibitor		
Drug Product Description	Pirtobrutinib tablets are supplied as 50 mg or 100 mg film-coated, debossed tablets for oral administration. The 50 mg tablet is a blue, arc-triangle tablet debossed with “Lilly” over “50” on one side and “6902” on the other. The 100 mg tablet is blue, round tablet debossed with “Lilly” over “100” on one side and “7026” on the other.		
Co-packaged product information	N/A		
Device information:	N/A		
Storage Temperature/ Conditions	Store at 20°C-25°C (68°F-77°F); excursions permitted between 15°C and 30°C (59°F and 86°F)		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Kanny Wan	Katherine Windsor

	Drug Product/ Labeling	Yang Nan	Sherita McLamore
	Manufacturing	Diane Goll	Zhaoyang Meng
	Biopharmaceutics	Gerlie Gieser	Qi Zhang
	Microbiology	N/A	N/A
	Other (specify):	None	None
	RBPM	Dahlia Walters	
	ATL	Yang Nan	
Consults	None		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: An expiration dating period of **24 months** when stored at 20°C-25°C is granted (b) (4)

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

OPQ recommends ***APPROVAL*** of NDA 216059 for the commercialization of JAYPIRCATM (pirtobrutinib) tablets, 50 mg and 100 mg. Based on our evaluation of the available information, the Applicant provided sufficient information to support an approval recommendation from the drug product quality perspective. The Applicant provided adequate information on the proposed drug product to ensure the identity, strength, purity, and quality of the proposed drug product. The overall manufacturing inspection recommendation is approval for all the facilities associated with this application. The proposed labeling and labels include adequate information to meet the regulatory requirements.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Quality Labeling	**-**	**Adequate**
Manufacturing	**-**	**Adequate**
Biopharmaceutics	**-**	**Adequate**
Microbiology	**-**	**N/A**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments: None

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Methods Validation or Verification Package

Assessment: *Adequate*

Refer to 3.2.P.5.3.

Comparability Protocols

Assessment: N/A

There is no comparability protocol submitted in the application.

Lifecycle Management Considerations

None

DRUG PRODUCT LIST OF DEFICIENCIES

None

CHAPTER III: ENVIRONMENTAL

R. REGIONAL INFORMATION

Environmental

Assessment: *Adequate*

Since pirtobrutinib is a new molecular entity, Environmental Assessment (EA) Team is responsible for the environment analysis. Dr. Xiaoqin Wu from the EA Team provided the following assessment:

"*The applicant provided a claim for a categorical exclusion from an environmental assessment (EA) in accordance with 21 CFR Part 25.31(b). The maximum expected introduction concentration (EIC) provided for pirtobrutinib is* (b) (4)*, which is* (b) (4) *of magnitude below the 1 µg/L (ppb) categorical exclusion value. The calculation appears accurate and reasonable. Therefore, the categorical exclusion claim is appropriate for the anticipated amount of drug to be used. In addition, a statement of no extraordinary circumstances was provided. FDA reviewed the physicochemical and ecotoxicity data provided by the applicant, and agrees that these data do not indicate any potential for significant environmental impact of pirtobrutinib in this application. The claim for a categorical exclusion from an EA is acceptable.*"

CHAPTER IV: LABELING

ASSESSMENT OF LABELING

Assessment of Product Quality-Related Information in the PI:
Adequate

HIGHLIGHTS OF PRESCRIBING INFORMATION

Information provided in the submission

The original draft of PI is provided via this link.

Assessment: Acceptable.

FULL PRESCRIBING INFORMATION

SECTION 2 DOSAGE AND ADMINISTRATION

Assessment: Acceptable.

SECTION 3 DOSAGE FORMS AND STRENGTHS

Information provided in the submission

3 DOSAGE FORM AND STRENGTHS

Tablets:
Each 50 mg tablet is blue, arc-triangle shaped, film-coated, and debossed with “Lilly 50” on one side and “6902” on the other side.

Each 100 mg tablet is blue, round, film-coated, and debossed with “Lilly 100” on one side and “7026” on the other side.

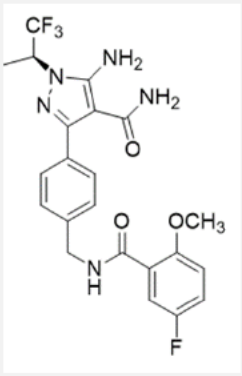
Assessment: Acceptable.

SECTION 11 DESCRIPTION

Information provided in the submission

11 DESCRIPTION

Pirtobrutinib is an orally available, small molecule ATP-competitive inhibitor of BTK. The active pharmaceutical ingredient is pirtobrutinib with the molecular formula $C_{22}H_{21}F_4N_5O_3$ and a molecular weight of 479.44 g/mol. The chemical name for pirtobrutinib is 5-amino-3-{4-[(5-fluoro-2-methoxybenzamido)methyl]phenyl}-1-[(2*S*)-1,1,1-trifluoropropan-2-yl]-1*H*-pyrazole-4-carboxamide.



Pirtobrutinib is a white to practically white to yellow to brown solid. The aqueous solubility of pirtobrutinib is considered practically insoluble, or insoluble, across the pH 1 to pH 7 range.

