CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210923Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 210923
Review #1

Drug Name/Dosage Form	Mulpleta® (lusutrombopag) tablets
Strength	3 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	Shionogi Inc.
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	26-Sept-17	All
Amendment (SD 0002)	26-Dec-17	DS
Amendment (SD 009)	01-Feb-18	DP
Amendment (SD 008)	01-Feb-18	DP
Amendment (SD 0012)	16-Mar-18	DP
Amendment (SD XXX)	3-Apr-18	DP
Amendment (SD 0013)	28-Mar-18	DS
Amendment (SD 0019)	10-May-18	Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Gene Holbert	Charles Jewel
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process	Ziyang Su	Rakhi Shah
Microbiology	n/a	n/a
Facility	Ziyang Su	Ruth Moore
Biopharmaceutics	Yang Zhao	Banu S. Zolnik
Regulatory Business Process Manager	Rabiya Laiq	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Rajiv Agarwal	Anamitro Banerjee

APPEARS THIS WAY ON ORIGINAL

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104047	Original IND for Lustrombopag

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 210923 for Mulpleta® (lusutrombopag) tablets, 3 mg. As part of this action, OPQ grants a (b) (4) month re-test period for the drug substance when stored (b) (4) and a 36-month drug product expiration period when stored at stored at controlled room temperature. There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 210923 was submitted for Mulpleta® (lusutrombopag) tablets, 3 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Lusutrombopag is a once daily, orally bioavailable, small-molecule, thrombopoietin (TPO) receptor agonist indicated for the treatment of patients with thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with elective invasive procedures. Lusutrombopag is an NME which was originally investigated under IND 104047 and received Fast Track designation in March of 2017 for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with elective invasive procedures.

Lusutrombopag is a small (b) (4) molecule that is manufactured (b) (4) . The drug product, Mulpleta® (lusutrombopag) tablets, is presented as a 3-mg, immediate-release solid oral dosage form. It is a light red, round, film-coated tablet debossed on one side with the Shionogi trademark above the identifier code "551", and debossed on the other side with the strength "3". (b) (4)

The recommended dosing regimen for Mulpleta® (lusutrombopag) tablets is one 3-mg tablet once daily for 7 days.

Based on the information provided in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 210923 and grants a (b) (4) month re-test period for the drug substance when stored (b) (4) and a **36**-month expiration period for the drug product when stored at USP controlled room temperature in the proposed commercial packaging.

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with invasive procedure
Duration of Treatment	Seven (7) days
Maximum Daily Dose	3 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

(b) (4)

(b) (4). Lusutrombopag is a white to slightly yellowish white, non-hygroscopic powder that is freely soluble in *N,N*-dimethylformamide; slightly soluble in ethanol, methanol and pH 11 buffer solution and practically insoluble in pH 1 to pH 9 buffer solutions. (b) (4)

Lusutrombopag drug substance is (b) (4)
(b) (4)

The drug substance is stored (b) (4)
(b) (4)

The drug substance specification include tests and acceptance criteria for description, identification (IR and UV), assay, related substances, (b) (4) residual solvents, water content, residue on ignition and particle size. Specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the

safety and efficacy of the drug product. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters - system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions are provided in the NDA.

(b) (4)

The application is recommended for approval from a drug substance perspective.

Drug Product

The drug product, Mulpleta® (lusutrombopag) tablets, is presented as 3-mg immediate-release solid oral dosage form. It is a light red, round, film-coated tablet containing the active, microcrystalline cellulose, D-mannitol, sodium lauryl sulfate, hydroxypropyl-cellulose, (b) (4) calcium and magnesium stearate. (b) (4) hypromellose, triethyl citrate, titanium dioxide, red ferric oxide and talc. (b) (4) The drug product formulation contains no novel excipient. All excipients are compendial and commonly used in solid oral dosage forms and demonstrate good compatibility with the drug substance.

Mulpleta® (lusutrombopag) tablets are debossed on one side with the Shionogi trademark above the identifier code "551", and debossed on the other side with the strength "3".

The QTPP was established and the CQAs were identified. CQAs for the drug product include appearance, assay, impurity content, uniformity of dosage units, and dissolution. (b) (4)

The drug product is manufactured by QS Pharma LLC at a commercial batch size of *ca.* (b) (4) Kg which corresponds to (b) (4) tablets. The drug product is packaged in blister packs (b) (4) The container closure system complies with the standards set by the Consumer Product Safety Commission (CPSC) in 16 CFR 1700.

The drug product specifications are consistent with ICH Q6A and are based on batch analyses as well as stability data. The specifications provide adequate controls to ensure the quality of the drug product throughout the product expiry. Of note, the (b) (4)

The proposed specification and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 36-month expiry, the applicant provided 24-months of stability data for three registration batches of the drug product (batches 1504034, 1504036, and 1504037). The batches were stored for 24 months under the long-term condition (25°C/60% RH) and 6 months under the accelerated conditions (40°C/75% RH). The applicant also completed bulk hold study, photostability, temperature cycle and forced degradation studies for the drug product. The stability studies were executed in accordance with the ICH 1A and Q1B. The available stability data shows consistency over time and support the proposed expiry. Based on the 24 months of stability data included in this application, Shionogi Inc. proposed and the FDA accepts the expiration dating period of **36-months** for the drug product when stored at stored at USP controlled room temperature.

The application is recommended for approval from a drug product perspective.

Process

The drug product is manufactured by QS Pharma LLC (b) (4) (b) (4)

The proposed process parameters and in-process controls were described in sufficient detail and justified. The applicant demonstrated the suitability of the manufacturing

process for the drug product at commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters.

The application is recommended for approval from a manufacturing process perspective.

Biopharmaceutics

The acceptability of the proposed dissolution method and acceptance criterion for the routine QC testing of the proposed drug product at batch release and on stability was assessed. The dissolution method included a USP Apparatus II (Paddle) at 75 rpm in 900 mL of (b) (4) The proposed dissolution acceptance criterion is Q= (b) (4)% in 30 minutes. The applicant used comparative dissolution testing to bridge the various tablet presentations used during the phase I (pivotal) clinical study. The applicant confirmed that all of the tablet presentations have similar dissolution profiles as evidenced by the calculated f_2 values.

Both the proposed dissolution method and acceptance criterion were deemed acceptable and the f_2 values were sufficiently similar to substantiate the bridge and thus the bridging is acceptable.

This application is recommended for approval from a biopharmaceutics perspective.

