CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214801Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 214801
Review # 01

OPQ RECOMMENDATION: Approval

Drug Substance Retest Period:

A [(b) (4)] month retest period is proposed for futibatinib drug substance at the recommended storage temperature of less than [(b) (4)] C ([(b) (4)] F), excursion permitted up to [(b) (4)] C ([(b) (4)] F), when packaged and stored in [(b) (4)] container.

FDA Assessment: Retest date of [(b) (4)] months may be granted when stored at the proposed storage conditions

Drug Product Expiration Dating Period:

A 36-month shelf-life is proposed for futibatinib tablets packaged in [(b) (4)] Aluminum blister pack at the recommended storage condition of "Store below 30°C (86°F)".

FDA Assessment: An expiration dating period of 36 months may be granted when stored at the proposed storage conditions.

[Applicant will complete this section.]

Drug Name/Dosage Form	Futibatinib Tablet, Film-coated
Strength	4 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Locally advanced metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions
Applicant	Taiho Oncology Inc.
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	January 31, 2022
Received Date(s)	January 31, 2022
PDUFA Goal Date	September 30, 2022
Division/Office	Division of Oncology 3/Office of Oncologic Diseases

FDA assessment is indicated in colored fonts

Review Completion Date	July 11, 2022
Established Name	Futibatinib
(Proposed) Trade Name	Lytgobi
Pharmacologic Class	kinase inhibitor
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	09/03/2021	CMC
Original Submission	11/05/2021	DP, OPMA
Response to IRs	12/09/2021	OPMA
Original Submission	12/20/2021	DP, OPMA
Response to IRs	04/01/2022	OPMA
Response to IRs	04/15/2022	DP
Response to IRs	05/04/2022	DS
Response to IRs	05/31/2022	DS
Labeling	07/08/2022	DP

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Raymond Frankewich	Haripada Sarker
Drug Product	Xiao Hong Chen	Xing Wang
Process and Facility	Sridhar Thumma	Zhaoyang Meng
Microbiology	Sridhar Thumma	Zhaoyang Meng
Biopharmaceutics	Mei Ou	Mei Ou
Regulatory Business Process Manager	Anita Brown	-
Application Technical Lead	Xing Wang	-
ORA Lead	Caryn McNab	Cassandra Abellard
Environmental	Xiao Hong Chen	Xing Wang

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	III		(b) (4)	NA (not reviewed)	Adequate information regarding (b) (4) was provided in the NDA
	III			Adequate	Active and supporting approved A/NDAs
	III			Adequate	Active and supporting approved A/NDAs

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

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	121062	Futibatinib Tablets

CONSULTS

[FDA will complete this section.]

None

TABLE OF CONTENTS

Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

[To the Applicant: Insert text here.] Report any differences in formulation, manufacturing, container closure system, presentation, etc. ***Do not include labeling differences***.

#	FDA (US)	(b) (4)
1.	Secondary package is Dosepak to meet child resistance requirements.	

1. EXECUTIVE SUMMARY

[FDA ATL will complete this section.]

a. Summary of Rationale for Recommendation:

The applicant provided sufficient information to assure the identity, strength, purity, quality, and bioavailability of the proposed drug product. The key review issues (the cGMP status of drug substance and key intermediate facilities, the drug product Child-Resistant Packaging (CRP) statement) have been adequately resolved and were deemed to have minimal likely impact on patient efficacy or safety and do not preclude approval of this product. The labels and labeling include adequate quality information as required. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 214801 for Lytgobi (Futibatinib) Tablets, 4mg, for oral use.

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	**-**	**Adequate**

Life Cycle Considerations:
[FDA ATL to include any life-cycle considerations here]
None

2. APPLICATION BACKGROUND

[Applicant will complete this section.] Include information such as IND references, BTD/Fastrack/Orphan designations, etc.

Referenced IND 121062

FDA granted Breakthrough Therapy designation for futibatinib for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring *FGFR2* gene rearrangements, including gene fusions, dated Feb. 11, 2021.

FDA granted Fast Track Designation for the investigation of futibatinib for the first-line treatment of patients with unresectable or metastatic CCA harboring *FGFR* gene fusions to demonstrate a statistically significant improvement in overall survival for patients randomized to receive futibatinib as compared to those randomized to receive cisplatin and gemcitabine, dated Aug. 20, 2018.

Futibatinib received Orphan-Drug Designation from FDA for the "treatment of (b) (4) cholangiocarcinoma (b) (4)", dated May 23, 2018.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

Include CMC meeting dates and any Pre-NDA agreements

Type B Guidance Meeting, January 30, 2019 (IND 121062):

- Four regulatory starting materials were discussed and agreed.
- Control strategy for genotoxic impurities was agreed.

Pre-NDA, CMC Meeting, July 8, 2020 (IND 121062):

- [redacted] (b) (4) risk assessment strategy was agreed.
- Agreed requirement for bulk stability data on primary batches.
- Agreed requirement on bridging stability data at the commercial site.
- Two-stage manufacturing process validation strategy was agreed.
- Agreed to complete child resistant testing of the commercial container closure as per 16 CFR 1700 prior to the approval of the NDA.

Type B Initial Multidisciplinary Breakthrough Therapy Designation Meeting, June 14, 2021 (IND 121062):

- Agreed to the proposed rolling submission schedule and content.
- Agreed with elemental impurities specification strategy for drug substance.
- FDA acknowledged that particle size testing strategy for the drug substance during stability is acceptable.
- Risk assessment for elemental impurities in the drug product was considered adequate.
- Agreed on the stability data requirement for original NDA submission.
- Proposed data for debossed tablets was deemed sufficient.
- Confirmed the validation strategy for the proposed commercial packager, a different site than the bulk product manufacturer.
- Agreed on the executed batch record requirement to support filing and review of the proposed NDA.

Email advice from FDA on August 10, 2021 (IND 121062):

- The response by the applicant on FDA's dissolution questions appeared reasonable. Agreed to submit complete dissolution method development report and requested data profiles. Also agreed on the rolling submission schedule for dissolution data.

FDA's assessment: Note that the method development of an initial in vitro dissolution method [*USP Apparatus II (Paddle), 50 rpm, 900 mL o*[redacted] (b) (4) *pH 6.8* [redacted] (b) (4) *with 0.5% (w/v) polysorbate 80, 37°C*] was submitted in the IND 121062 amendment SDN-0210 dated 05/27/2020 and amendment SDN-0278 dated 06/30/2021. The Division of Biopharmaceutics reviewed the above two amendments on 10/02/2020 and 08/10/2021, respectively, and found the initial dissolution method was deemed appropriate. The Applicant proposed the current dissolution method [*USP Apparatus II (Paddle), 50 rpm, 900 mL of 0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80, 37°C*] and provided the complete dissolution method development and data in this NDA to support the currently proposed dissolution method.

The FDA's Assessment: ***Consistent with FDA's records***

[FDA will complete this section.]

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

A claim for categorical exclusion from conducting an environmental impact assessment (EA) is made under 21 CFR 25.31 on the basis that estimated concentration of the active moiety into the aquatic environment is less than 1 part per billion (ppb). A statement of "no extraordinary circumstances" is provided.

The FDA's Assessment: ***Adequate***

The claim for categorical exclusion from conducting an environmental impact assessment (EA) is deemed acceptable based on the estimated concentration of the active moiety into the aquatic environment is less than 1 part per billion (ppb) and no extraordinary circumstances exist per Applicant's claim.

5. FACILITIES

Drug substance manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)			
TAIHO PHARMACEUTICAL CO., LTD. 200-22, Motohara, Kamikawa-machi, Kodama-gun, Saitama, 367-0241, Japan	3002646390/695734327	Manufacture of drug substance (b) (4) Packaging and labeling Quality control testing and release Stability testing	Profile: CSN Approve based on 704(a)(4)

Drug product manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)			

(b) (4)

The FDA's Assessment: *Adequate*

[FDA will complete this section.]

I) Drug Product Facilities

1) (b) (4)

(b) (4) is responsible for manufacturing and QC release of DP. The firm has acceptable compliance status and TCM profile from several recent inspections.

- The PoAI in (b) (4) covered Quality, Production, Material, Facility & Equipment, Packaging & Labeling, and Laboratory Controls System and TCM and CHG profiles (NAI)
- Surveillance inspection in (b) (4) (NAI)- coverage provided during this inspection indicates the firm capabilities to manufacture under profile TCM.

The DP is manufactured using a (b) (4) (b) (4) that warrant a PAI. The firm has several approved solid dosage forms (capsules and tablets per exhibit 1 of (b) (4) inspection) and hence has experience manufacturing such dosage forms. Based on a review of the inspectional history of the firm, the firm appears to be acceptable to support manufacturing operations for this NDA. No PAI is recommended.

2) (b) (4)

Firm is listed as responsible for primary and secondary packaging of DP. The most recent surveillance inspection in (b) (4) covered Quality System, Production System, Packaging and Labeling System, and Facilities and Equipment System with NAI outcome. The past inspections since (b) (4) have all been NAIs. No recalls/FARs reported in CMS. The firm has adequate experience in packaging of solid dosage forms and is recommended approval based on its compliance history.

3) (b) (4)

(b) (4) is listed as responsible for release, and stability testing of DP. All the prior inspections since (b) (4) were NAIs. A recent 704a4 records review

(CMS [redacted] (b) (4)) covered laboratory system (including stability) with no issues identified. CTX (LCP) is acceptable as of [redacted] (b) (4) per FACTS.