Pirtobrutinib tablets are supplied as 50 mg or 100 mg film-coated, debossed tablets for oral administration. Each tablet contains inactive ingredients of hypromellose acetate succinate, microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, silicon dioxide, magnesium stearate, hypromellose, titanium dioxide, triacetin, and FD&C Blue #2.

Assessment

The excipients in the last paragraph are not organized alphabetically. We recommended revision of the last paragraph as follows:

Pirtobrutinib tablets are supplied as 50 mg or 100 mg film-coated, debossed tablets for oral administration. Each tablet contains inactive ingredients of croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, microcrystalline cellulose and silicon dioxide. The tablet film coating material contains FD&C Blue No.2, hypromellose, titanium dioxide and triacetin.

The Applicant accepted our recommendation by email dated November 28, 2022.

SECTION 16 HOW SUPPLIED/STORAGE AND HANDLING

Information provided in the submission

16 HOW SUPPLIED/STORAGE AND HANDLING

JAYPIRCA tablets are supplied as follows:

Tablet Strength	Description	Package Configuration	NDC Number
50 mg	Blue, film coated, arc-triangle shaped tablets debossed with "Lilly 50" on one side and "6902" on the other side.	Bottle with child-resistant closure. Each bottle contains 30 tablets.	#####-###-##
100 mg	Blue, film coated, round tablets debossed with "Lilly 100" on one side and "7026" on the other side.	Bottle with child-resistant closure. Each bottle contains (b) (4) 60 tablets.	#####-###-## (b) (4)

16.1 Storage and Handling

Store tablets at (b) (4)

Assessment: The proposed storage conditions are not satisfactory as the FDA does not accept custom storage conditions. The drug product storage conditions should reflect the general storage locations used in pharmacies, hospitals, warehouses, and homes (i.e., controlled room temperature, refrigerator, or freezer). We recommend revision of the storage conditions to USP controlled room temperature:

Store JAYPIRCA tablets at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) ([see USP Controlled Room Temperature]).

The Applicant accepted our recommendation by email dated November 28, 2022.

OTHER SECTIONS OF THE PI
N/A

END OF THE PI (AFTER SECTION 17)

Information provided in the submission

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

Assessment: Acceptable.

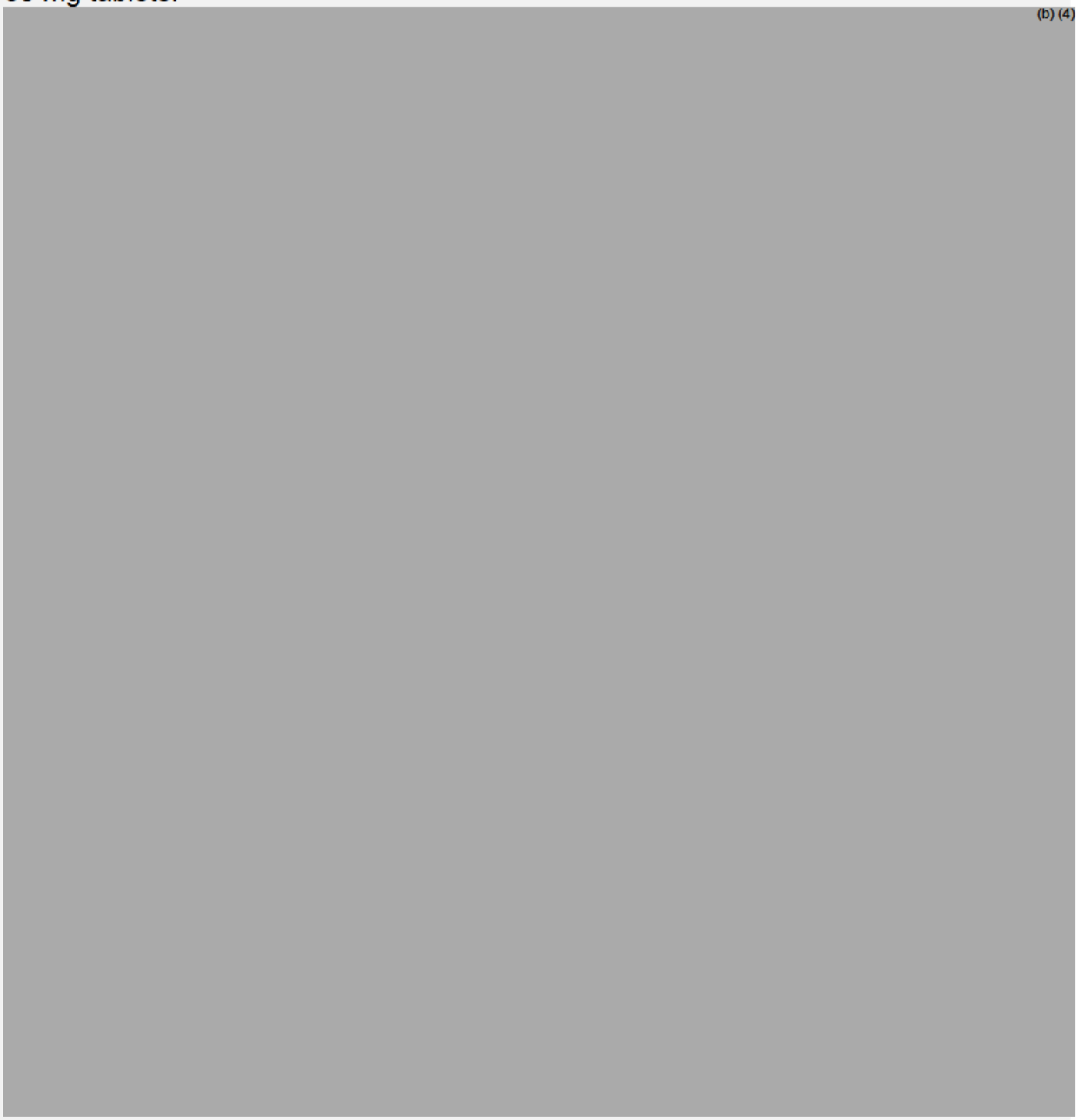
Assessment of Product Quality-Related Information in the Container Labels and Carton Labeling