Facilities

There were 3 sites included in this application:

- QS Pharma LLC – Manufacture, release and stability testing of drug product.
- (b) (4)
- Shionogi Pharma Chemicals Co., Ltd - Manufacture, packaging, release and stability testing of drug substance

DRUG SUBSTANCE:

Drug substance, lusutrombopag, is manufactured by Shionogi Pharma Chemicals Co., Ltd of the Japan (FEI 3008353674). This site was responsible for drug substance manufacture, packaging, release and stability testing. Based on the initial risk assessment, this site was considered high risk due to the New Molecular Entity (NME) (b) (4) proposed drug substance. A PAI inspection was scheduled and conducted in August of 2016. The PAI inspection resulted in a 13-item 483 Corrective measures were taken to address the deficiencies and concerns outlined in the 483. Based on relevant recent PAI inspection (2016), previous NAI GMP inspection (2015) and risk assessment, the compliance status of this firm and the demonstrated controls and capabilities of the quality unit in controlling and releasing manufactured substance, this site is recommended for approval under this application.

DRUG PRODUCT:

Drug product, Mulpleta® (lusutrombopag) tablets, is manufactured, release and stability tested by QS Pharma LLC of Boothwyn, PA (FEI 3003882011). The drug product manufacturing process includes (b) (4)

(b) (4). Although the site was considered "medium" risk by virtue of the drug substance being designated as a new molecule entity (NME) the process risk and facility risk components were considered "low" as, the unit operations are routine for table dosage production and the proposed control strategy was deemed adequate. The facility was last inspected in October of 2017. A two-item 483 was issued and the inspection was classified VAI. Accordingly, a PAI was not requested and the QS Pharma LLC site was recommended for approval for the aforementioned operations based on the information provided in the submission and satisfactory compliance history.

(b) (4)) was included in this NDA as a site to preform drug product packaging. This facility was last inspected in (b) (4). The inspection was classified as NAI. Based on the risk assessment and on its compliance history, the (b) (4) site is recommended for approval for the packaging of the drug product.

Environmental Assessment

The approval of this application will increase the use of lusutrombopag; however, the estimated concentration of the substance at the point of entry into the aquatic environment is below 1 ppb (i.e. (b) (4) ppb). The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(b). The categorical exclusion cited is appropriate based on the estimated amount of drug to be produced for direct use. The claim of categorical exclusion is therefore acceptable and should be granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Appended at the end of the drug product review.

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LABELING

R Regional Information

1.14 Labeling

Labeling & Package Insert

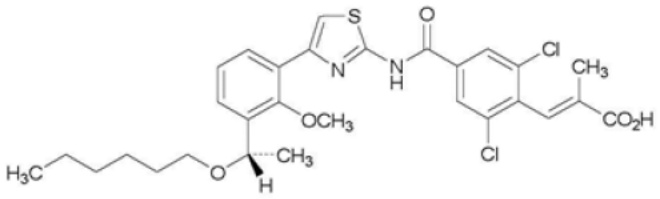
DESCRIPTION section:

11 DESCRIPTION

MULPLETA (lusutrombopag), a thrombopoietin (TPO) receptor agonist, contains lusutrombopag as the active ingredient.

The chemical name for lusutrombopag is (2*E*)-3-{2,6-Dichloro-4-[(4-{3-[(1*S*)-1-(hexyloxy) ethyl]-2-methoxyphenyl}-1,3-thiazol-2-yl) carbamoyl]phenyl}-2-methylprop-2-enoic acid.

The structural formula is:



The empirical formula for lusutrombopag is $C_{29}H_{32}Cl_2N_2O_5S$ and the molecular weight is 591.54.

Lusutrombopag is a white to slightly yellowish white powder, and is freely soluble in *N,N*-dimethylformamide, slightly soluble in ethanol (99.5%) and methanol, very slightly soluble in acetonitrile, and practically insoluble in water. Lusutrombopag is slightly soluble in the buffer solution at pH 11 and practically insoluble in buffer solutions with pH ranges of 1 to 9.

MULPLETA (lusutrombopag) tablets for oral use contain lusutrombopag 3 mg.

Excipients are D-mannitol, microcrystalline cellulose, magnesium oxide, sodium lauryl sulfate, hydroxypropyl cellulose, carboxymethylcellulose calcium, magnesium stearate, hypromellose, triethyl citrate, titanium dioxide, red ferric oxide, and talc.

Is the information accurate? ☒ Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section:

16 HOW SUPPLIED/STORAGE AND HANDLING

MULPLETA is supplied as 3-mg lusutrombopag tablets in a child-resistant blister pack containing 7 tablets - NDC 59630-551-07.

Store MULPLETA in the original package at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

i) Is the information accurate? ☒ Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Begin MULPLETA dosing at least 8 -14 days prior to the scheduled procedure.

Patients should undergo their procedure within 2- (b) (4) days after the last dose.

The recommended dosage of MULPLETA is 3 mg taken orally once daily with or without food for 7 days. In the case of a missed dose of MULPLETA, patients should take the missed dose as soon as possible on the same day and return to the normal schedule the following day.

MULPLETA has been investigated only as a single 7-day once daily dosing regimen in clinical trials in patients with chronic liver disease *[see Clinical Studies (14)]*. MULPLETA should not be administered to patients with chronic liver disease in an attempt to normalize platelet counts.

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)?
☒ Yes ☐ No ☐ N/A

If "No," explain.

R Regional Information

1.14 Labeling

Commercial packaging:

Immediate Container Label (7 tablets in blisters): Front panel

(b) (4)

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Reviewer's Assessment: *The applicant responsed to deficiencies and revised the label as recommended. Adequate.*

Reviewer's Assessment:

The labeling of the PI and container labels is revised per lebelling tools and https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM569607.pdf *guidance to have the most current information of the labels.*

The deficiencies were identified and communicated to the applicant by DDMAC and the review was carried out on 5-MAY-2018 . The applicant responded satisfactorily to the deficiencies identified for container closures and PI.

The container labeling and PI is now adequate. A final version of the agreed upon PI will be reviewed by the ATL and included in their memo.