II) Drug Substance Facilities

4) *Taiho Pharmaceutical Co., Ltd (FEI 3002646390)*

The firm is responsible for manufacturing ([redacted] (b) (4) only), packaging, labeling, release, and stability testing of DS (profile CSN). CSN profile AC as of 05/15/2015 per FACTS. The manufacturing process of DS is performed in [redacted] (b) (4) as follows [redacted] (b) (4)

The firm had only one FDA inspection, pre-approval, and surveillance GMP inspection in 05/2015. However, this inspection was comprehensive and covered CSN profile with Quality, Facilities and Equipment, Materials, Production, Packaging and Labeling systems, and Laboratory Control system for NDA 207981 and resulted in a NAI classification and recommended approval of this application. A surveillance 704a4 records review per CMS WA 338918 was performed in May 2020. Per the memo dated 08/24/2020, this review seems to be acceptable with few additional items identified for a follow up during next inspection. Per Site dossier (CMS WA #334616), [redacted] (b) (4) . There is no FDA reported history of FARs, incidents, recalls, consumer complaints, or MedWatch reports. Considering the acceptable CSN profile, the site is deemed approval in support of this NDA. A DFR was requested. A limited 704a4 was recommended by ORA.

Based on the 704a4 assessment, the site is deemed approvable in support of the proposed responsibilities (refer CMS WA 454639 for details). A post-approval inspection is recommended by ORA based on the fact that the last physical inspection of the site was more than 7 years.

5) [redacted] (b) (4)

The firm is listed as responsible for manufacture of [redacted] (b) (4) which are deemed [redacted] (b) (4) per DS reviewer. There is no FDA inspectional history for this site and hence a PAI is requested. Based on a recent inspection by [redacted] (b) (4) covering the [redacted] (b) (4) [redacted] (b) (4), a 704 (a)(4) in lieu of PAI was performed. Based on the 704a4 assessment, the site is deemed approvable in support of the proposed responsibilities (refer CMS [redacted] (b) (4) for details).

107 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

(b) (4)

[redacted]

R. REGIONAL INFORMATION

Executed batch record, and method validation package are submitted in the NDA.

Comparability Protocols for post-approval changes and comparability protocols for facilities or manufacturing (if any)

The FDA's Assessment: Choose an item.

No comparability protocol was submitted.

8. BIOPHARMACEUTICS

a. BCS CLASSIFICATION

Applicant to fill:	FDA assessment (FDA to fill):
BCS Classification: BCS II	Acceptable

Information to support the BCS Class I designation request, if applicable.
Link: n/a Page#: *n/a*

FDA comments: the formal request of BCS designation is not submitted/provided.

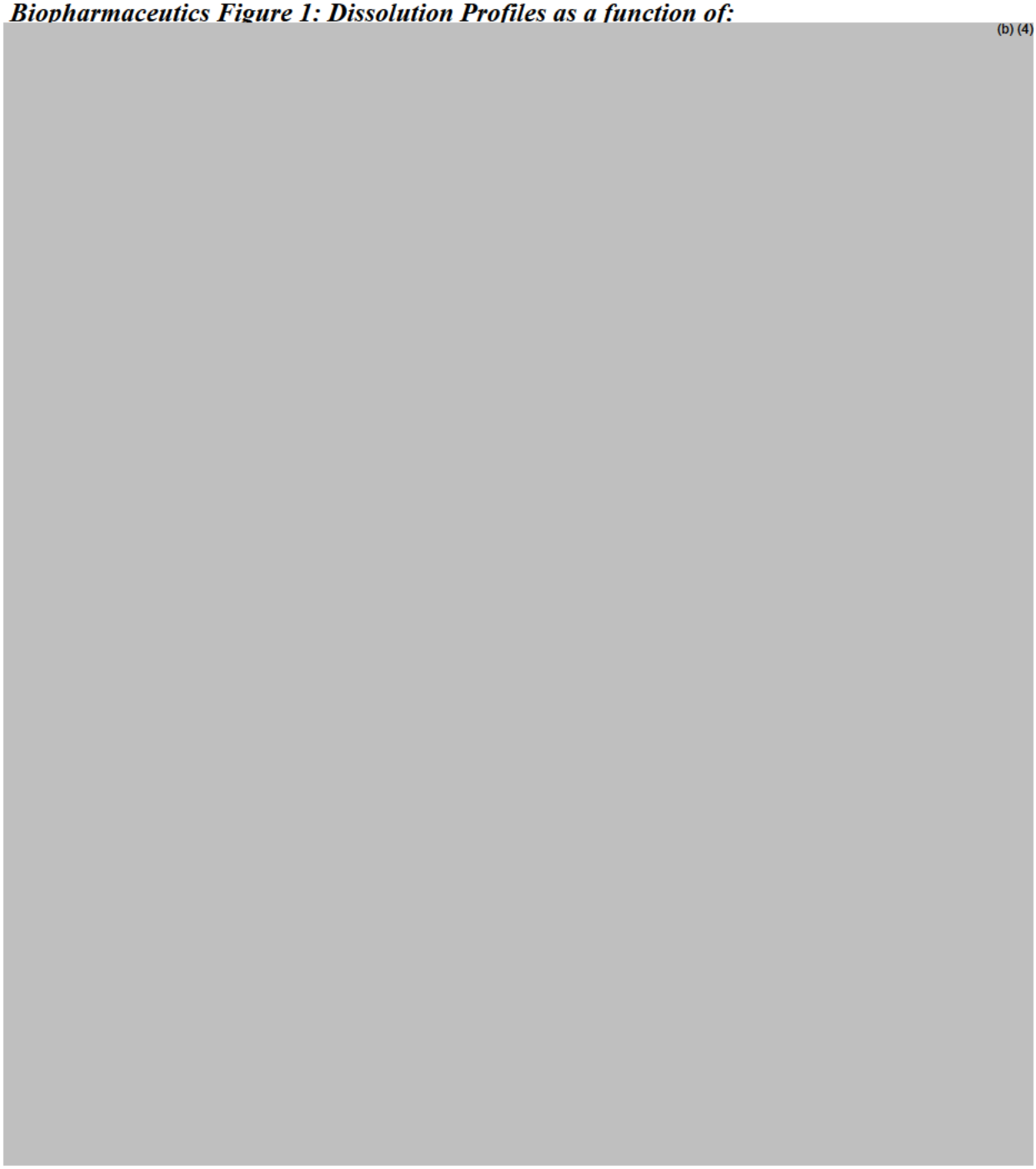
b. DISSOLUTION TEST

[Applicant to fill]

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
Apparatus 2 (Paddle)	50 ± 2 rpm	900 mL	37 °C ± 0.5 °C	0.05 M potassium dihydrogen phosphate, pH 6.8 with 0.5 w/v% polysorbate 80	Q = (b) (4) % at 30 minutes

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

(b) (4)



(b) (4)

FDA Comment: The selection of using 0.05 M potassium dihydrogen phosphate pH 6.8 medium is acceptable. Please see Biopharmaceutics review below for details.

(b) (4)

FDA Comment: The selection of using USP Apparatus 2 Paddle and 50 rpm is acceptable. Please see Biopharmaceutics review below for details.

(b) (4)

(b) (4)

FDA Comment: The selection of using 0.5% polysorbate 80 in dissolution medium is acceptable. Please see Biopharmaceutics review below for details.

d. Impact of parameter Y on dissolution (add as appropriate)

Applicant to insert figure here:	Applicant's comments:
N/A	

FDA Comment: n/a

e. Impact of parameter Z on dissolution (add as appropriate)

Applicant to insert figure here:	Applicant's comments:
N/A	

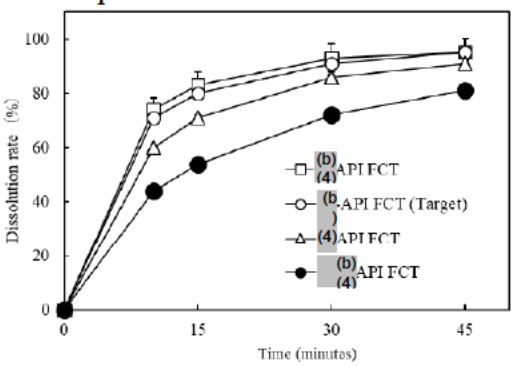
FDA Comment: n/a

f. Justification for selection of the acceptance criteria (or criterion)

(b) (4)

(b) (4)

FDA Comment: The proposed dissolution acceptance criterion of Q=(b) (4)% in 30 minutes is acceptable. Please see Biopharmaceutics review below for details.

	Applicant to fill:	FDA assessment:
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) The target PSD of API is controlled by the drug substance specification, which corresponds to "(b) (4) of API". To evaluate the discrimination ability of the dissolution method, futibatinib FCT were made with APIs having different PSD including the "(b) (4)". A decreased dissolution rate was observed for (b) (4) (b) (4) of API FCT when compared with (b) (4) of API FCT, and when compared statistically gave an f2 value of 31, which indicated that the profiles are not similar.  	Discriminating	Agree
Link[1]:Section 3.2.P.2.2		Page#: 35-39
ii) Polymorph/solid state form	Not applicable	Agree

Link[1]:		Page#:
iii) Formulation variations	Not discrimitating	Agree
Link[1]:		Page#:
iv) Manufacturing process variations	Discriminating	Agree

A difference in dissolution rate was observed with different (b) (4) processes during technology transfer to commercial manufacturing site demonstrating discriminatory power of the method.