Container Labels

Information provided in the submission

50 mg tablets:

(b) (4)



(b) (4)

Assessment: Acceptable. The proposed storage conditions are consistent with USP controlled room temperature, but we recommend a minor revision to be consistent with the those in the section 16 of USPI.

Carton Labeling:
Cartons are not used in the packaging of JAYPIRCA therefore there are no carton labels.

ITEMS FOR ADDITIONAL ASSESSMENT

None

Yang Nan

Digitally signed by Yang Nan
Date: 11/28/2022 07:27:06PM
GUID: 520bd6c90002b3b0320380334e69a817
Comments: The Applicant's response to the labeling review just came today (November 28, 2022). Thus, our review has to be updated accordingly.

Sherita McLamore

Digitally signed by Sherita McLamore
Date: 11/28/2022 07:33:28PM
GUID: 5032579500004157554 92db5bb8b1a5c

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CHAPTER VI: BIOPHARMACEUTICS

Product Information	
NDA Number	NDA 216059 Associated IND: 139876
Assessment Cycle Number	Original (Rolling) NDA
Drug Product Name/ Strength	Pirtobrutinib Film-Coated Tablets/ 50 mg and 100 mg
Route of Administration	Oral
Applicant Name	Loxo Oncology
Therapeutic Classification/ OND Division	Bruton Tyrosine Kinase (BTK) Inhibitor/ Division of Hematologic Malignancies 2 (DHM2)
Proposed Indication	Treatment of adult patients with mantle cell lymphoma (MCL) who have previously been treated with a BTK inhibitor Proposed Dosage: 200 mg Once Daily (reduce dose to manage toxicity); swallow whole with or without food.

Assessment Recommendation: **Adequate**

Assessment Summary:

The proposed QC dissolution method (*USP Apparatus 2/paddle at 75 rpm, 900 mL of pH 6.8* (b) (4) *buffer; 37 ±* (b) (4) *°C*) and the revised dissolution acceptance criterion (*Q =* (b) (4) *% at 30 min*) are acceptable for the dissolution testing of pirtobrutinib film-coated tablets at batch release and during stability testing/shelf-life. Note that the submitted Physiologically Based Pharmacokinetics Model (PBPK) for Biopharmaceutics Applications/PBBM was not deemed sufficient to support the Applicant's initially proposed (wider) dissolution acceptance criterion.

There are adequate *in vitro* and *in vivo* data (***i***) to support bridging of the final proposed to-be-marketed drug product (50 mg and 100 mg) to the tablet lots that were evaluated in pivotal clinical trial (100 mg) and registration/stability studies (50 mg and 100 mg), and (***ii***) to grant the Applicant's biowaiver request for the 50 mg strength of the proposed drug product, pursuant to 21 CFR 320.22(d)(2).

CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Assessment Cycle # 1	Comments
Dissolution	Moderate	The [redacted] (b) (4) API exhibits low solubility, per BCS criteria. [redacted] (b) (4) .	Low	The approved QC dissolution specifications are expected to be capable of rejecting pirtobrutinib tablet batches that develop at least [redacted] (b) (4)

List of Submissions Assessed:

Submission	Date Received
SN-1 (Wave 1: mainly non-clinical sections)	12/10/2022
SN-2 (Wave 2: includes majority of Module 3, and Module 2.3 QOS)	1/28/2022
SN-4 (Wave 2b: includes primary stability data and dissolution datasets)	3/30/2022
SN-5 (Response to Quality IR – includes robustness data for dissolution method validation)	4/21/2022
SN-6 (Response to Biopharm IR – part a)	5/11/2022
SN-7 (Response to Biopharm IR – part b)	5/23/2022
SN-8 (Wave 3: includes Clinical, Clinical Pharmacology, Biopharmaceutics; New NDA)	5/27/2022
SN-10 (Response to Biopharm IR – final PBBM files)	6/10/2022
SN-12 (Response to Biopharm IR)	6/21/2022
SN-16 (Response to Biopharm IR – process validation lot/teleconference discussion)	7/1/2022
SN-31 (Response to Biopharm IR – dissolution profile data of Process Validation Lots)	8/29/2022
SN-34 (Response to Biopharm IR – dissolution acceptance criteria)	9/29/2022
SN-36 (Response to Biopharm IR – [redacted] (b) (4) lots comparability)	10/11/2022
SN-37 (Response to Quality IR – level of [redacted] (b) (4) API in stressed tablets)	10/14/2022

Concise Description of Outstanding Issues:

- None

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested nor required.*

Drug Substance Solubility: [redacted]