Conclusion: *Labels and Labeling are adequate from a CMC stand point.*

Primary Labeling Reviewer Name and Date:

Rajiv Agarwal, Ph.D, 10-MAY-2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Anamitro Banerjee, PhD, 10-MAY-2018

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
Date: 5/21/2018 08:38:48AM
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Anamitro Banerjee

Digitally signed by Anamitro Banerjee
Date: 5/21/2018 08:49:02AM
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BIOPHARMACEUTICS

Application No: NDA-210923-ORIG-1

Drug Product Name/Strength: MULPLETA® (Lusutrombopag) Tablets/3 mg

Route of Administration: Oral

Applicant Name: Shionogi Inc.

List Submissions being Reviewed:
Original NDA-210923 submitted on December 26, 2017;
Applicant's Response dated April 3, 2018 to the Information Request dated March 19, 2018

Review Recommendation: **ADEQUATE**

Review Summary:

Submission: Shionogi Inc. submitted this NDA seeking approval for Lusutrombopag Tablets, 3 mg under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

Review Objective: The Biopharmaceutics Review evaluates the adequacy of (1) the proposed dissolution method and acceptance criterion for routine QC testing of the proposed drug product at batch release and during stability, and (2) bridging of different formulations used in clinical studies.

Dissolution Method and Acceptance Criterion: The following Applicant's proposed dissolution method and dissolution acceptance criterion are acceptable for batch release and stability testing of the proposed Lusutrombopag Tablets, 3 mg.

Final dissolution method and acceptance criterion for Lusutrombopag Tablets, 3 mg

USP Apparatus	Speed (rpms)	Medium/Temp	Volume (mL)	Acceptance Criterion
2 (paddle)	75	Mixture of pH 6.8 phosphate buffer solution and water (v/v, 1:1) containing 0.3% Triton X-100/37 °C	900	NLT (b)(4)% (Q) in 30 minutes

Bridging of Formulations: The Applicant provided adequate data to support the bridging of different strengths and formulations for Lusutrombopag Tablet used in clinical studies. The bridging is acceptable.

Biowaiver Request: Biowaiver Request is not submitted nor required.

Overall Review Recommendation: From the Biopharmaceutics perspective, NDA-210923 for Lusutrombopag Tablets, 3 mg is recommended for **APPROVAL**.

- ***SIGNATURES***

Primary Biopharmaceutics Reviewer Name and Date:

Yang Zhao, PhD 5/18/2018
Biopharmaceutics Reviewer
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

Secondary Reviewer Name and Date:

Banu S. Zolnik, PhD 5/21/2018
Acting Biopharmaceutics Lead
Division of Biopharmaceutics-Branch 1
Office of New Drug Products

BIOPHARMACEUTICS ASSESSMENT

Lusutrombopag (S-888711) is an orally active, small-molecule thrombopoietin (TPO) receptor agonist. It acts on the transmembrane domain of human TPO receptors to stimulate megakaryocytes to proliferate and differentiate via the signal transduction pathway, thus upregulating platelet production. Lusutrombopag Tablets are indicated for the treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with invasive procedures. The recommended dose in adults is one 3-mg tablet taken orally once daily with or without food for 7 days. It is recommended to initiate Lusutrombopag tablets a minimum of 8 days prior to the procedure.

1. DRUG SUBSTANCE:

1.1 Solubility:

The Applicant reported that lusutrombopag is a low water-solubility drug (Table 1).

Table 1. Solubility of lusutrombopag

Solvent	Solubility (mg/mL)	Descriptive Term
Water	BLQ [a]	Practically insoluble
JP-1 [b]	BLQ [a]	Practically insoluble
JP-2 [c]	BLQ [a]	Practically insoluble
pH 1 Buffer solution [d]	BLQ [a]	Practically insoluble
pH 3, pH 5, pH 7 Buffer solutions [e]	BLQ [a]	Practically insoluble
pH 9 Buffer solution [e]	0.003	Practically insoluble
pH 11 Buffer solution [e]	1.67	Slightly soluble

a. BLQ: below limit of quantitation (0.0001 mg/mL)
b. JP-1: 2.0 g of sodium chloride is dissolved in 7.0 mL of hydrochloric acid and water to make 1000 mL to create a clear and colorless solution with pH 1.2.
c. JP-2: A mixture of phosphate buffer solution, pH 6.8 and water (1:1)
d. Clark and Lubs buffer solution: hydrochloric acid, potassium chloride
e. Britton-Robinson buffer: phosphoric acid, acetic acid, boric acid, sodium hydroxide

1.2 Permeability:

The Applicant demonstrated the permeability of lusutrombopag in Caco-2 monlayer ($Papp_{A\rightarrow B}$: $0.13–0.30\times10^{-6}$ cm/sec, $Papp_{B\rightarrow A}$: $1.2–1.6\times10^{-6}$ cm/sec, efflux ratio ranging from 5.2–9.1).

1.3 BCS designation:

The Applicant did not submit BCS designation request for lusutrombopag.

2. DRUG PRODUCT:

Lusutrombopag Tablets, 3 mg is an immediate release formulation for oral administration. Lusutrombopag Tablets, 3 mg are light red, round, film-coated tablets debossed on one side with Shionogi trademark above the identifier code "551", and debossed on the other side with the strength "3".

Per the Applicant, the target formulation for Lusutrombopag Tablets was optimized to improve drug product stability and to minimize the formation of (b) (4) (see more information in the section of "Bridging").

Table 2. Composition of Lusutrombopag Tablets 3 mg

Component	Function	Quality Standard	Weight per Tablet (mg)
Lusutrombopag [a]	Active Ingredient	In-house standard	3.0
D-Mannitol [a]	(b) (4)	USP/Ph.Eur./JP	(b) (4)
Microcrystalline Cellulose		NF/Ph.Eur./JP	
Magnesium Oxide		USP/JP	
Sodium Lauryl Sulfate		NF/Ph.Eur./JP	
Hydroxypropylcellulose		NF/Ph.Eur./JP	
Carboxymethylcellulose Calcium (b) (4)		NF/Ph.Eur./JP	
Magnesium Stearate		NF/Ph.Eur./JP	
		(b) (4	
Hypromellose		USP/Ph.Eur./JP	
Triethyl Citrate		NF/Ph.Eur./JPE	
Titanium Dioxide		USP/Ph.Eur./JP	
Red Ferric Oxide		NF/Commission Regulation (EU) [d]/JPE	
Talc		USP/Ph.Eur./JP	
		(b) (	
Total Weight of Coated Tablet			189.0

a (b) (4)

b Ph.Eur. name.

(b) (4)

d Commission Regulation (EU) No. 231/2012.

