

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213411Orig1s000**

**PRODUCT QUALITY REVIEW(S)**



NDA-OPQ Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

All FDA assessment is indicated in blue colored fonts

Drug Substance Retest Period: (b) (4) Months at (b) (4)

FDA Assessment: Adequate.

Drug Product Intermediate Retest Period: (b) (4)

FDA Assessment: Granted

Drug Product Expiration Dating Period: 24 Months at Controlled Room Temperature 20–25°C (68–77°F)

FDA Assessment: Granted

NDA 213411

Review # 1

Table with 2 columns: Drug Name/Dosage Form, Strength, Route of Administration, Rx/OTC Dispensed, Indication, Applicant, US agent, if applicable. Row 1: Tucatinib Tablets, 50 mg and 150 mg, Oral, Rx, Tucatinib in combination with trastuzumab and capecitabine is indicated for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received at least 3 prior HER2-directed agents separately or in combination, in the neoadjuvant, adjuvant, or metastatic setting., Seattle Genetics, Inc., Not applicable.

[FDA will complete these sections.]

<b>Submit Date(s)</b>	12/20/2019
<b>Received Date(s)</b>	12/20/2019
<b>PDUFA Goal Date</b>	08/20/2020
<b>Division/Office</b>	Division of Oncology I/Office of Oncologic Diseases
<b>Review Completion Date</b>	04/16/2020
<b>Established Name</b>	Tucatinib tablets
<b>(Proposed) Trade Name</b>	Tukysa
<b>Pharmacologic Class</b>	Reversible HER2-targeted small molecule tyrosine kinase inhibitor (TKI)
<b>Recommendation on Regulatory Action</b>	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Pre-Submission 0001	11/11/2019	Facility
Quality Response to IR 0005	12/05/2019	Facility
Original NDA 0012	12/20/2019	DS, DP, Manufacturing, Biopharm.
Quality Amendment 0016	01/16/2020	Process and Facility
Quality Amendment 0019	01/24/2020	Process and Facility
Quality Amendment 0025	02/13/2020	Facility
Quality Amendment 0031	02/28/2020	Process, Label
Quality Amendment 0037	03/11/2020	DP
Quality Amendment 0039	03/17/2020	Process
Quality Amendment 0041	03/23/2020	DP, Process
Quality Amendment 0049	03/31/2020	Response to Swissmedic IR
Quality Amendment 0056	04/16/2020	DP, Process

**Quality Review Team**

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Ali Al-Hakim
Drug Product	Rajiv Agarwal	Anamitro Banerjee
Process and Facility	Feiyan Jin, Haitao Li	Steve Rhieu
Microbiology	N/A	
Biopharmaceutics	Mei Ou	Banu Zolnik
Regulatory Business Process Manager	Kristine Leahy	
Application Technical Lead	Xiao Hong Chen	
ORA Lead	Ashar P Parikh	
Environmental	Rajiv Agarwal	Anamitro Banerjee

*ORBIS Partner Agency Quality Review Team*

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
Health Canada Drug Substance Drug Product		
HAS Singapore		
TGA Australia		
Swissmedic		

**RELATED/SUPPORTING DOCUMENTS**

**DMFs:**

				[FDA will complete]	
DMF #	Type	Holder	Item Referenced	Status	Comments
(b) (4)	III		(b) (4)	Active	*See the footnote
	III			Active	*See the footnote
	III			Active	*See the footnote

*\*Citation of the CFR reference for direct food contact is considered sufficient as per MaPP 5015.5*

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	78304	The development of tucatinib was initiated under IND 78304 with the first-in-human protocol ARRAY-380-101 in 2007, and all CMC and nonclinical information are included in this IND.
IND	119421	IND 119421 was opened in 2013 and clinical development in HER2-positive breast cancer proceeded under this IND, with reference to IND 078304 for CMC, nonclinical and historical clinical information.

**CONSULTS**

None

## Evaluation of the Quality Information

### 1 EXECUTIVE SUMMARY

The applicant submits a 505b(1) NDA for immediate release Tucatinib tablets to seek regular approval of Tucatinib tablets. Tucatinib is a reversible HER2-targeted tyrosine kinase inhibitor, and it is developed as a combination therapy with trastuzumab and capecitabine for the treatment of patients with locally advanced unresectable or metastatic HER2+ breast cancer, including patients with brain metastases. The IND (78304 and 119421) that the NDA originated from received fast track and breakthrough designation and orphan status. The clinical benefit for the proposed drug is based on efficacy and safety data from a single randomized (2:1), double-blind, placebo-controlled clinical trial (HER2CLIMB) in 612 patients with advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have received prior trastuzumab, pertuzumab, and T-DM1. Patients were randomized to either tucatinib or placebo, with trastuzumab and capecitabine. The trial demonstrated statistically significant and clinically meaningful improvements in the primary efficacy outcome of progression-free survival (PFS) and the key secondary outcome of overall survival. The NDA is submitted in the RTOR and ORBIS programs.