Pirtobrutinib drug substance was previously known as LOXO-305 and LY3527727. Based on the pH-solubility profile data of the pirtobrutinib drug substance in various pH media and biorelevant media at 37 °C (in Table 2.3.P.2.1.1-1), pirtobrutinib can be classified as a low solubility compound, per BCS criteria. Per the Applicant, [redacted]

Of note, [redacted]

Drug Substance Permeability: *High Permeability* [redacted]

The Applicant reported (and the Clinical Pharmacology Reviewer confirmed) that in Study LOXO-BTK-20007/Part 2, the absolute bioavailability (F_{po}) of pirtobrutinib (administered as two 100 mg "T2" pirtobrutinib tablets; pivotal clinical trial Lot 19-0216-2) is 85.5% (relative to intravenously administered solution containing radiolabeled drug substance, [redacted] The F_{po} >85% indicates that pirtobrutinib can be considered a high permeability drug substance per BCS criteria.

Note that this Reviewer did not consider [redacted]

[redacted] (b) (4) Note also that *in vitro* permeability data using a Caco-2 model were not provided.

Based on relative solubility and animal relative BA data, the oral BA in humans is anticipated to be higher for the oral tablet manufactured [redacted] (b) (4)

Drug Product Dissolution: *Slow to Very Rapid Across the Physiologic pH Range*

Pirtobrutinib tablets are designed for immediate drug release. The proposed drug product's dissolution is pH dependent, showing slow dissolution in various pH media [redacted] (b) (4), except that in pH 6.8 [redacted] (b) (4) buffer [redacted] (b) (4) For details, refer to the comparative dissolution profile data of the "T2" tablets (100 mg Development Lot BREC-2224-035) in various pH and biorelevant media in Table 3.2.P.2.2.1.5.3.1.3-1, as well as in Figure 3.2.P.2.2.3.1.1-1. Also refer to Figure 3.2.P.2.2.3.2.2-1 to Figure 3.2.P.2.2.3.2.2-3 for the pH-dissolution profile data of 100 mg Primary Registration Lot D345037. A similar pH-dissolution trend was observed for the 50 mg strength T2 tablet.

Reviewer Notes: The proposed maximum tablet strength is 100 mg. Per the proposed labeling, the maximum single dose of pirtobrutinib is 200 mg orally.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: *Adequate*

DISSOLUTION METHOD – *Proposed Dissolution Method Acceptable*

The parameters of the final proposed dissolution method (Method G2535) for QC dissolution testing of pirtobrutinib tablets are shown in the excerpted table below.

Table 2. Dissolution Conditions

Parameter	Description
Apparatus	USP Apparatus II (stainless steel paddles)
Degassing	Helium Sparge (1 minute/liter) Alternatively, degas according to USP General Chapter <711>
Dissolution Medium	Sodium Phosphate Buffer, pH 6.8
Vessel Volume	900 mL
Vessel Temperature	37°C ± 0.3°C
Shaft Speed	75 rpm
Sampling Time Points (minutes)	5, 10, 15, 20, 30, 45, 60, Infinity*
Sampling Volume	1.5 (Autosampler and Manual Sample with Full Flow Filters); 10 mL (Manual Sampling with syringe filters)
Number of Units	1 tablet per vessel
Prime/Purge Time (Autosampler)	60 Seconds

*Infinity is defined as a shaft speed of 250 rpm for an additional 15 minutes

Source: 3.2.P.5.3 Analytical Validation

Note that during early clinical development, [redacted] (b) (4)

Justification for Chosen Method Parameters

Per the Applicant, pH 6.8 [redacted] (b) (4) buffer was selected as the final QC dissolution medium [redacted] (b) (4) because sink conditions and complete dissolution are achieved at pH 6.8 [redacted] (b) (4) additionally, the selected medium was sufficient to achieve dissolution method discriminating power for changes in critical quality attributes of the drug product as describe below.

To achieve complete dispersion [redacted] (b) (4) to reduce dissolution data variability, Apparatus 2 (paddle) at 75 rpm with 900 mL medium was chosen [redacted] (b) (4) .

Sink Conditions

Given that the solubility [redacted] (b) (4)

Discriminating Power

The Applicant has identified the following quality attributes to have the potential to impact drug product performance: [redacted] (b) (4) particle size [redacted] (b) (4)

(b) (4)

(b) (4)

(b) (4)

The proposed dissolution method was shown to be discriminating for differences

(b) (4)

Additionally, the proposed dissolution method was able to produce the anticipated rank-order relationship between (b) (4) and dissolution rate, as shown in excerpted Figure 3.2.P.2.2.3.1.3.1-4. It also appears from excerpted Figure 3.2.P.2.2.3.1.3.1-3 that as the level of (b) (4) increases, the dissolution decreases.

(b) (4)

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Analytical Method Validation

HPLC with UV detection at (b) (4) nm is used to quantify the drug in dissolution samples. The analytical method was investigated for linearity, accuracy, precision, range, robustness (with respect to dissolution method and HPLC method parameters), standard and sample solutions stability, filter compatibility (Full Flow cannula filters, (b) (4) and sampling type (automatic or manual). The method was reported to be robust (b) (4) The sample solutions were reported to be stable for at least 3 days at ambient conditions and protected from light. Per the Drug Product Reviewer, the analytical method validation for dissolution is adequate.