(b) (4) process	Dissolution rate at 30 minutes
(b) (4)	52%
	82%
	88%

Link[1]: Section 3.2.P.2.3		Page#: 38-45
v) Other (specify):	Not applicable	Not applicable
Link[1]:		Page#:

[1]The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed.

FDA Comment: Overall, the proposed dissolution method [USP Apparatus II Paddle, 50 rpm, 900 mL of 0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80, 37°C] and the proposed acceptance criterion (Q= (b) (4) % in 30 minutes) are acceptable as a quality control (QC) test for the proposed drug product, Futibatinib Film-Coated Tablets, 4 mg, for batch release and stability testing. Please see Biopharmaceutics review below for details.

c. BRIDGING THROUGHOUT DRUG PRODUCT DEVELOPMENT (FORMULATION, PROCESS, OR SITE CHANGE)

A schematic representation of the development of the proposed drug product from initial IND-product to the to-be-marketed product, including all the formulation/manufacturing/ process changes that occurred throughout development and the studies bridging those products (in vitro or in vivo) bridging those products, and the PK, clinical, stability-registration studies in which those products were used.

(b) (4)

Taiho - Overview of Futibatinib Formulation Development

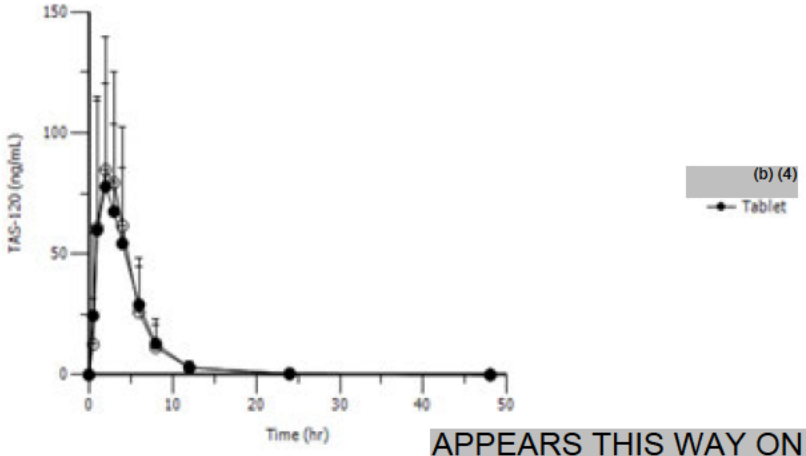
Taiho - Relationship of formulation and PK, clinical and registration-stability studies

Formulation	Strength (mg)	Batch size	Manufacturing Site	Use of Batch
Early formulation (b) (4) (Capsule)	4	(b) (4)	(b) (4)	• Phase 1 Escalation and Expansion study • Phase 1 Escalation study
	20			• Phase 1 Escalation and Expansion study • Phase 1 study • Phase 1 Escalation study
Late formulation (Tablet)	4	(b) (4)	Tokushima	• Phase 1 Escalation and Expansion and Phase 2 study • Phase 1 Food effect study • Phase 1 study • Phase 1 Expansion study • Phase 1 Expansion, Phase 2 study

Formulation	Strength (mg)	Batch size	Manufacturing Site	Use of Batch
	20	(b) (4)	Tokushima	• Phase 1 Escalation and Expansion study • Phase 1 PK/bioequivalence study
				• Phase 1 Escalation and Expansion
Commercial formulation (Tablet)	4		Kitajima	• Registration Stability Study and Phase 1 study
			(b) (4)	• Bridging Stability Study

Bridging methods

1) The bridging PK comparison between early and late formulation for 20 mg is provided below.



APPEARS THIS WAY ON ORIGINAL

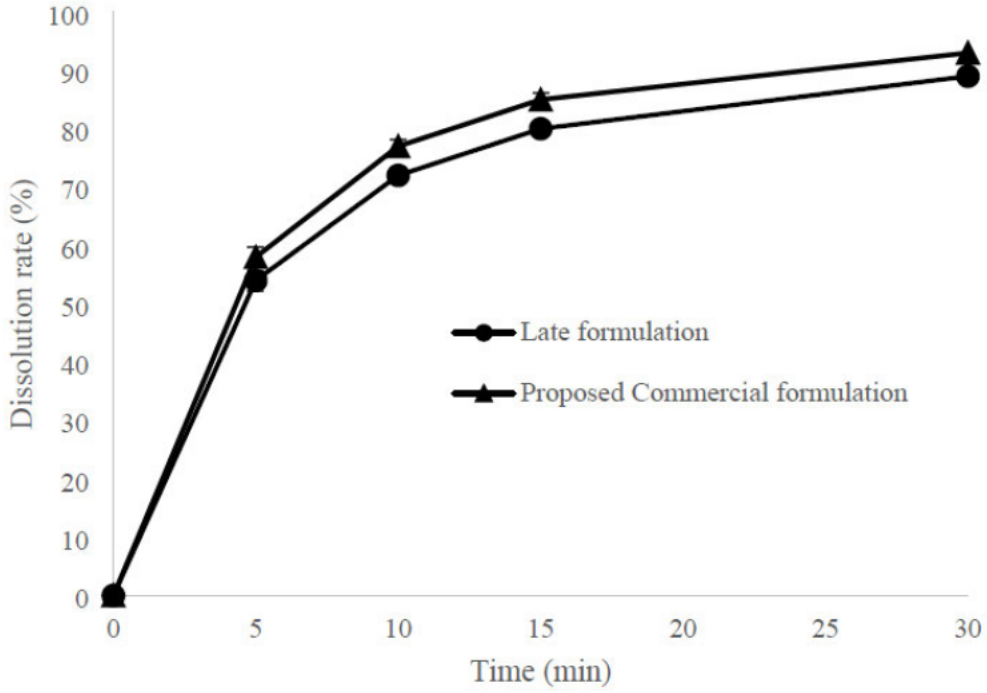
Abbreviations: hr = hours; (b) (4) (Early formulation); TAS-120 = futibatinib; tablet = film-coated tablet (Late formulation)
Note: Each plot and bar represent the mean and standard deviation, respectively (n=24 per treatment group).

Taiho - Mean Plasma Concentration-Time Profiles of Futibatinib After Administration of Late Formulation and Early Formulation

2) The bridging was performed between Late and Commercial formulations for 4 mg using PK study and dissolution profiles.

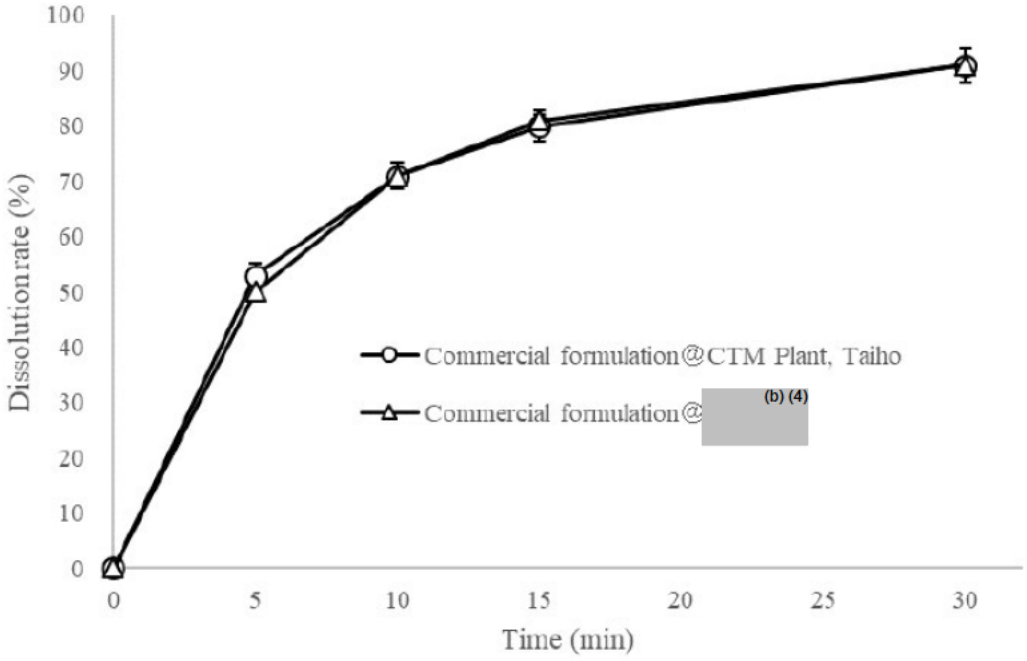
a) The bridging PK comparison is provided in Table 22 in Section 2.7.1. The values for C_{max}, $AUC_{0\text{-}inf}$, and t_{max} are comparable among the studies. These results demonstrated that the "Proposed Commercial formulation" and the "Late formulation" have equivalent biopharmaceutical properties, ensuring comparable in vivo exposure.

b) The comparison of dissolution profiles is provided below. The similarity factor (*f*2) between the formulations was 66. The dissolution data demonstrates that none of the changes described have impacted the release profile of the drug product.



Taiho - Dissolution Profiles of Futibatinib FCTs (Comparison of Late Formulation and Proposed Commercial Formulation) (N=12, Mean ± SD)

3) The bridging between Commercial formulations for 4 mg produced at Kitajima and (b) (4) sites was performed using a dissolution study. A comparison of the dissolution profiles is shown below. The similarity factor (*f*2) between the formulations was 97. The dissolution data demonstrates that the change in manufacturing site and debossing did not impact the release profile of the drug product.