3. PROPOSED DISSOLUTION METHOD AND DISSOLUTION ACCEPTANCE CRITERION:

The proposed dissolution method and dissolution acceptance criterion for Lusutrombopag Tablets are as follows:

Apparatus:	USP apparatus 2 (Paddle)
Paddle speed:	75 rpm
Medium:	A mixture of pH 6.8 phosphate buffer solution and water (v/v, 1:1) containing 0.3% Triton X-100
Volume:	900 mL
Temperature:	37 °C
Dissolution acceptance criterion:	Q = (b) (4) % dissolved in 30 minutes.

3.1 Rationale for the paddle speed:

The Applicant provided the dissolution data of Lusutrombopag Tablets tested in the same medium [A mixture of pH 6.8 phosphate buffer solution and water (v/v, 1:1) containing 0.3% Triton X-100 (polyoxyethylene octylphenyl ether)] at the paddle speed of (b) (4) 75 rpm. (b) (4)

(b) (4)

(b) (4) at 75 rpm, dissolution was not influenced by the (b) (4) position.

Therefore, the Applicant selected 75 rpm as the paddle speed; 75 rpm paddle speed is acceptable for the dissolution testing for Lusutrombopag Tablets.

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3.4 Discriminating ability of the proposed dissolution method:

The Applicant provided the data to support discriminating ability of the proposed dissolution method.

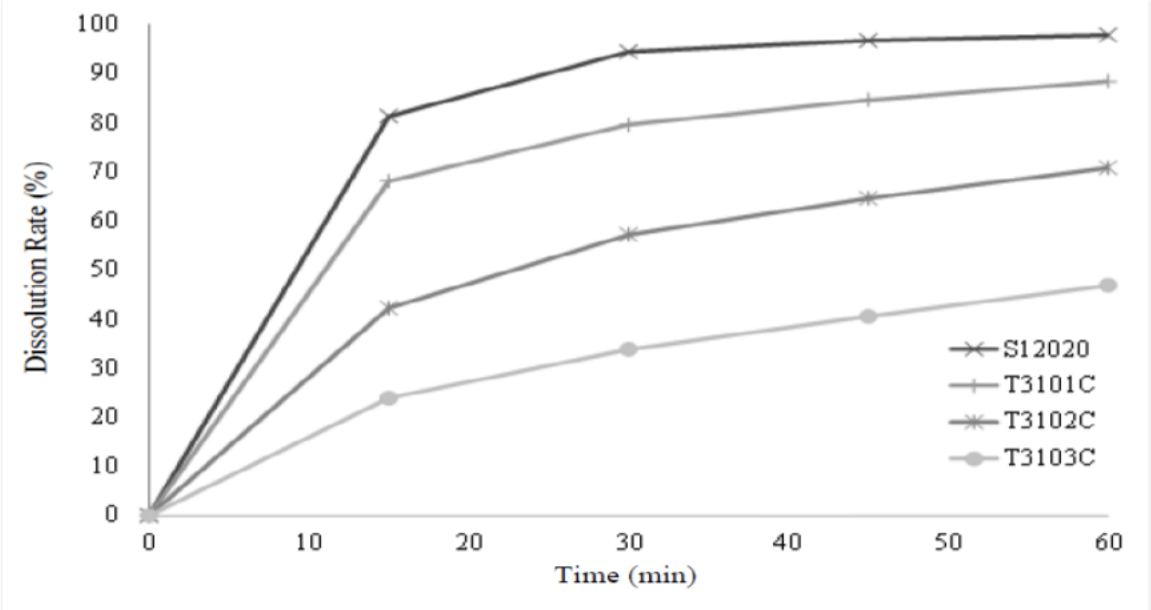
3.4.1 Drug substance particle size:

To investigate the impact of the drug substance particle size on the dissolution of the drug product, the Applicant manufactured coated tablets of 4 mg and 3 mg strengths with the same formulation using drug substance of various particle sizes. (b) (4) (b) (4) particle size distribution was determined by a laser diffraction method. The drug product and the drug substance batches with corresponding particle size (D_{90}) used in this dissolution study are provided in Tables 6 and 7. It should be noted that although the 4 mg strength tablets are not subject to approval and included as part of the development, the proposed dissolution method was discriminating towards the changes in drug substance particle size (D_{90} range tested: (b) (4) µm) (see Table 6 and Figure 2). The Lusutrombopag Tablets 4-mg strength Batch S12020 was used in the relative bioavailability study and food effect study in Japan (Study No. M061A). (b) (4) this Reviewer considered that the proposed dissolution method is projected to be discriminating towards the changes in drug substance lusutrombopag particle size for Lusutrombopag Tablets, 3 mg.

Table 6. Tested Lusutrombopag Tablets 4 mg manufactured with drug substance of different particle sizes

Drug Product Batch No.	Drug Substance Batch No.	D_{90} (µm)
S12020	A73001	(b) (4)
T3101C	T2Z01-9	
T3102C	T2Z01-8	
T3103C	T2Z01-3	

Figure 2. Dissolution profiles for tested Lusutrombopag Tablets 4 mg manufactured with drug substance of different particle sizes