The drug substance (DS) is manufactured in a (b) (4). The applicant reported that a process impurity, (b) (4). The applicant conducted a toxicology study to qualify this impurity up to (b) (4)%, which has been reviewed by the nonclinical reviewer and found acceptable. The DS has demonstrated acceptable physicochemical stability under (b) (4) month retest date.

To improve (b) (4). The proposed dissolution method showed acceptable discriminating ability with regards to material variables (e.g., tablet hardness). However, the method is not discriminating (b) (4). The DP displays fairly stable physicochemical stability. Based on stability data, the proposed 24 month expiry for the DP stored under the long term conditions (20-25°C) is deemed acceptable. The FDA agreed that the DP manufacturing (b) (4).

The applicant proposed concurrent release of the PPQ batches prior to the NDA submission. In addition, the applicant proposed to release registration batches due to the unavailability of the commercial supply upon NDA approval at anticipated early action date of April 17, 2020. Product quality team has reviewed and discussed this approach

(concurrent release and release of registration batches for initial commercial distribution) in an internal meeting and in a teleconference with the applicant on April 1, 2020 (refer to the meeting memo in Panorama). With the clinical input on the importance of drug availability upon approval and taking the benefit/risk into consideration, the product quality team found the approach acceptable based on the review of totality data. The NDA submission includes a comparability protocol for [REDACTED] (b) (4). The input from the OLDP branch on the comparability protocol has been sought, and the proposed approach is deemed acceptable.

## 2 APPLICATION BACKGROUND

**Table 1: Application background**

Reference	Date	Designation	Comment
IND 119421 (Ref ID 3950721)	24Jun2016	Fast Track designation	Fast Track designation granted for the treatment of advanced HER2+ metastatic breast cancer
File No. 16-5707	05Jun2017	Orphan Drug Designation (ODD)	ODD granted for the treatment of breast cancer patients with brain metastases
IND 119421 (Ref ID 4534656)	18Dec2019	Breakthrough Therapy Designation (BTD)	BTD granted for tucatinib, in combination with trastuzumab and capecitabine, for treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases, who have been treated with trastuzumab, pertuzumab, and T-DM1

### 3 SUMMARY OF CMC SPECIFIC PRESUBMISSION/SUBMISSION REGULATORY ACTIVITY

The Applicant's Position:

The development of tucatinib in subjects with advanced cancer was initiated by Array BioPharma, Inc. under investigational new drug (IND) 78304 in 2007. In 2013, tucatinib was licensed to Cascadian Therapeutics, Inc. (Cascadian; formerly Oncothyreon, Inc.), and clinical development in HER2+ BC continued under IND 119421. After Seattle Genetics' acquisition of Cascadian, sponsorship of both INDs was transferred on 28 Sep 2018. A list of relevant regulatory CMC history is provided in Table 2 for IND 78304, Table 3 for IND 119421, and Table 4 for NDA 213411.

**Table 2: Summary of regulatory CMC history for IND 78304**

Date	Description	Reference
24 Jul 2007	Study May Proceed	Reference ID 4063834
06 Oct 2011	Introduction of new drug substance (DS) supplier (b) (4) Introduction of new tucatinib drug product (DP) formulation (tablets) manufactured by (b) (4)	SN0025
16 Sep 2013	Updates to (b) (4) (150 mg tablets)	SN0032
15 Aug 2014	Updates to (b) (4) (50 mg tablets)	SN0035
12 Jan 2017	Introduction of the following new manufacturing sites: <ul style="list-style-type: none"> <li>• DS: (b) (4)</li> <li>• (b) (4)</li> <li>• DP (tucatinib and placebo tablets): (b) (4)</li> </ul>	SN0045
07 Jul 2017	Introduction of (b) (4) for the manufacture of DS	SN0046
25 Oct 2017	Type C CMC Meeting to discuss definition of starting materials, suitability of proposed specifications and overall quality development plans to support an NDA. <b>Starting materials</b> The Agency indicated that (b) (4) in selecting the starting materials would ensure acceptability of starting materials at the time of the NDA. <b>Specifications</b> The Agency provided advice on the proposed DS specifications. The dissolution test for primary stability testing and commercial product was presented, and the Agency accepted the proposed plan to conduct further studies to support the method. The CMC reviewers agreed that mutagenic impurities will be controlled under ICH S9 pending confirmation by the clinical/nonclinical division under IND 119421. The clinical division confirmed and recommended the Sponsor follow ICH S9 for nonclinical development on 06 December 2017 via email.	Meeting Request: SN0048  Meeting Materials: SN0049  Meeting Minutes: Reference ID 4184952
13 Apr 2018	Updates to analytical methods and updated stability data for DS (b) (4) DP and placebo tablets	SN0050
28 Sep 2018	Updated stability data for DS, (b) (4) DP and placebo tablets, and introduction of a new reference standard	SN0053
18 Jun 2019	Updated the description of DP and placebo tablets to register debossed tablets, updated the DS, DP and placebo specification and justification of specification, and addition of new packaging and labeling sites for DP and placebo tablets.	SN0056
27 Sep 2019	Updates to DP specifications and justification of specifications and to available stability data for DS, (b) (4) DP (active and placebo).	SN0058