Mean±SD (12 vessels), Apparatus 2 (paddle), 50 rpm

Taiho - Comparison of Dissolution Profiles of Futibatinib FCT Commercial Formulation 4 mg Manufactured at Taiho Kitajima and (b) (4)

In conclusion, bridging has been demonstrated between early, late and commercial formulations including changes in manufacturing site and process adequately.

Link: Section 3.2.P.2.2	Page#: 4 – 23
Link: Section 3.2.P.2.3	Page#: 4 – 47
Link: Section 2.7.1	Page#: 9 – 15, 44 – 49

The FDA's Assessment: ***Adequate***

The overall pharmacokinetics (PK) information and the comparative dissolution data profiles support the scientific bridging from Early Formulation, Late Formulation to Commercial Formulation. Imprinting/debossing of the final commercial formulation has no impact on drug product dissolution. No additional bridging studies are needed. Please see Biopharmaceutics review below for details.

d. BIOWAIVER REQUEST

The Applicant's Position:

The NDA does not contain a biowaiver request

[To the Applicant: Insert text here]
The FDA's Assessment: ***Adequate***

Biowaiver is not applicable/needed for this NDA.

e. DATA TO SUPPORT IVIVC AND/OR PBBM MODELING, IF APPLICABLE.

Not applicable. No IVIVC is claimed for this product; PBBM modeling has not been performed.

The FDA's Assessment: ***Adequate***

IVIVC/PBBM modeling are not applicable/submitted in this NDA.

BIOPHARMACEUTICS REVIEW

SUMMARY: Futibatinib (also known as TAS-120) is a potent and highly selective kinase inhibitor of fibroblast growth factor receptor (FGFR) 1-4, that irreversibly blocks FGF/FGFR signaling by its covalent mechanism of binding and decreases cell viability in cancer cell lines with FGFR alterations that results in constitutive FGFR activation, including FGFR fusions/rearrangements, amplifications or mutations.

The proposed drug product, Futibatinib Film-Coated Tablets (FCT), 4 mg, is an immediate-release solid dosage form, debossed with "4MG" on one side, and "FBN" on the other side, for oral administration for the treatment of patients with previously treated locally advanced or metastatic cholangiocarcinoma harboring FGFR2 gene rearrangements, including gene fusions. The recommended dose is 20 mg of futibatinib (five 4 mg tablets) taken orally once daily (QD) until disease progression or unacceptable toxicity occurs.

For the current NDA 214081, the Biopharmaceutics Review focuses on the evaluation of (1) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, (2) scientific bridging.

In Vitro Dissolution Testing: The following dissolution method and acceptance criterion have been reviewed and are acceptable as the QC test for the proposed drug product for batch release and stability testing:

USP Apparatus	Apparatus II Paddle
Rotation Speed	50 rpm
Medium	0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80
Volume	900 mL
Temperature	37°C
Acceptance Criteria	Q= (b) (4) % in 30 minutes

Scientific Bridging: The overall pharmacokinetics (PK) information and the comparative dissolution data profiles support the scientific bridging from Early Formulation, Late Formulation to Commercial Formulation. Imprinting/debossing of the final commercial formulation has no impact on drug product dissolution. No additional bridging studies are needed.

RECOMMENDATION: From the Biopharmaceutics perspective, NDA 214801-ORIG-1 for the proposed drug product, Futibatinib Film-Coated Tablets, 4 mg, is recommended for **APPROVAL.**

BIOPHARMACEUTICS REVIEW:

1. Drug Substance Solubility and Permeability

Per the Applicant, the drug substance, Futibatinib is a BCS Class 2 compound with low solubility and high permeability, as presented in Table 1 below.

Table 1: Biopharmaceutical Characteristics System of Futibatinib Drug Substance (*From Table 1 in M.2.7.1*)

Characteristics	**Results**
Highest dose administered:	20 mg
Solubility (37°C):	0.685 mg/mL; pH 1.2 0.011 mg/mL; pH 3.0 0.004 mg/mL; pH 4.5 0.003 mg/mL; pH 6.8
Dose solubility:	6667 mL (at pH 6.8 - lowest solubility) i.e. > 250 mL
BCS class:	Futibatinib is a low solubility compound Futibatinib is a high permeability compound Futibatinib is a BCS class 2 compound

2. In Vitro Dissolution Method

The proposed dissolution method and acceptance criterion are listed as below:

USP Apparatus	Apparatus II (Paddle)
Rotation Speed	50 rpm
Medium	0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80
Volume	900 mL
Temperature	37°C
Acceptance Criterion	Q= (b) (4)% in 30 minutes

(1) Selection of the Dissolution Medium

Note that the method development of an initial in vitro dissolution method [*USP Apparatus II (Paddle), 50 rpm, 900 mL of* (b) (4) *pH 6.8* (b) (4) *with 0.5% (w/v) polysorbate 80, 37°C*] was submitted in the IND 121062 amendment SDN-0210 dated 05/27/2020 and amendment SDN-0278 dated 06/30/2021. The Division of Biopharmaceutics reviewed the above two amendments on 10/02/2020[1] and 08/10/2021[2], respectively, and found the initial dissolution method was deemed appropriate. However, the Applicant proposed the current dissolution method [*USP Apparatus II (Paddle), 50 rpm, 900 mL of 0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80, 37°C*] and provided the complete dissolution method development and data in this NDA to support the currently proposed dissolution method.

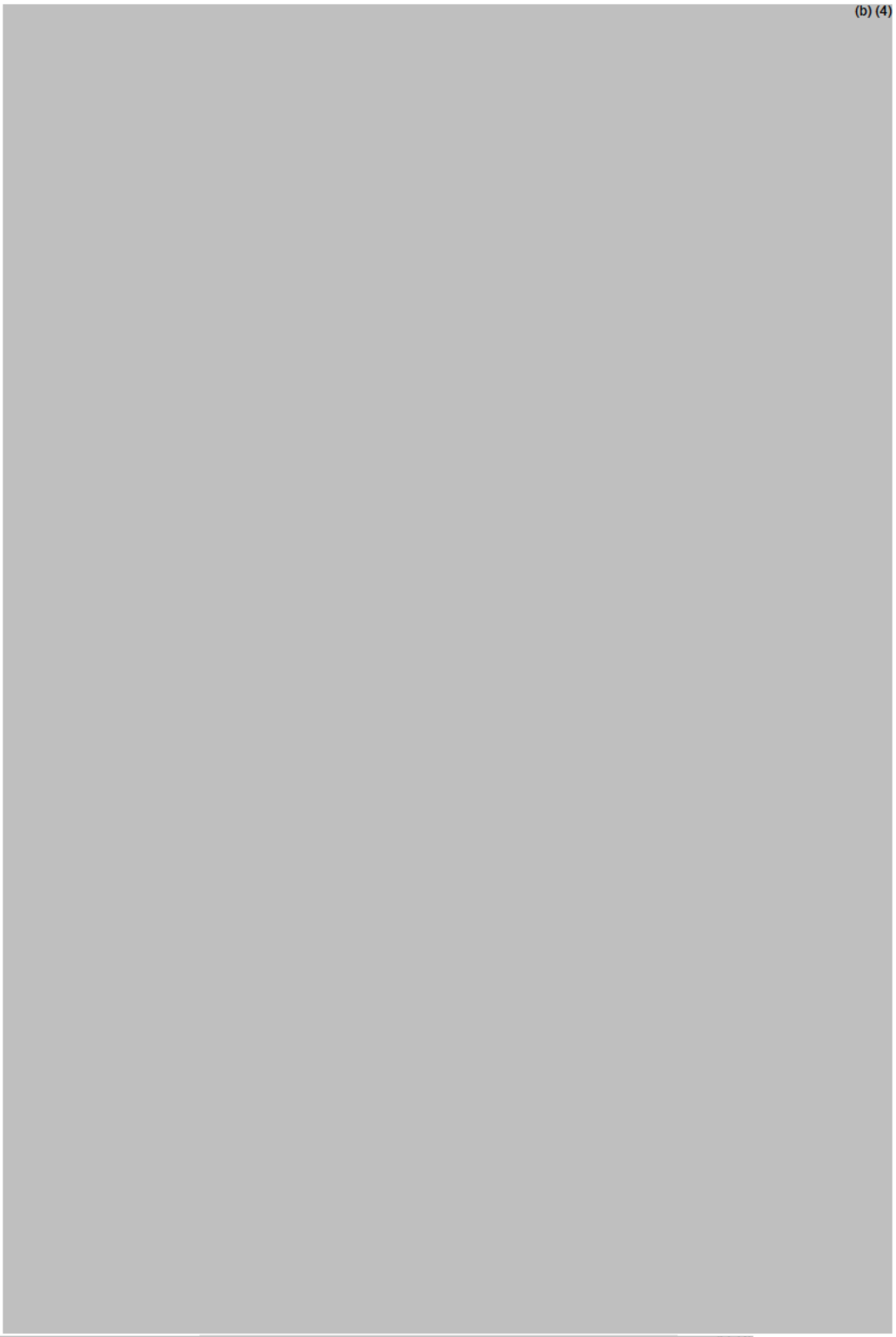
(b) (4)

[redacted]

[1] Biopharmaceutics Review for IND 121062 dated 10/02/2020: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8059d612&_afrRedirect=2745741656537800

[2] Biopharmaceutics Review for IND 121062 dated 08/10/2021: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8060a6bb&_afrRedirect=2745785576635002

(b) (4)



(b) (4)

From the data presented in Table 2 and Figure 5 below, 0.5% (w/v) polysorbate 80 in pH 6.8 medium was selected.