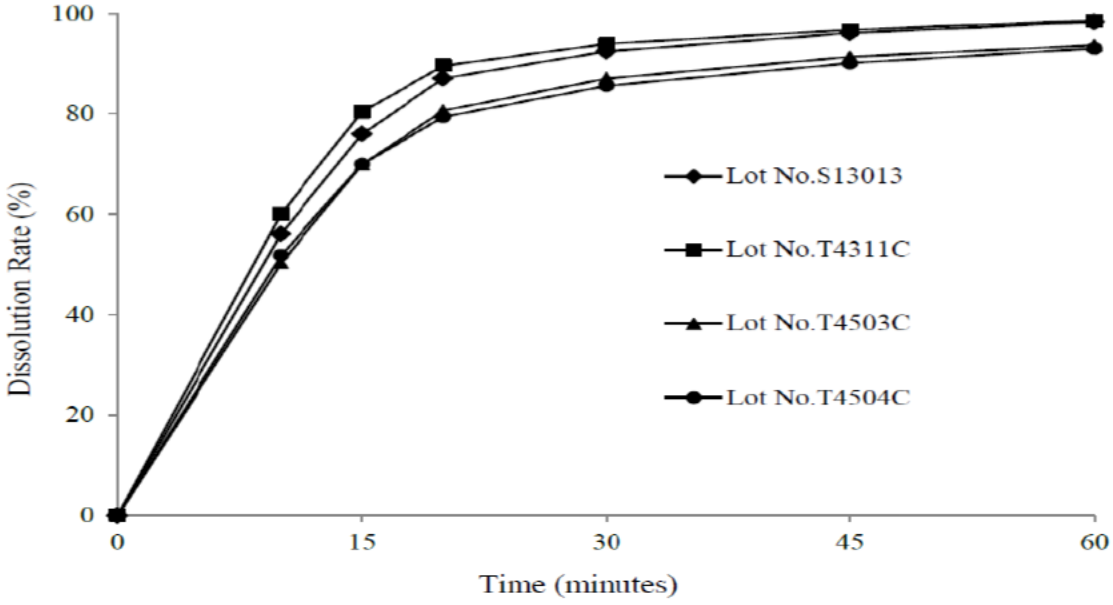


Drug substance further (b) (4) to different particle sizes (D_{90} range: (b) (4) µm) were formulated into 3-mg strength Tablets. It is demonstrated that the proposed dissolution method was not discriminating towards the changes in drug substance (D_{90} range tested: (b) (4) µm) (see Table 7 and Figure 3). The Applicant reported that the specification for drug substance particle size was established as "D_{90}: NMT (b) (4) µm", however, the acceptability of the particle size specification will be assessed by the assigned DMF Reviewer.

Table 7. Tested Lusutrombopag Tablets, 3 mg manufactured with drug substance of different particle sizes

Drug Product Batch No.	Drug Substance Batch No.	D_{90} (µm)
S13013 (control)	B33003	(b) (4)
T4311C	B33002	
T4503C	TA4206	
T4504C	TA4502	

Figure 3. Dissolution profiles for tested Lusutrombopag Tablets 3 mg manufactured with drug substance of different particle sizes



3.4.2 Effects of the amounts of (b) (4) in the formulation:

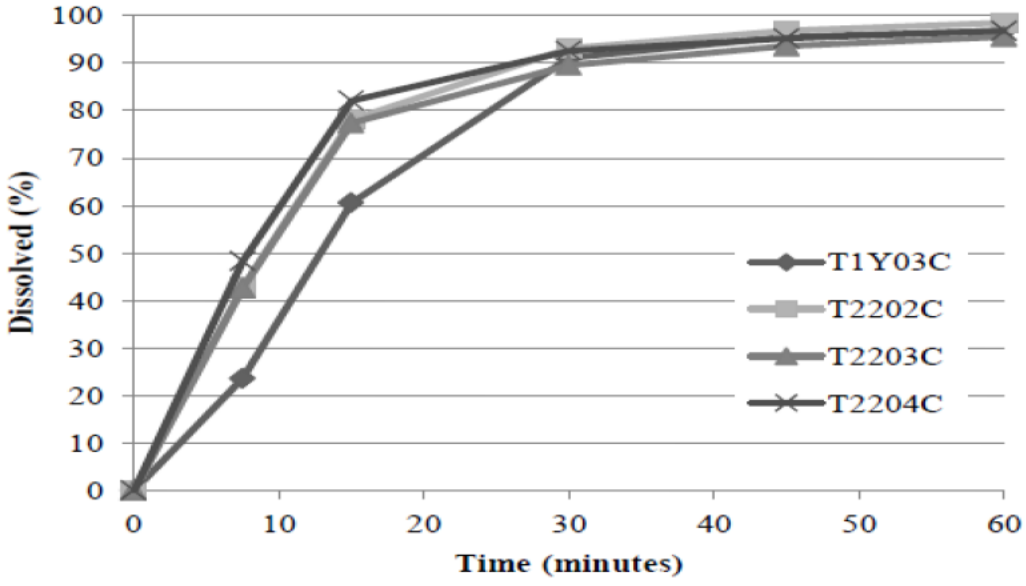
(b) (4)

The proposed dissolution method was not discriminating towards the changes in the amounts of (b) (4) in the Lusutrombopag Tablets, 2 mg formulation (Figure 4). It is noted that this discriminating ability investigation was performed in early development stage Lusutrombopag 2 mg strength Tablets, but not with the final 3 mg strength.

Table 8. Tested Lusutrombopag Tablet 2 mg composition for investigation of optimal (b) (4) (b) (4)

Batch No.	T1Y03C	T2202C	T2203C	T2204C
Component /tablet (mg)	(b) (4)			

Figure 4. Dissolution profiles of tested Lusutrombopag Tablets 2 mg formulations manufactured with different amounts of (b) (4)

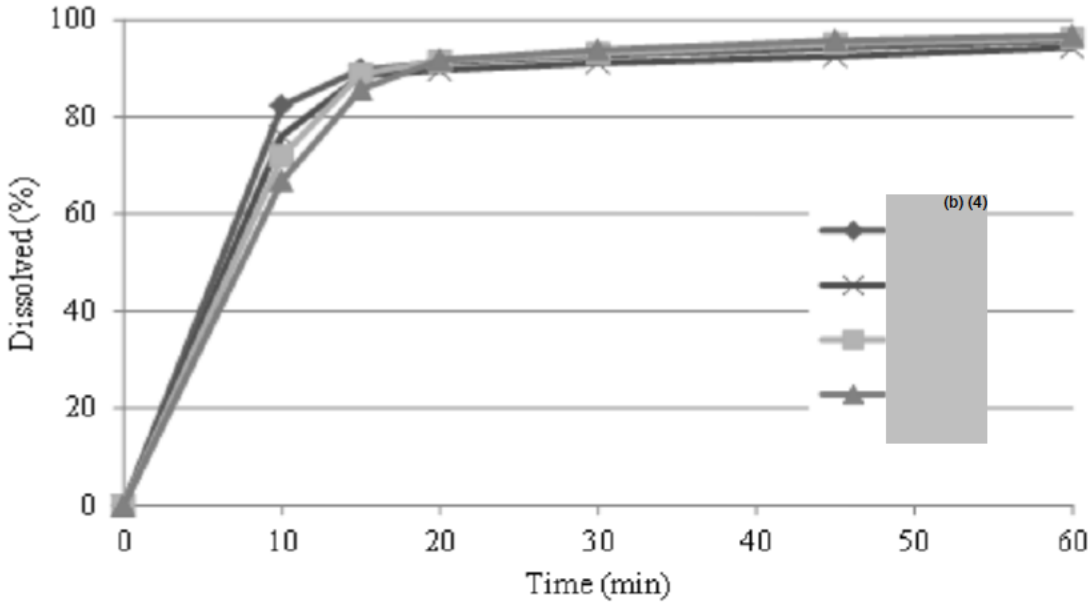


3.4.3 Effects of (b) (4), tablet thickness, and tablet hardness:

It is demonstrated that the proposed dissolution method was not discriminating towards the changes in the (b) (4)), tablet thickness (range tested: (b) (4)

mm), and tablet hardness (range tested: (b) (4) kp) for the Lusutrombopag Tablets 3 mg formulation (Figure 4).