DISSOLUTION ACCEPTANCE CRITERIA – *Revised Acceptance Criterion Acceptable*

The (initially) proposed dissolution acceptance criterion is "Q = (b) (4)% at 30 min".

Based on the dissolution profile data of the four pivotal clinical trial lots (i.e., 100 mg T2 tablet lots D322845 and D322846 used in supporting stability studies, and 100 mg T2 tablet lots D345038 and D345039 used in primary stability studies) as generated by the proposed QC dissolution method (Method G2535), this Reviewer recommends tightening of the dissolution acceptance criterion to "Q = (b) (4)% at 30 min"; refer to **Reviewer Figure 1** below and the Applicant's IR response in SN-6.

Tightened dissolution acceptance criterion (Q = (b) (4)% at 30 min) is also justified when considering the rapid to very rapid dissolution characteristics of other three additional pivotal clinical trial 100 mg "T2" tablet lots (as generated by the penultimate QC dissolution method; **Reviewer Figure 2**), and upon considering this Reviewer's observation that similar (if not faster) dissolution can be achieved using the final QC dissolution method.

Based on the comparison of dissolution profile data generated for one developmental drug product lot (i.e., 100 mg BREC-2224-035) using both penultimate and final QC dissolution methods, it appears that the dissolution profiles from the two methods are similar, with the final Method G2535 being expected to produce a *slightly higher* dissolution profile (i.e., at 30 minutes, (b) (4)% higher dissolution value) than penultimate Method BTP-548; refer to **Reviewer Figure 3**). Thus, for any given drug product lot, the dissolution data at the same dissolution sampling time point (e.g., 30 minutes) is also projected to be slightly higher if generated by the final dissolution method than as generated by the penultimate dissolution method. Thus, based on the relationship of the dissolution profile data generated using the penultimate and

the final dissolution methods, this Reviewer projects that any lot that achieved a Q of at least (b) (4)% at 30 min using the penultimate dissolution method is anticipated to also achieve a Q of at least (b) (4)% at 30 minutes using the final QC dissolution method.

(b) (4)

(b) (4)

(b) (4)

Additionally, it appears that 'Q = (b) (4) at 30 min' will be sufficient to reject coated tablet batches with unacceptable quality attributes including those with significantly slower-than-target dissolution profiles similar to the ones containing (b) (4)

This Reviewer believes that it is important to evaluate further the capability of the one-point dissolution acceptance criterion to reject batches with (b) (4) (refer to **Reviewer Figure 4** below).

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(b) (4)

Additionally, even though pirtobrutinib drug substance is a low solubility compound per BCS criteria, a 2nd/earlier dissolution specification value/time point is not deemed necessary (i.e., to guard against ultrafast dissolution which could potentially result in shorterTmax and higher Cmax) for the following reasons/considerations: (***i***) Based on **Reviewer Figure 1** above, some of the pivotal clinical trial lots exhibited very rapid dissolution (i.e., at least 85% within 15 minutes). (***ii***) As well, the proposed commercial product as represented by the primary registration and process validation lots of this (b) (4) immediate release drug product exhibited very rapid dissolution (mean >85% in 15 minutes) in the proposed QC dissolution medium over 12 months of long-term storage. (***iii***) Furthermore, per the proposed labeling (and as confirmed by the CDER QT-IRT), in a Thorough QT Study, a supratherapeutic dose (i.e., 900 mg) of pirtobrutinib did not result in a clinically relevant QT prolongation in healthy subjects. (***iv***) Per the revised Multi-Disciplinary Assessment Aid (and as confirmed by the Pharmacometrics Reviewer, Dr. Elyes Dahmane), based on exposure-response analyses of efficacy and safety in MCL patients, pirtobrutinib is not a narrow therapeutic index drug.