Table 2: Solubility and Sink Condition Factor of Futibatinib in pH 6.8 Phosphate Buffer with Various Surfactants (37°C)
(From Table 3.2.P.2.2-15 in M.3.2.P.2)

Solutions[a]	Surfactants	CMC (w/v%)	Concentration (w/v%)	Solubility (µg/mL)	Sink condition factor[b]
pH 6.8 Phosphate buffer	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Polysorbate 80		0.5	28.5	6.4

[a] 0.05M potassium dihydrogen phosphate buffer solution (b) (4) following the preparation method of "Simulated Intestinal Fluid" specified by the Pharmacopeias.
[b] Sink condition factor = solubility / [dose strength of futibatinib in futibatinib FCT, 4 mg (4) / volume of dissolution media (900)] / 1000

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's assessment:

(b) (4)

for the currently proposed dissolution method, the provided data and justification are considered to support the proposed dissolution medium as 0.05 M potassium dihydrogen phosphate pH 6.8 with 0.5% (w/v) polysorbate 80.

(2) Discriminating Ability of the Proposed Dissolution Method

The following potential critical material attributes (p-CMAs), potential critical process parameters (p-CPPs) and potential critical formulation variables (p-CFVs) that may affect dissolution (Table 3 below) were evaluated to assess the discriminating ability of the proposed dissolution method.

Table 3: List of p-CMAs, p-CPPs and p-CFV Evaluated to Confirm Discriminating Ability of Futibatinib FCT Dissolution Method
(*From Table 3.2.P.2.2-16 in M.3.2.P.2*)

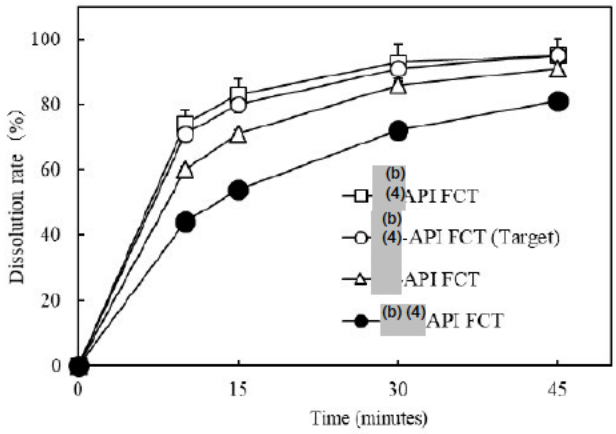
(b) (4)

(a) Discriminating ability regarding drug substance particle size distribution (DS PSD)

As the data information presented in Table 4 and Figure 7 below, the proposed dissolution method is considered to have acceptable discriminating ability with regards to DS PSD when API has (b) (4) particle size distribution. Note that the proposed DS PSD specification in M.3.2.S.4 is: d_{10}: NLT (b) (4) µm, d_{50}: (b) (4) µm, d_{90}: NMT (b) (4) µm.

Table 4: Information of PSD of API
(From Table 3.2.P.2.2-17 in M.3.2.P.2)

Figure 7: Dissolution Profile of Futibatinib FCT with Variations in PSD of API
(*From Figure 3.2.P.2.2-11 in M.3.2.P.2*)



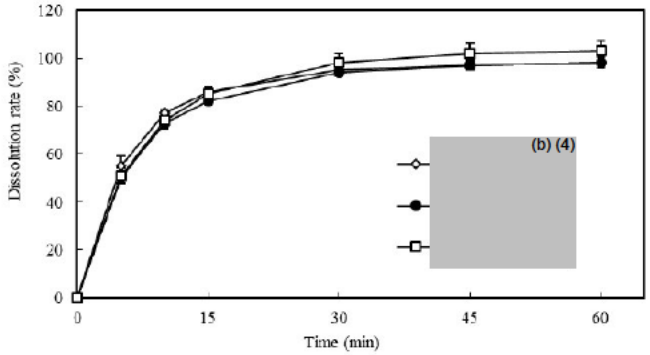
Mean±SD (12 vessels), Apparatus 2 (paddle), 50 rpm

(b) Discriminating ability regarding PSD of (b) (4)

The drug products were manufactured with (b) (4) having particle size distribution (PSD) as shown in Table 5 below. No difference in dissolution profile was observed (Figure 8 below).

(b) (4)

Figure 8: Dissolution Profile of Futibatinib FCT with Variations in PSD of (b) (4) (*From Figure 3.2.P.2.2-12 in M.3.2.P.2*)



Mean±SD (3 vessels), Apparatus 2 (paddle), 900 mL, 50 rpm, pH 6.8 Phosphate buffer with 0.5 w/v% polysorbate 80

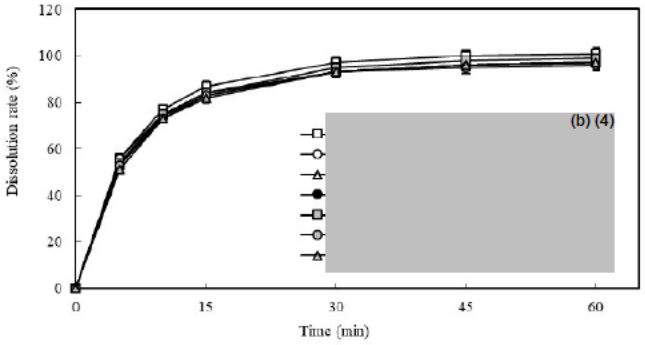
(c) Discriminating ability regarding variations for degree of (b) (4) and (b) (4)

As the data information presented in Table 6 and Figure 9 below, no difference in dissolution profiles was observed for the tablets with various (b) (4) and (b) (4)

(b) (4)

Figure 9: Dissolution Profile of Futibatinib FCT with Variations for (b) (4)

(*From Figure 3.2.P.2.2-13 in M.3.2.P.2*)

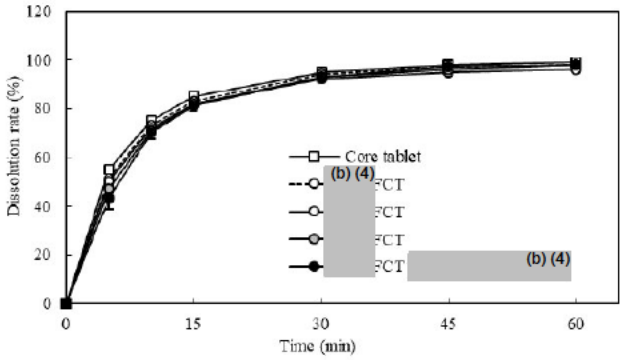


Mean±SD (3 vessels), Apparatus 2 (paddle), 900 mL, 50 rpm, pH 6.8 Phosphate buffer with 0.5 w/v% polysorbate 80

(d) Discriminating ability regarding variations for coating amount

From the results presented in Figure 10 below, no difference in dissolution profiles was observed for tablets with various coating amount from (b) (4)% to (b) (4)%. Note the target coating amount is (b) (4)%.

Figure 10: Dissolution Profile of Futibatinib FCT with Variations for Coating Amount
(*From Figure 3.2.P.2.2-14 in M.3.2.P.2*)



Mean±SD (3 vessels), Apparatus 2 (paddle), 900 mL, 50 rpm, pH 6.8 Phosphate buffer with 0.5 w/v% polysorbate 80

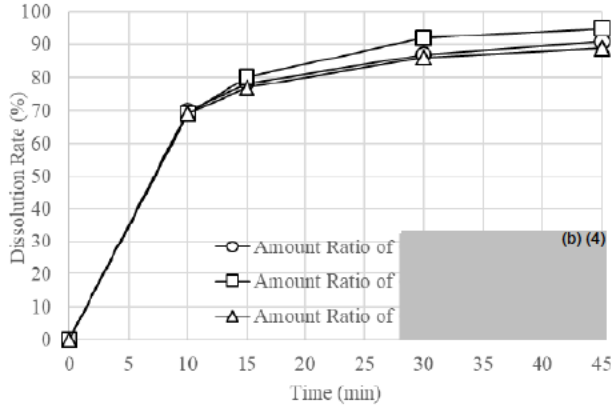
(e) Discriminating ability regarding variations in amount of (b) (4)

From the results presented in Table 7 and Figure 11 below, no difference in dissolution profiles was observed for tablets with different level of (b) (4) from low ((b) (4)%), target ((b) (4)%) to high ((b) (4)%).

Table 7: Tablet Properties Containing Varying Amounts of (b) (4)
(*From Table 3.2.P.2.1-17 in M.3.2.P.2*)

(b) (4)

Figure 11: Dissolution of Futibatinib FCT Containing Varying Amounts of (b) (4)
(*From Figure 3.2.P.2.1-8 in M.3.2.P.2*)



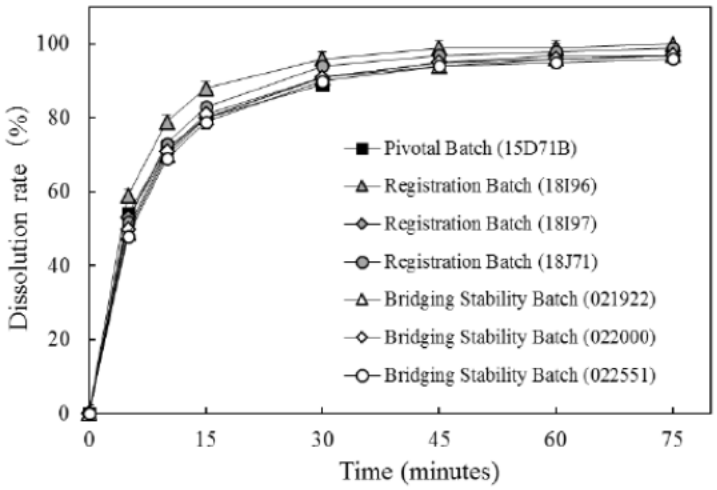
Reviewer's assessment:

Overall, the proposed dissolution method showed acceptable discriminating ability with regards to DS PSD when API has (b) (4) particle size distribution, however, other CMA/CPP/CFV parameters (e.g., (b) (4) did not affect drug product dissolution.