Figure 4. Dissolution profiles of tested Lusutrombopag Tablets, 3 mg with different (b) (4), tablet thickness, and tablet hardness (n=6). (b) (4)



Reviewer's Assessment: The Applicant's proposed dissolution method [*USP 2 at 75 rpm, 900 mL of a mixture of pH 6.8 phosphate buffer solution and water (v/v, 1:1) containing 0.3% Triton X-100 at 37 °C]* is discriminating towards drug substance particle size. The proposed dissolution method is acceptable for the QC dissolution method of batch release and stability testing of Lusutrombopag Tablets, 3 mg.

3.5 Dissolution data for Lusutrombopag Tablets, 3 mg:

The Applicant provided the dissolution profile data for Lusutrombopag Tablets, 3 mg clinical batches, registration/primary stability batches, and process validation batches (see Tables 9–11, Figure 5).

Table 9. Dissolution profile data for Lusutrombopag Tablets 3 mg clinical batches

Batch No.		S13013	1411175
Strength (mg)		3	3
Dissolution (%) mean (min - max)	30 min [c]	94.0 (b) (4) (b) (4)	93.5

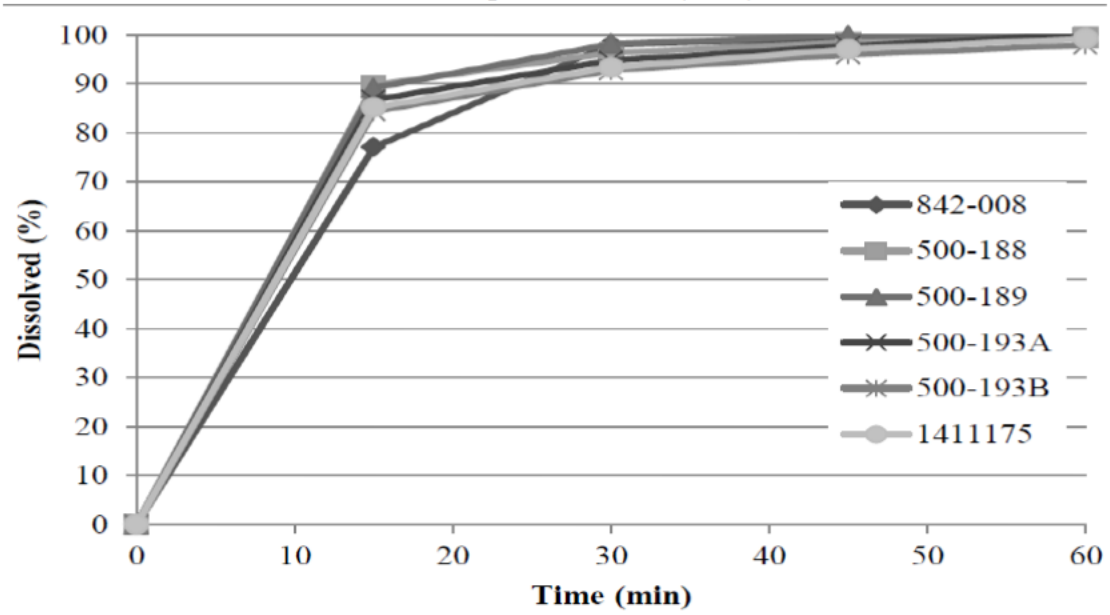
Table 10. Dissolution profile data for Lusutrombopag Tablets 3 mg registration/primary stability batches

Batch No.		1504034	1504036	1504037
Dissolution (%) Mean (min - max)	30 min [b]	92.8 (b) (4)	91.2 (b) (4)	94.6 (b) (4) (b) (4)

Table 11. Dissolution profile data for Lusutrombopag Tablets 3 mg process validation batches

Batch No.		C15001	C15002	C15003
Dissolution (%) Mean (min - max)	30 min [b]	90.6 (b) (4)	94.6 (b) (4)	92.6 (b) (4) (b) (4)

Figure 5. Dissolution profiles of Lusutrombopag coated Tablets 3 mg clinical batches and early development batches (n = 6)



The Applicant provided 24 months long term (25 °C/60% RH) and 6 months accelerated (40 °C/75% RH) stability data (n=6) for different batches (1504034, 1504036, 1504037). The stability dissolution data for these batches demonstrated more than 90% drug release in 30 minutes. The proposed drug product is stable with regards to dissolution for at least 24 months under long term storage conditions.

The proposed dissolution acceptance criterion "NLT (b) (4) % (Q) in 30 minutes" is permissive and not acceptable. Based on the dissolution data provided, in the Information Request dated March 19, 2018, the Applicant was requested to revise the dissolution acceptance criterion and the Agency recommended the dissolution acceptance criterion for Lusutrombopag Tablets, 3 mg to be "NLT (b) (4) % (Q) in 30 minutes". In the Response dated April 3, 2018, the Applicant accepted the

Agency's recommendation and tightened dissolution acceptance criterion to "NLT [redacted] % (Q) in 30 minutes".

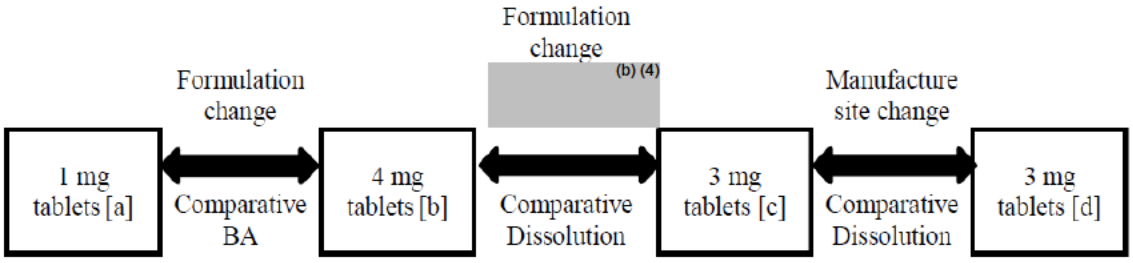
Reviewer's Assessment: The revised dissolution acceptance criterion of "NLT [redacted] % (Q) in 30 minutes" is acceptable for the quality control of Lusutrombopag Tablets 3 mg.