Dissolution on Stability

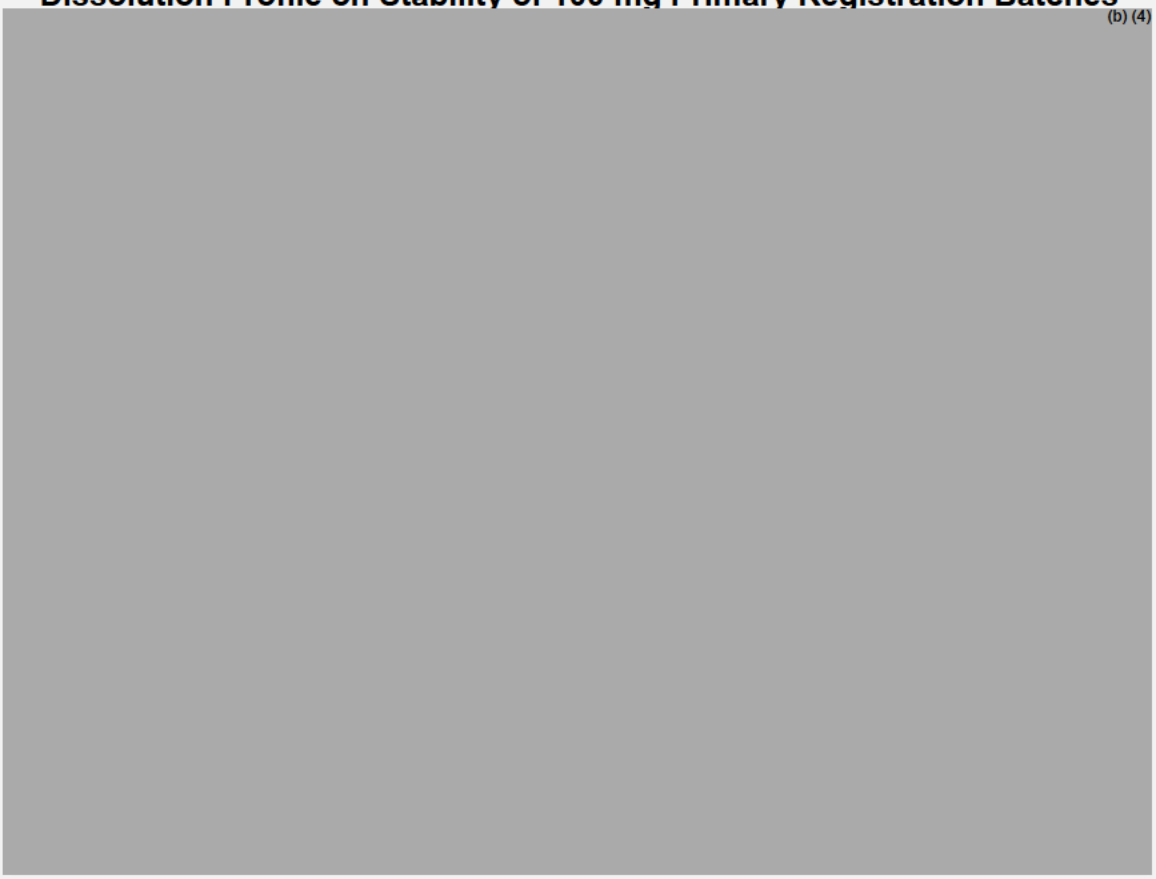
Based on 12 months of long-term (30ºC/65% RH) and 6 months of accelerated (40ºC/75% RH) stability data for three primary stability batches of the 50 mg and 100 mg strength tablets in HDPE bottles, the initially proposed expiration dating period for the coated tablets is 24 months when stored in the proposed packaging configuration(s) under long-term and accelerated conditions. Of note, the final proposed QC dissolution method (Method G2535) was used to generate all the dissolution profiles on stability data of the primary registration/stability lots. Per the Applicant (and as confirmed by this Reviewer), there were no observed stability trends in dissolution data at 30 minutes over the 12 months long-term stability study duration, as shown in Figure 3.2.P.8.3.1.6.3-1 and Figure 3.2.P.8.3.1.6.3-2. From **Reviewer Figure 5**, there appears to have been very slight decrease in the dissolution profile of both tablet strengths at the Month 6 of accelerated stability testing; however the data was still within the Applicant's proposed dissolution tolerance limits (Q = (b) (4) at 30 min) and this Reviewer's tightened dissolution acceptance criterion (Q = (b) (4) at 30 min).

Note that two of the three primary stability lots of the 100 mg strength (i.e., D345038 A/C and D345039 A/C) were used in the pivotal clinical trial when they were 10 months to 11 months old. **Reviewer Figure 5** below shows that these two pivotal clinical trial/primary stability (as well as the other primary stability)

lots did not exhibit any storage-time dependent changes in dissolution profiles over 12 months of long-term storage. The two other pivotal clinical trial lots (D322845, D322846) were 7 months to 11 months old at the time of pivotal clinical trial use.

Reviewer Figure 5
Dissolution Profile on Stability of 100 mg Primary Registration Batches

(b) (4)



In SN-34, the Applicant (i) agreed to this Reviewer's recommendation to tighten the dissolution acceptance criterion from "Q = (b) (4)% at 30 min" to "Q = (b) (4)% at 30 min" based on the available dissolution profile data of the pivotal clinical trial lots, primary registration/stability lots, and process validation lots, as well as based on this Reviewer's assessment of the PBBM modeling results, (ii) revised the finished product QC specifications and other pertinent NDA documents accordingly, and (iii) provided confirmation that based on the dissolution on stability data gathered to date (and evidence that the drug product is stable), the registration lots are able to conform (and are expected to be able to conform) to the revised dissolution acceptance criterion throughout its shelf-life.

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B.12 BRIDGING

Assessment: *Adequate*

The final proposed commercial drug product "T2" *formulation* and the *commercial process type* [redacted] were used in the manufacture of the pivotal clinical trial (Phase 1/2 Study 18001 or J2N-OX-JZNA) lots (i.e., 100 mg supporting stability D322845 and D322846, primary stability lots D345038, D345039) and other clinical study lots including those in other ongoing Phase 3 clinical studies(e.g., 100 mg supporting stability D322844, D322845, and D322846), as well as the 50 mg lots (D345034, D345035, D345036) used in primary registration/stability studies.

Additionally, the primary registration/stability batches (three lots each for the 100 mg and 50 mg 'T2' strengths) and the 100 mg 'T2' supporting stability lots (as shown in Table 2.3.P.8.3.1-1 and Table 2.3.P.8.3.2.1-1, respectively) were manufactured by the proposed commercial *tablet manufacturing site* (Lilly del Caribe/Puerto Rico) at [redacted] commercial scale using a process that is representative of commercial process, commercial scale equipment, [redacted]

To support the proposed commercial minor CMC changes in input drug substance manufacturing process and site, and the final commercial image of the 50 mg and 100 mg pirtobrutinib tablets, adequate evidence was provided to demonstrate that the *in vitro* dissolution profile data of representative process validation drug product batches were comparable to counterpart primary registration drug product lots.