3. In Vitro Dissolution Data and Acceptance Criterion

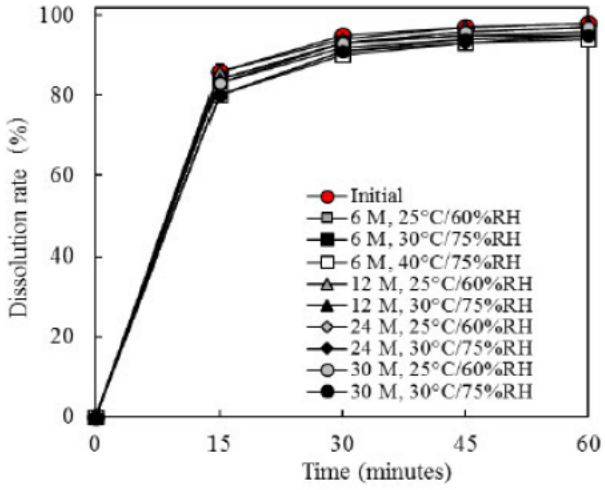
From the dissolution data profiles of a pivotal clinical batch (Lot 5D71B), three registration batches (Lot 18I96, 18I97 and 18J71), and three commercial batches (Lot 021922, 022000 and 022551) (Figure 12 below), the proposed dissolution acceptance criterion of "Q= (b) (4) % in 30 minutes" is acceptable.

Figure 12: The dissolution profiles of the proposed Futibatinib FCT, 4 mg, by using the proposed dissolution method (n=12)
(*From Figure 3.2.P.5.6-7 in M.3.2.P.5.6*)



The stability batches also showed consistent dissolution data under long-term stability conditions (25°C/60%RH and 30°C/75%RH) for up to 30 months with no trends being observed. The representative dissolution profile data of one registration batch (Lot 18I97) are presented in the following Figure 13 and Table 8.

Figure 13: The dissolution profiles of the proposed Futibatinib FCT Lot 18I97 in various stability conditions
(*From Figure 3.2.P.5.6-6 in M.3.2.P.5.6*)



Mean±SD (6 vessels)

Table 8: The dissolution data of the proposed Futibatinib FCT (Lot 18I97) in various stability conditions
(*From Table 3.2.P.5.6-15 in M.3.2.P.5.6*)

Storage Condition	Period	Dissolution Rate (%) [a]			
		15 min.	30 min.	45 min.	60 min.
40°C/75%RH	Initial	86±1.8	95±1.1	97±1.0	98±1.0
	3 months	82±0.8	91±0.6	94±0.5	95±0.5
	6 months	80±1.4	90±1.4	93±1.5	94±1.4
25°C/60%RH	Initial	86±1.8	95±1.1	97±1.0	98±1.0
	3 months	85±1.6	94±1.3	96±1.1	96±1.2
	6 months	84±1.8	93±1.9	95±1.9	95±2.1
	12 months	86±1.6	94±1.4	97±1.1	98±1.3
	24 months	83±0.7	92±0.9	94±1.0	95±1.0
	30 months	83±1.0	93±1.1	96±1.2	97±1.3
30°C/75%RH	Initial	86±1.8	95±1.1	97±1.0	98±1.0
	3 months	83±1.9	93±1.7	95±2.0	96±1.9
	6 months	84±0.7	93±0.8	95±0.8	96±1.0
	12 months	84±1.3	93±1.0	96±1.6	97±1.5
	24 months	80±1.3	91±1.0	93±0.9	95±1.0
	30 months	80±1.3	91±0.8	94±0.7	95±0.6

Apparatus: 2 (paddle), Paddle rotation Speed: 50 rpm, Dissolution medium: 0.05 M potassium dihydrogen phosphate, pH 6.8 with 0.5 w/v% polysorbate 80
[a] Dissolution rate (%) shows Mean± SD

Reviewer's assessment:
Overall, the proposed dissolution method [USP Apparatus II Paddle, 50 rpm, 900 mL of 0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80, 37°C] and the proposed acceptance criterion (Q= (b) (4) % in 30 minutes) are acceptable as a QC test for the proposed drug product, Futibatinib Film-Coated Tablets, 4 mg.
4. Scientific Bridging

The different formulations used in clinical trials are summarized in Figure 14 and Table 9 below. The bridging strategy is presented in Table 10. Note that there were three formulations in the pharmaceutical development, which were "Early Formulation" (b) (4) "Late Formulation" ((b) (4) (b) (4) and the proposed "Commercial Formulation" (Futibatinib FCT tablets).

Figure 14: Overview of Formulation Development
(*From Figure 3 in M.2.3.1*)

Table 9: Futibatinib formulation used in clinical trials included in this NDA
(*From Table 2 in M.2.7.1*)

Formulation (Strength)	Clinical use
Early formulation (4 mg and 20 mg)	**Phase 1/2:** TPU-TAS-120-101* Phase 1 Dose Escalation (QOD) part Phase 1 Dose Escalation (QD) part * This formulation was used for initiation of this study **Phase 1:** 10059010 Phase 1 Dose Escalation (QOD) part Phase 1 Dose Escalation (QD) part Phase 1 Expansion (QOD) part Phase 1 Expansion (QD) part **Phase 1:** 10059020
Late formulation (4 mg and 20 mg)	**Phase 1/2:** TPU-TAS-120-101 Phase 1 Dose Escalation (QOD) part Phase 1 Dose Escalation (QD) part Phase 1 Expansion (QD) part Phase 2 part **Phase 1:** 10059010 Phase 1 Dose Escalation (QOD) part Phase 1 Dose Escalation (QD) part Phase 1 Expansion (QOD) part Phase 1 Expansion (QD) part **Phase 1:** 10059020 **Phase 1:** TAS-120-102 **Phase 1:** TAS-120-103 **Phase 1:** TAS-120-104 **Phase 1:** TAS-120-105
Proposed Commercial formulation (4 mg)	**Phase 1:** TAS-120-107

Table 10: Schematics of futibatinib formulations used and bridging of the products (*From Table 3 in M.2.7.1*)

Stage (Study)	Formulation	Bridging Strategy	Bridging Data Shown in
Phase 1 DE (QD/QOD) part (Study TPU-TAS-120-101)	Early formulation (4 mg, 20 mg)		
	Late formulation (4 mg, 20 mg)		
Phase 1 Expansion (QD) part (Study TPU-TAS-120-101)	Late formulation (4 mg, 20 mg)		
PK Comparison (Study 10059020)	Early formulation (20 mg)	PK comparison	Section 2.7.1.3.1.1
	Late formulation (20 mg)	Dissolution	Section 2.7.1.3.1.2
Phase 2 (Study TPU-TAS-120-101)	Late formulation (4 mg)		
Phase 1 (Study 10059010)	Late formulation (4 mg)	PK comparison	Section 2.7.1.3.1.2
	Late formulation (20 mg)		
Registration stability study	Proposed Commercial formulation (4 mg)	Dissolution	Section 2.7.1.3.1.3
Phase 1 (Study TAS-120-102, 103, 104)	Late formulation (4 mg)	PK comparison	Section 2.7.1.3.1.3
Phase 1 (Study TAS-120-107)	Proposed Commercial formulation (4 mg)		

For all formulations, no process changes occurred during the studies.

The compositions of different formulations are presented in Table 11 and 12 below. The core composition between Late Formulation and Commercial Formulation are the same.

There are no changes of manufacturing process from Late Formulation to the Commercial Formulation.

Table 11: Composition of Early Formulation
(*From Table 4 in M.2.7.1*)

Components	4 mg	20 mg
	Quantity (mg) / Capsule	
Futibatinib	4	20
(b) (4)		

Table 12: Composition of Late Formulation and the Proposed Commercial Formulation
(*From Table 5 in M.2.7.1*)

Function	Components	Late formulation		Proposed Commercial formulation
		4 mg	20 mg	4 mg
		Quantity (mg) / Tablet		
Active ingredient	Futibatinib	4	20	4
(b) (4)	Sodium lauryl sulfate			(b) (4)
	Lactose monohydrate			
	Corn starch			
	(b) (4) mannitol			
	Microcrystalline cellulose			
	(b) (4) Hydroxypropyl cellulose			
	Crospovidone			
	Magnesium stearate			
(b) (4) Film-Coating	Hypromellose			
	Polyethylene glycol			
	Titanium dioxide			
	(b) (4)			
(b) (4)	Magnesium stearate			
Total for tablet (mg)			(b) (4)	82.4024

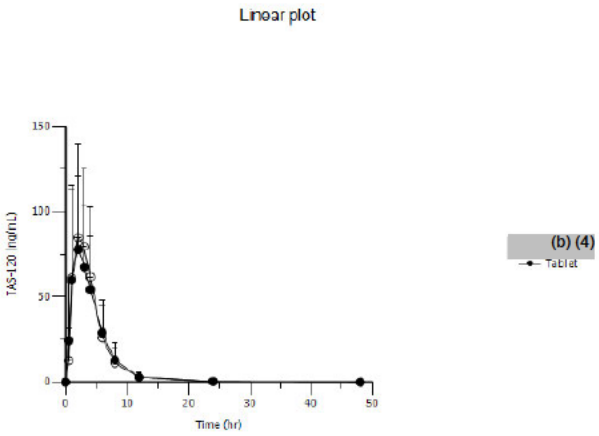
(1) From "Early Formulation" to "Late Formulation"

Pharmacokinetics (PK) information of Early Formulation ((b) (4) and Late Formulation (Tablet) were collected in the relative bioavailability (BA) study 10059020, titled as "*Phase 1, open-label, randomized, 2-period, 2-sequence, 2 single-dose, crossover study to evaluate the PK of 2 oral formulations and safety of futibatinib in healthy male subjects*".