4. BRIDGING OF FORMULATIONS:

4.1 Different Lusutrombopag Tablet formulations and strengths:

The Applicant provided an overview of their approaches used for establishing the bridging between the different tablet formulations and strengths in Figure 6.

Figure 6. Bridging of the different Lusutrombopag Tablet formulations



BA = bioavailability

[a] Used in the Phase 2 dose finding study in CLD in Japan (Study M0626).

[b] Used in the Phase 1 relative BA of 4-mg tablet and food effect study in Japan (Study M061A).

[c] Used in the Phase 3 study in Japan (Study M0631).

[d] The drug product intended for marketing and used in the global Phase 3 study (Study M0634).

Source: CTD Section 3.2.P.2.2

Lusutrombopag Tablets of 0.1 mg, 0.25 mg, 1 mg, 2 mg, and 10 mg strengths (used in the **early-stage clinical studies, Table 12**) were manufactured with [redacted]. Lusutrombopag 0.1, 0.25, 2, and 10 mg tablets were primarily used in the early-stage clinical studies up to Study M0625 (Phase 2a, high-dose study).

The Applicant conducted Phase 2b dose-finding Study M0626, with 1 mg tablet strength (with evaluated doses of 2, 3, and 4 mg, being achieved by intake of multiple 1 mg tablets) and food effect study with the 4 mg strength.

In order to improve the tablet stability and minimize the formation of [redacted], the formulation was modified and an optimized tablet formulation was developed in 4 mg and 3 mg strengths. The 4 mg and 3 mg tablets differ from the earlier development stage lusutrombopag tablets regarding [redacted]. [redacted]

(b) (4)

, the differences (b) (4) are not expected to impact dissolution. **The formulation of the Phase 3 clinical study is the same as that of commercial Lusutrombopag Tablets, 3 mg**.

Table 12. Composition of Lusutrombopag Tablets used in the clinical studies and proposed for marketing

Batch No.		A8101 A9Y01	A8102	A8Y01	A8Y02,A9401, A9Y01, A9Y02, A0701	S12003	S12020	S13013 1411175
Development Phase		Phase 1 & 2	Phase 1	Phase 1	Phase 1 & 2	Phase 1 & 2	Phase 1	Phase 1, 2 & 3
Strength (mg)		2	10	0.1	0.25	1	4	3
Component /amount (mg)	Lusutrombopag	(b) (4)						
	D-Mannitol							
	Microcrystalline Cellulose							
	Magnesium Oxide							
	(b) (4)							
	Sodium Lauryl Sulfate							
	Hydroxypropyl Cellulose							
	Carboxymethylcellulose Calcium							
	Magnesium Stearate							
	Hypromellose							
	Triethyl Citrate							
	Titanium Dioxide							
	Red Ferric Oxide							
	Talc							
Total (mg)								

4.2 Bioequivalence between 1 mg strength and 4 mg strength:

To bridge 1-mg strength tablets and 4-mg strength tablets (b) (4)), the Applicant conducted a comparative bioavailability study (M061A, \\cdsesub1\evsprod\nda210923\0002\m5\53-clin-stud-rep\531-rep-biopharm-stud\5312-compar-ba-be-stud-rep\1218m061a\1218m061a-body.pdf) between 4×1-mg tablets (Batch S12003) and 1×4-mg tablets (Batch S12020) in 15 Japanese subjects. This study showed the main PK parameters (179 ng/mL vs. 165 ng/mL for C_{max}, 5124 ng·hr/mL vs. 4685 ng·hr/mL for AUC_{0-t}, 5220 ng·hr/mL vs. 4776 ng·hr/mL for $AUC_{0-\infty}$, between the treatments of 4×1-mg tablets vs. 1×4-mg tablets under fasted condition) and met the criterion for bioequivalence. The adequacy of the BE study will be determined by the OCP reviewer.

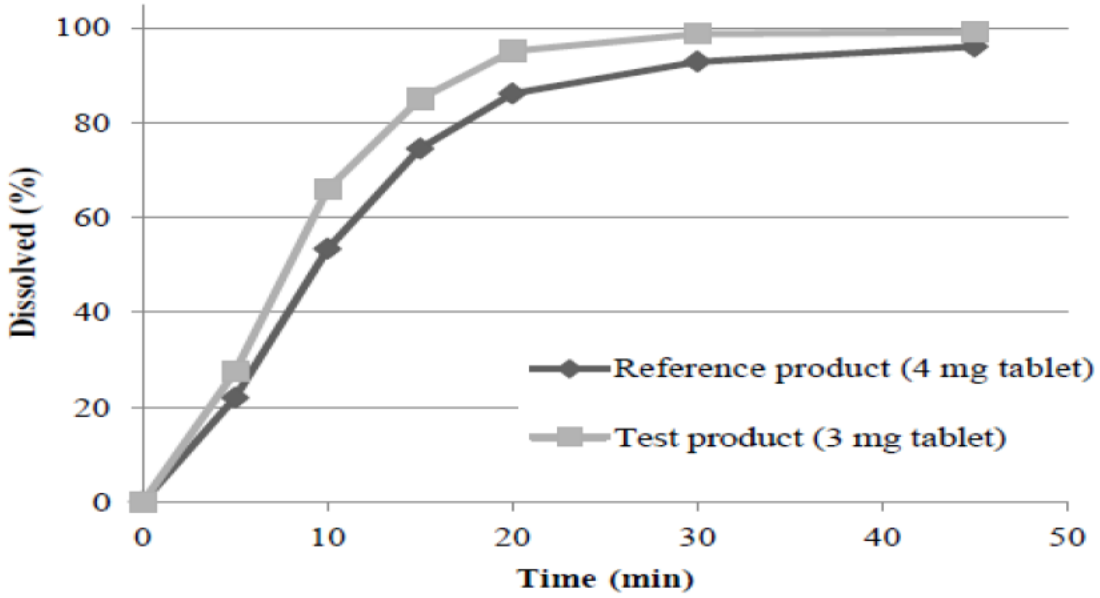
4.3 Comparative dissolution profiles of 3 mg and 4 mg Lusutrombopag Tablets:

To bridge 4 mg and 3 mg strength tablets, the Applicant conducted comparative dissolution testing between 4 mg tablets (Batch S12020) and 3 mg tablets (Batch S13013) using the proposed dissolution method. It is demonstrated that the 4 mg and 3 mg tablets generated comparable dissolution profiles (see Figure 7, similarity factor=56 calculated by this Reviewer).