A. Change in Drug Substance Manufacturing Process and Site: [redacted] → → *Eli Lilly Kinsale Limited/Ireland* [redacted]

As shown in Reviewer Table 1 above, [redacted]

- The Drug Substance Reviewer (Dr. Kanny Wan) concluded that based on the batch analysis data of the pre-change and post-change drug substance lots, the description of the known differences between Processes [redacted]

[redacted] the drug substance lots used to produce the pivotal 'T2' clinical trial lots are considered comparable to the primary registration/stability drug substance lots manufactured at [redacted] as well as to the process validation drug substance lots manufactured at commercial scale by the Eli Lilly Kinsale facility using the [redacted] process [redacted]

- In SN-31, the Applicant provided the requested comparative *in vitro* dissolution profile data for proposed commercial Drug Product lots (50 mg D526997 and 100 mg D527251) that were manufactured using process validation drug substance (DS) lot D441190. It was demonstrated that the change in DS manufacturing process and site (as well as final commercial image of the tablet) did not impact the dissolution profile of the 50 mg and 100 mg pirtobrutinib tablet lots; both primary stability/reference/pre-change drug product lots and process validation/test/post-change drug product lots exhibited very rapid dissolution when tested using the proposed QC dissolution method (as shown in Figure 1/Table 3 of the SN-31 IR Response).

B. *Change in Drug Product Manufacturing Site During Clinical Development:*

As indicated above, two of three 100 mg 'T2' primary stability lots and two additional 100 mg 'T2' supporting stability lots produced by the proposed commercial drug product manufacturing site (Lilly del Caribe, Inc./Puerto Rico) were used in the pivotal clinical trial.

- Note that the other 100 mg "T2" drug product lots (19-0216, 20-0206, 20-0207 in Table 1 of the IR Response in SN-6) used in the pivotal clinical trial were manufactured by [redacted] instead of Lilly del Caribe/Puerto Rico; refer to Table 3.2.P.5.4.1-6 and Table 3.2.P.5.4.1-7 for the batch analysis data of these [redacted] manufactured pivotal clinical lots. The Applicant provided *in vitro* data/information to support comparability of the two drug product manufacturing sites, as follows. Note that all these three pivotal clinical trial lots used [redacted]

  - Per the Applicant, the dissolution profiles of the 100 mg tablets manufactured at the two sites, [redacted] and Lilly del Caribe (Puerto Rico) were similar (f_2 >50, [redacted] in multiple pH media [redacted] including the final proposed QC dissolution medium and test parameters (refer to the profiles of pre-change lot BREC-2224-035 and post-change lot D345037 in Figure 3.2.P.2.2.3.2.2-1 to Figure 3.2.P.2.2.3.2.2-3). Note that Development Lot BREC-2224-035 and Primary Registration Lot D345037 differ also in terms of [redacted]

[redacted] Of note, the Drug Substance Reviewer confirmed comparability of DS Lot 60397-19-001 and DS Lot D306056/CR-C19090929-CF20003 [redacted] Additionally, the Process Reviewer (Dr. Diane Goll) confirmed comparability of [redacted] Lot BREC-2129-042 and [redacted] Lot D306800/19IN7801.HQ00004 (produced by [redacted] based on the batch analysis data (provided in the SN-36 IR Response) and the batch release and stability data of these two [redacted] lots as provided in the NDA.

- Additionally, based on the available dissolution profile data of the 100 mg T2 pivotal clinical trial lots (i.e., three manufactured by [redacted] and four manufactured by Lilly del Caribe), and bridging data of the penultimate and final QC dissolution methods [as depicted in the three Reviewer Figures 1 to 3 in Section B.2 above], this Reviewer surmises that the pivotal clinical lots produced by both manufacturing sites to be comparable, i.e., in terms of exhibiting very rapid dissolution when using the final proposed QC dissolution method, which then overall supports the change in drug product manufacturing site during the course of the pivotal clinical trial. [Also as indicated in Section B.2. above, this Reviewer considers the final proposed QC dissolution method to be adequate for routine QC testing and *in vitro* comparative dissolution testing of the proposed drug product.]

C. Appearance

Per Table 1 of the IR Response in SN-7, Table 1 of the IR response in SN-6, and Table 2.3.P.5.4.1-1, 100 mg "T2" primary stability/pivotal clinical trial lots D345038 and D345039 possessed different tablet debossing characteristics (but otherwise the same physical appearance) as compared to the same strength tablets proposed for marketing in the US. Per the proposed labeling, the 50 mg tablet is a blue, film-coated arc-triangle tablet debossed with "Lilly" over "50" on one side and "6902" on the other side. The 100 mg tablet is blue, film-coated round tablet debossed with "Lilly" over "100" on one side and "7026" on the other.

- As indicated in the section above, sufficient data are available to show that the change in the debossing design of the tablets after conducting the primary stability/clinical studies did not impact the *in vitro* dissolution profile data of the final to-be-marketed 50 mg and 100 mg pirtobrutinib tablets.