Reviewer's assessment:

The final data assessment will defer to the Office of Clinical Pharmacology (OCP). On face, the Early Formulation ((b) (4) and Late Formulation (Tablets) showed bioequivalence (BE) with respect to the Cmax and AUC within 80-125% 90% CI (Figure 15, Table 13 and 14 below). The scientific bridging between the Early Formulation ((b) (4) and the Late Formulation (Tablets) is considered being established.

Figure 15: Mean Plasma Concentration-Time Profiles of Futibatinib after Administration of Late Formulation and Early Formulation (Study 10059020)
(*From Figure 1 in M.2.7.1*)



Abbreviations: hr = hours; (b) (4) (Early formulation); TAS-120 = futibatinib; tablet = film-coated tablet (Late formulation)
Note: Each plot and bar represent the mean and standard deviation, respectively (n=24 per treatment group).
Source: Figure 1 (Study report 15DA25)

Table 13: Pharmacokinetic Parameters of Futibatinib after Administration of Early Formulation and Late Formulation (Study 10059020)
(*From Table 15 in M.2.7.1*)

Formulation	Descriptive statistics	kel (1/hr)	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-48} (ng*hr/mL)	AUC_{inf} (ng*hr/mL)	Vz/F (L)	CL/F (L/hr)	MRT (hr)
Early formulation	N	24	24	24	24	24	24	24	24	24
	Arithmetic mean	0.364	2.28	2.00* (1.00, 4.00)	106.3	424	419	195.8	67.7	3.97
	SD	0.144	1.05		50.0	248	245	117.0	42.8	0.94
	CV (%)	39.5	46.2		47.1	58.3	58.4	59.8	63.2	23.8
	gMean	0.334	2.07		95.3	358	354	169.2	56.6	3.86
	gCV (%)	45.9	45.9		52.2	67.4	67.3	59.1	67.3	24.5
Late formulation	N	22	22	24	24	24	22	22	22	22
	Arithmetic mean	0.405	2.22	2.00* (1.00, 6.00)	102.6	412	428	154.0	53.5	4.08
	SD	0.182	1.33		38.1	166	149	78.9	21.5	1.59
	CV (%)	44.9	60.1		37.1	40.2	34.8	51.3	40.2	38.9
	gMean	0.360	1.92		94.4	376	401	138.3	49.8	3.78
	gCV (%)	56.2	56.2		47.9	48.8	39.4	48.5	39.4	42.4

Abbreviations: AUC_{0-48} = area under the plasma concentration-time curve from time 0 to 48 hours; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; CL/F = oral clearance; C_{max} = maximum plasma concentration; CV = coefficient of variation; gCV = geometric CV; gMean = geometric mean; hr = hours; kel = terminal elimination rate constant; MRT = mean residence time; N = number of observation; SD = standard deviation; $T_{1/2}$ = terminal phase elimination half-life; T_{max} = time to reach maximum plasma concentration; Vz/F = apparent volume of distribution
Note: Asterisks indicate the medians with minimum-maximum ranges in parentheses.
Source: Table 4 and Table 5 (Study report 15DA25)

Table 14: Geometric Mean Ratios (Late Formulation/Early Formulation) and the 90% Confidence Intervals for Pharmacokinetic Parameters of Futibatinib (Study 10059020)

(From Table 16 in M.2.7.1)

PK parameters	GMRs	90% CIs	
		Lower	Upper
C_{max}	0.991	0.834	1.177
AUC_{0-48}	1.050	0.939	1.175
AUC_{inf}	1.093	0.973	1.228

Abbreviations: AUC_{0-48} = area under the plasma concentration-time curve from time 0 to 48 hours; AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; CI = confidence interval; C_{max} = maximum plasma concentration; GMR = geometric mean ratio; PK = pharmacokinetic
Source: Table 8 (Study report 15DA25)

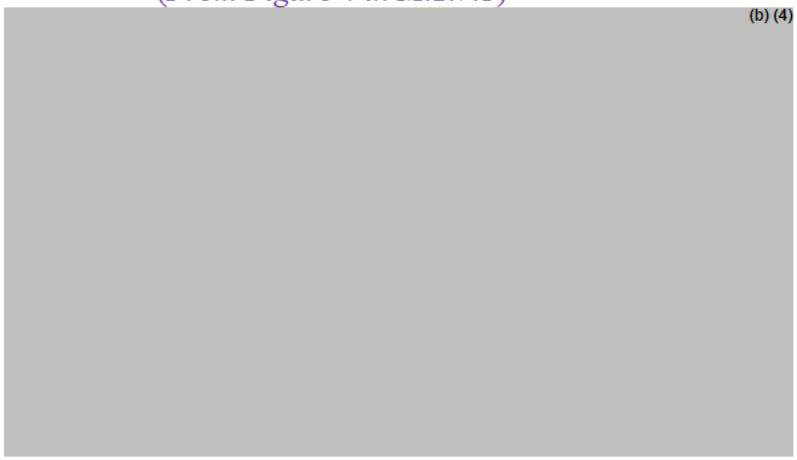
(2) Between "Late Formulation" 4 mg and 20 mg

PK information of the Late Formulation (Tablet) 4 mg and 20 mg were collected in the Dose Escalation Study 10059010, titled as "*Phase 1, Open-Label, Non-Randomized, Dose-Escalating, Safety, Tolerability, Pharmacokinetic, Pharmacodynamic and Efficacy Study of TAS-120 in Patients with Advanced Solid Tumors*". As the reported data, C_{max}/D for 20 mg and 4 mg is 10.2±3.5 and 13.3±7.1, respectively. AUC_{inf}/D for 20 mg and 4 mg is 69.5±25.3 and 53.5±31.6, respectively. T_{max} for 20 mg and 4 mg is 1.98 [0.52-4.07] hr and 1.98 [0.95-3.95] hr, respectively. The dose-normalization of C_{max} and AUC_{inf} was justified by dose proportionality in dose range from 8 mg to 160 mg.

Comparative dissolution testing was conducted between Late Formulation (Tablet) 4 mg and 20 mg by using the dissolution method: (b) (4)

ate Formulation (Tablet) 4 mg and 20 mg showed comparative dissolution profiles as presented in Figure 16.

Figure 16: Comparative Dissolution Profiles of Futibatinib FCTs (Late Formulation 4 mg and 20 mg) (N=6, Mean ± SD)
(From Figure 4 in M.2.7.1)



Reviewer's assessment:
Although the dissolution method used for comparing Late Formulation 4 mg and 20 mg was different from the proposed dissolution QC method, the Late Formulation 4 mg and 20 mg showed comparative dissolution profiles by using the same method. In addition, the PK information of Late Formulation (Tablet) 4 mg and 20 mg was collected and

deemed accepted by OCP, the scientific bridging between the Late Formulation (Tablet) 4 mg and 20 mg is considered being established.

(3) From "Late Formulation" to the proposed "Commercial Formulation"

The changes from the "Late Formulation" to the "Commercial Formulation" include: a) (b) (4)

Table 15: Summary of Changes to Commercial Formulation
(*From Table 3.2.P.2.2-8 in M.3.2.P.2*)

Tablet Formulation	Site	Formulation Change	Debossing	Equivalency established		Reference
				With	Method	
Late	Tokushima	N/A	N/A	Early	PK study	Module 2.7.1.3.1.1
Commercial	Kitajima	(b) (4)	No	Late	In vitro dissolution	Table 3.2.P.2.2-10
Commercial	(b) (4)	No	Yes	Commercial, Kitajima	In vitro dissolution	Table 3.2.P.2.2-12

PK information of Late Formulation was collected from clinical studies TAS-120-102 (a Phase 1, Food Effect Study), TAS-120-103 (a Phase 1, Drug-Drug Interaction study), and TAS-120-104 [a Phase 1, Drug Interaction with a Proton Pump Inhibitor (PPI) study)]. PK information of Commercial Formulation was collected from clinical study TAS-120-107 (a Phase 1, Thorough TQT study). As data presented in Table 16 below, C_{max}, AUC_{0-inf}, and T_{max} are deemed considered comparable among the studies per OCP.