Table 13. Lusutrombopag Tablets, 3 mg and 4 mg used in the comparative dissolution testing

Drug Product	Batch No.	Assay (% label claim)	Batch Size	Date of Manufacture	Site of Manufacture
3 mg tablets (test product)	S13013	101.7	(b) (4)	Jun 2013	Shionogi & Co., Ltd. Settsu Plant
4 mg tablets (reference product)	S12020	100.9		Dec 2012	

Figure 7. Comparative dissolution profiles for Lusutrombopag Tablets, 4-mg and 3-mg formulations using the proposed dissolution method



4.4 Comparative dissolution profiles of 3 mg Lusutrombopag Tablets manufactured at different sites:

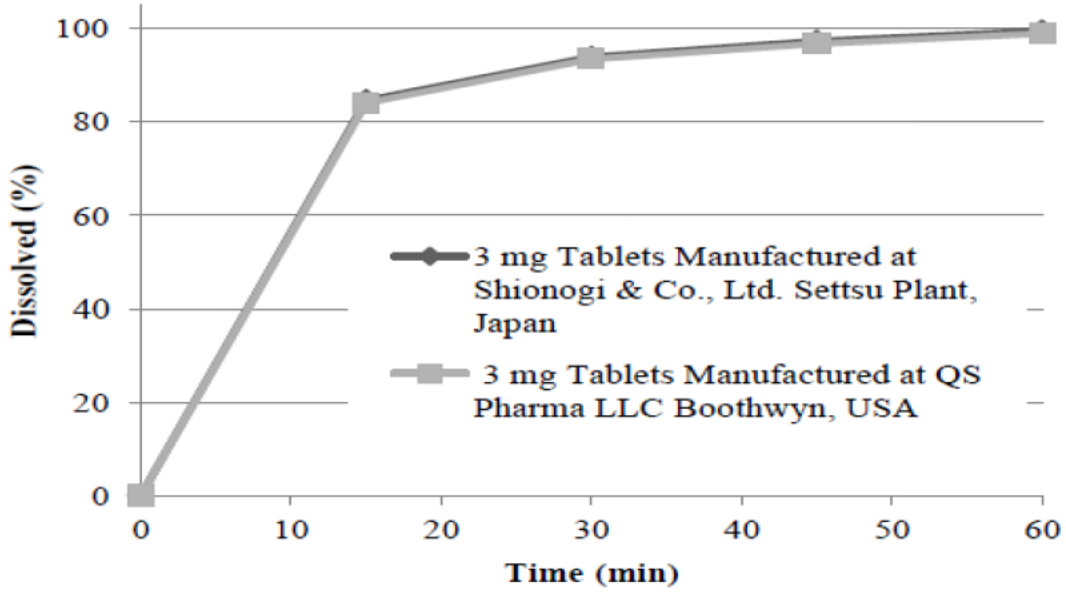
The Applicant conducted comparative dissolution testing between the tablets manufactured at the site of Shionogi & Co., Ltd (Batch S13013) and the tablets manufactured at the site of QS Pharma LLC (Batch 1411175) using the proposed dissolution method. The drug product for the Phase 3 confirmatory study (M0631), Lusutrombopag tablets 3 mg (Batch S13013) was manufactured at Shionogi & Co., Ltd. Settsu plant in Japan. The drug product used in the global Phase 3 study (M0634), Lusutrombopag tablets 3 mg (Batch 1411175) was manufactured at QS Pharma LLC, Boothwyn in the USA (commercial site). It is demonstrated that 3-mg strength tablets

manufactured at different sites generated comparable dissolution profiles (see Figure 8, similarity factor not calculated due to more than 85% release in 15 minutes).

Table 14. Lusutrombopag Tablets 3 mg manufactured at different sites used in the comparative dissolution testing

Batch No.	Assay (mg) (% label claim)	Batch size	Date of Manufacture	Manufacturer
S13013	101.7	(b) (4)	Jun 2013	Shionogi & Co., Ltd. Settsu Plant, Japan
1411175	101.0		Dec 2014	QS Pharma LLC Boothwyn, USA

Figure 8. Comparative dissolution profiles for Lusutrombopag Tablets 3 mg manufactured at different sites using the proposed dissolution method



Reviewer's Assessment: (1) The Applicant established the bridging between 1 mg strength and 4 mg strength by bioequivalence study. (2) The Applicant established the bridging between 3 mg and 4 mg strengths and different drug product manufacturing sites (Shionogi & Co., Ltd vs QS Pharma LLC) by using comparative dissolution profiles. This Reviewer considers the bridging among different formulations are adequately established.

APPENDIX I

The following Biopharmaceutics comment was conveyed to the Applicant in an Information Request dated March 19, 2018:

The proposed acceptance criterion of 'NLT (b)(4)% (Q) in 30 minutes' is permissive and not acceptable. Based on the provided dissolution data, a dissolution acceptance criterion of 'NLT (b)(4)% (Q) in 30 minutes' is recommended for Lusutrombopag Tablets, 3 mg, for batch release and during stability testing. Please revise the dissolution acceptance criterion in the specifications table and in other relevant selections of the Application.

Response: The Applicant stated that they agree to tighten the proposed dissolution acceptance criterion to NLT (b)(4)% (Q) in 30 minutes. The revised dissolution acceptance criterion is acceptable.

Yang Zhao

Digitally signed by Yang Zhao
Date: 5/26/2018 09:19:47AM
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Banu Zolnik

Digitally signed by Banu Zolnik
Date: 5/29/2018 09:54:36AM
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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay (API), stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Physical stability (solid state)	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	H	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipments • Site	M	Assessed during Development and controlled via specs	Acceptable	Controls are in place.
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	L	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval
Dissolution– BCS Class II & IV	• Formulation • Raw materials • Exclude major reformulations • Process parameters • Scale/equipments • Site	H	Assessed during Development and controlled via specs	Acceptable	Controls are in place, continue stability monitoring post approval

(b) (4)

Rajiv Agarwal

Digitally signed by Rajiv Agarwal
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Anamitro Banerjee

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Sherita McLamore

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Date: 5/30/2018 12:13:54PM
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