D. Packaging Configuration:

The tablets for commercial US supply will be packaged into 75 mL HDPE bottles with child-resistant closures and aluminum foil induction heat seal liner containing [redacted] 60 tablets for [redacted] 100 mg, respectively; refer to Table 3.2.P.7.1.1-2 or) 30 tablets [redacted] for 50 mg [redacted] respectively, per the proposed labeling. [A [redacted]

As indicated in Table 2.3.P.8.3.1-2, the primary stability batches (some of which were used in the pivotal clinical trial) were packaged in a container-closure system similar to that proposed for marketing the proposed drug product, with [redacted] tablets per bottle (depending on strength).

- The Drug Product Reviewer (Dr. Yang Nan) confirmed that the studied packaging configurations/presentations are representative of the final proposed commercial packaging configurations of the 50 mg and 100 mg strengths of pirtobrutinib tablets.

Bridging of Clinical Development Formulations

The "T1" formulation of pirtobrutinib tablets was used in early Phase 1 clinical studies (including the majority of the Phase 1 portion of the pivotal Phase 1/2 Study 18001 and Study 20014/Omeprazole DDI); refer to Table 1 and Table 8 of Section 2.7.1. For the compositions of the early T1 formulation and the final proposed T2 formulation, refer to 2.3.P.2.2.1 Formulation Development or Tables 2 and 3 of 2.7.1. Mainly because the two developmental formulations are not qualitatively similar [redacted] this Reviewer does not deem comparative *in vitro* dissolution profiling of T1 and T2 to be sufficient for formulation bridging. Note that per the 4/15/2021 Type B EOP1 CMC Meeting Minutes, FDA recommended the submission of *in vivo* PK data to bridge the T1 and T2 formulations of the proposed drug product.

The Applicant reported (and the Clinical Pharmacology Reviewer confirmed) that based on Population PK analysis of pivotal clinical Study 18001 data, the PK of "T1" and "T2" are comparable (as shown in Figure 4 of 2.7.1), thereby justifying formulation switching during the course of this clinical trial, as well as supporting the *in vivo* bridging of the T1 and T2 formulations.

B. 13 BIOWAIVER REQUEST

Assessment: *Granted*

The biowaiver request for the 50 mg strength of the proposed commercial "T2" pritobrutinib tablets can be granted based on the following data/information:

- As shown in Table 2 of the SN-7 IR Response, the 100 mg strength (as well as the 25 mg strength) of the "T2" pirtobrutinib tablet was used in the pivotal clinical trial (Study 18001). [The 50 mg strength (i.e., Lot D345034) of the T2 tablet was allocated for use in other later clinical studies (J2N-OX-JZNO/LOXO-BTK-20022/Relapsed CLL/SLL, J2N-OX-JZNP/LOXO-BTK-20021/Digoxin DDI, J2N-OX-JZNP/LOXO-BTK-20023/Untreated CLL/SLL) and is proposed for marketing along with the 100 mg strength. At the time of initial registration, clinical PK data using the 50 mg tablet were not available.]

- As confirmed by the Clinical Pharmacology Reviewer, the PK data/information submitted for the 100 mg strength of the T2 tablet is adequate.

- The 50 mg and 100 mg (as well as the "clinical only" 25 mg) strengths of the final "T2" formulation/proposed to-be-marketed pirtobrutinib tablet are compositionally proportional [redacted (b) (4)] as shown in Table APP.15, and use the same manufacturing process (Figure APP1).

- Using the proposed QC dissolution method (900 mL of pH 6.8 [redacted (b) (4)] Buffer; USP Apparatus 2 at 75 rpm), the dissolution profiles of the 50 mg strength were superimposable with that of the 100 mg strength (and the 25 mg strength), with >85% release within 15 minutes, as shown in Figure APP.4. Additionally, in lower pH media [redacted (b) (4)], the dissolution profiles of the 50 mg strength were comparable (with profile similarity f_2 >50) to both 25 mg and 100 mg clinical strengths (Figure APP.2 and Figure APP.3).

- Both the 25 mg and 100 mg strengths of the T2 tablet were used in the pivotal clinical study. Since the 50 mg strength T2 tablet is compositionally proportional to both 25 mg and 100 mg strength T2 tablets, the available clinical efficacy/safety/PK data could theoretically bracket the 50 mg strength.

- For the proposed indication, the proposed standard dosage of pirtobrutinib tablets is 200 mg once daily, which could be adjusted to as low as 50 mg once daily if there is toxicity. Per the Clinical Pharmacology Reviewer, pirtobrutinib exposure (AUC) and C_{max} increases proportionally following once daily doses ranging from 25 – 300 mg (0.125 to 1.5 times the recommended dosage) and following single doses ranging from 300 - 800 mg (1.5 to 4 times the recommended dosage), i.e., an overall dose range of 25 mg to 800 mg.

R. REGIONAL INFORMATION

Comparability Protocols

None

Post-Approval Commitments

None

Lifecycle Management Considerations

BIOPHARMACEUTICS LIST OF DEFICIENCIES

Primary Biopharmaceutics Assessor's Name and Date:
Gerlie Gieser, Ph.D. (11/10/2022)

Secondary Assessor Name and Date (and Secondary Summary, as needed): Qi Zhang, Ph.D. (11/15/2022)

Gerlie Gieser

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