Table 16: Plasma PK Parameters of TAS-120 Following Single Oral Administration of TAS-120 at 20 mg on Empty Stomach to Healthy Volunteers
(*From Table 22 in M.2.7.1*)

Study	Population	Formulation (# of Units)	N	Cmax (ng/mL) gMean	Cmax (ng/mL) gCV%	AUC0-inf (ng*hr/mL) gMean	AUC0-inf (ng*hr/mL) gCV%	Tmax (hr) Median	Tmax (hr) Range
TAS-120-102	Healthy volunteers	Late formulation (5 × 4 mg)	16	154.6	35.3	625.7	40.4	1.0	1.0-3.0
TAS-120-103	Healthy volunteers	Late formulation (5 × 4 mg)	20	222.4	44.9	954.9	36.0	1.336	0.66-6.01
TAS-120-104	Healthy volunteers	Late formulation (5 × 4 mg)	20	216.1	51.6	941.6	59.3	1.680	0.67-3.09
TAS-120-107	Healthy volunteers	Proposed Commercial formulation (5 × 4 mg)	45	165.2	52.3	713.5	68.2	1.538	0.69-4.01

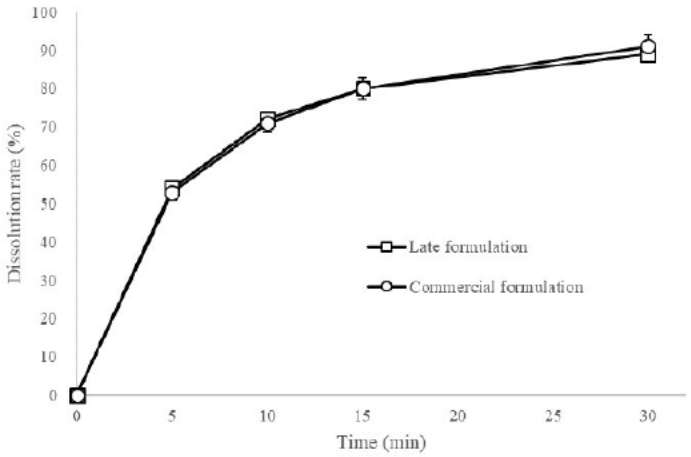
Abbreviations: AUC_{inf} = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum plasma concentration; gCV = geometric coefficient of variation; gMean = geometric mean; N = number of observation; TAS-120 = Futibatinib; T_{max} = time to reach maximum plasma concentration; PK = pharmacokinetic(s)
Source: Study TAS-120-102, Table 14.2.2; Study TAS-120-103, Table 11-5; Study TAS-120-104, Table 11-2; Study TAS-120-107, Table 11-8

Comparative dissolution test between the Late Formulation (Lot 15D71B) and the Commercial Formulation (Lot 18I97) was conducted by using the proposed dissolution method [USP Apparatus II Paddle, 50 rpm, 900 mL of 0.05 M potassium dihydrogen phosphate buffer pH 6.8 with 0.5% (w/v) polysorbate 80, 37°C] (Table 17 below). As the profiles presented in Figure 17 below, Late Formulation and Commercial Formulation have comparable dissolution by using the same dissolution method.

Table 17: Batch Information for Futibatinib Batches Used in Comparative Dissolution Study (Late Formulation vs Commercial Formulation)
(*From Table 3.2.P.2.2-9 in M.3.2.P.2*)

	Lot Number	15D71B (Late Formulation)	18I97 (Commercial Formulation)
Drug Product	Manufacturing site	Clinical Manufacturing Facility, Taiho in Tokushima	CTM Plant, Taiho in Kitajima
	Strength	4 mg	4 mg
	Batch Size	(b) (4)	
Drug Substance	**Lot Number**	**KMBH491**	**180410**
	Manufacturer	(b) (4)	Taiho
	PSD		(b) (4)

Figure 17: Comparative Dissolution Profiles between Late Formulation and Commercial Formulation of Futibatinib FCT
(*From Figure 3.2.P.2.2-2 in M.3.2.P.2*)



Mean±SD (12 vessels), Apparatus 2 (paddle), 50 rpm

Reviewer's assessment:

Both the PK information and the comparative dissolution data profile support that the scientific bridging between the Late Formulation and the Commercial Formulation has been established.

(4) Imprinting of the Commercial Formulation

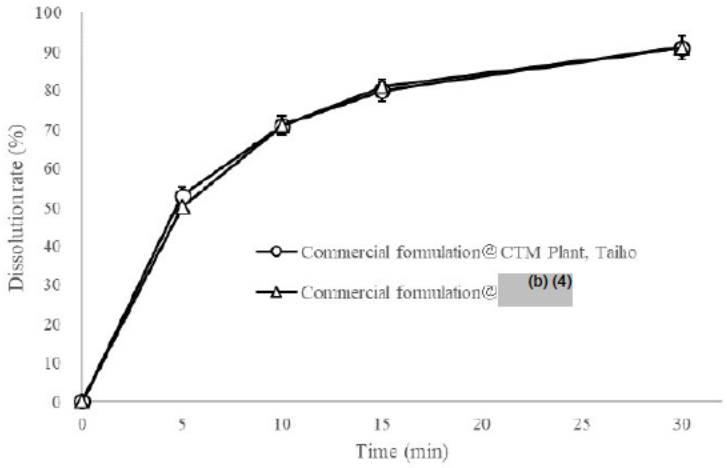
The final commercial formulation was debossed with "FBN" on one side and dose strength "4MG" on the other side of the tablets, during the manufacture of bridging stability batches at the commercial production site at (b) (4) (Table 18 below). Other than the debossing/imprinting, there were no other changes between the registration stability batches and commercial batches.

Table 18: Manufacturing details for registrational stability and commercial / bridging stability batches
(*From Table 3.2.P.2.2-11 in M.3.2.P.2*)

Use	Registrational stability	Bridging Stability (with Imprinting) / Commercial
Manufacturing Site	CTM Plant, Kitajima, Taiho	(b) (4)
Batch Size	(b) (4)	
Lot Numbers	18I96, 18I97, 18J71	021922, 022000, 022551
Manufacturing Process	The flow diagram of the manufacturing process is provided in Section 3.2.P.3.3.1. The manufacturing process between the two sites is same and equipment are comparable (Section 3.2.P.2.3).	

Comparative dissolution test between the registration/stability batch (Lot 18I97, without debossing) and the commercial batch (Lot 022000, with debossing) was conducted by using the proposed dissolution method. As the dissolution data profiles presented in the Figure 18 below, these two batches showed comparative dissolution profiles.

Figure 18: Comparative Dissolution Profiles of Futibatinib FCT Commercial Formulation Manufactured at Taiho (Lot 18I97) and (b) (4) (Lot 022000)
(*From Figure 3.2.P.2.2-3 in M.3.2.P.2*)



Mean±SD (12 vessels), Apparatus 2 (paddle), 50 rpm

Reviewer's assessment:
The debossing/imprinting has no impact on the drug product dissolution.

9. LABELING

[FDA will complete this section.]

USPI

Highlights: ***Adequate***

Adequate information is provided in the Highlights section, i.e., "Dosage Forms and Strength: Tablets: 4 mg"

Section 2 (if relevant): ***Adequate***

The following relevant information is provided in 2.2 Recommended Dosage: The recommended dosage of TRADENAME is 20 mg (five 4 mg tablets) taken orally once daily until disease progression or unacceptable toxicity occurs.

Section 3 Dosage Forms and Strengths: ***Adequate***

The following relevant information is provided in 3 Dosage Forms and Strengths: "Tablets: 4 mg: round, white, film-coated tablets debossed with "4MG" on one side, and "FBN" on the other side."

Section 11 Description: ***Adequate***

If the following excipients used in the drug product, include warning/declaration in the USPI:

(b) (4)

Adequate information is provided in the Description section. It contains chemical name and structure, molecular weight and formula, physicochemical properties and qualitative composition of the drug product.

Section 16 How Supplied/Storage and Handling: ***Adequate***

Adequate information is provided in the section 16. It includes tablet description, NDC numbers for various product presentations and storage conditions, that reads: "Store LYTGOBI tablets at room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F to 86°F) See USP Controlled Room Temperature."

Manufacturer Information (Name and Address): ***Provided: Adequate***

The applicant provided its own name under "Manufactured for" and the distributor's names and address under "Distributed by". This is acceptable.

Carton/Container Label ***Adequate***

FINAL RISK ASSESSMENTS

[FDA will complete this section.]
To the Review Team: *Keep the appropriate Table; delete the rest*

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Medium	(b) (4)	Low	
(b) (4)				(b) (4)	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Low		Low	
Dissolution – BCS Class II & IV	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Medium		Low	

RECOMMENDATION PAGE

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Raymond Frankewich, Ph.D. Date: July 8, 2022
Secondary Reviewer: Haripada Sarker, Ph.D. Date: July 11, 2022

Drug Product: Approval

Primary Reviewer: Xiao Hong Chen, Ph.D. Date: July 8, 2022
Secondary Reviewer: Xing Wang, Ph.D. Date: July 8, 2022

Process and Facility: Approval

Primary Reviewer: Sridhar Thumma, Ph.D. Date: May 25, 2022
Secondary Reviewer: Zhaoyang Meng, Ph.D. Date: May 25, 2022

Biopharmaceutics: Approval

Primary Reviewer: Mei Ou, Ph.D. Date: May 4, 2022
Secondary Reviewer: Mei Ou, Ph.D. Date: May 4, 2022

Application Technical Lead: Approval

Xing Wang, Ph.D. Date: July 11, 2022

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XING WANG
07/13/2022 12:25:24 PM

RAYMOND P FRANKEWICH
07/13/2022 01:01:35 PM

HARIPADA SARKER
07/13/2022 01:23:13 PM
DS review

XIAOHONG CHEN
07/13/2022 01:36:48 PM

SRIDHAR N THUMMA
07/13/2022 01:49:37 PM

ZHAOYANG MENG
07/13/2022 01:52:39 PM

MEI OU
07/13/2022 01:55:22 PM

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XING WANG
07/11/2022 10:51:45 AM