**Table 3: Summary of regulatory CMC history for IND 119421**

Date	Description	Reference
18 Oct 2013	Study May Proceed	Reference ID 3392509
25 Feb 2019	<p>Type B Pre-NDA Content/Format meeting to discuss DP process performance qualification and DP stability data for expiration dating to support NDA.</p> <p><b>Process performance qualification</b> The Agency stated that process validation protocols and reports are not approved during application review. The actual protocols, acceptance criteria, study outcomes, and supportive information will be evaluated during an inspection of the manufacturing site.</p> <p><b>Stability</b> The Agency stated that the stability data obtained from the clinical batches will be considered as supportive stability batch data and will be used to help assign the expiration dating period. The Agency also stated that the sponsor may submit 9 months and the 12 months stability data during NDA review as they become available.</p>	<p>Meeting Request: SN0142</p> <p>Meeting Materials: SN0148</p> <p>Meeting Minutes: Reference ID 4398497</p>
22 Nov 2019	<p>Type B CMC Pre-NDA meeting to seek feedback on a proposal to conduct concurrent validation of DP, (b) (4) and a proposal to include a post-approval change protocol in the NDA for (b) (4)</p> <p><b>Concurrent validation</b> The Agency agreed to the proposed concurrent release of the process performance qualification (PPQ) batches given that all DP PPQ batches are manufactured after the API manufacturing process is successfully validated. The Agency also recommended to use the newly validated (b) (4) method for all testing to be conducted in the DS and DP process validations and commercialization. Upon further correspondence, the Agency stated that the proposed control strategy to monitor this impurity (b) (4) appears acceptable if the Sponsor can demonstrate that (b) (4)</p> <p><b>Post approval change protocol</b> The Agency agreed to the Sponsor's approach to submit a post approval change protocol to (b) (4) and recommended to submit a CBE-30 supplement for the proposed change.</p>	<p>Meeting Request: SN0244</p> <p>Meeting Materials: SN0251</p> <p>Preliminary &amp; Final Meeting Minutes Reference ID 4521463</p>

**Table 4: Summary of regulatory CMC communication for NDA 213411**

Date	Description	Reference
06 Dec 2019	A teleconference was held to discuss CMC manufacturing timelines for drug availability in relation to tucatinib NDA review and action date. The Sponsor provided options to move in drug availability timing including the use of registration batches.	Not available
17 Dec 2019	The Agency provided feedback that the proposal to utilize the DP from registration batches for a short period until the DP from concurrent validation of (b) (4) is available may be acceptable and the acceptability of this approach will be taken at the time of NDA review based on the data available in the submission.	SN0009

DP=drug product; PPQ=process performance qualification

The FDA’s Assessment:

The summary is consistent with FDA’s records.

**4 ENVIRONMENTAL ASSESSMENT**

The Applicant’s Position:

Seattle Genetics is requesting a categorical exclusion for tucatinib in accordance with 21CFR § 25.31(b), Environment Impact Considerations.

The estimated concentration of tucatinib at the point of entry into the aquatic environment was calculated using the equation provided in FDA Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications, 1998.

The estimated highest quantity of tucatinib (as active moiety) expected to be produced for direct use in any of the next five years is (b) (4) kg/year.

Therefore, the total amount of the active moiety introduced in the aquatic environment (EIC) as a result of maximum use of this product is estimated at (b) (4) ppb and is well below the allowable EIC of 1 ppb per 21 CFR §25.31(b)

Seattle Genetics is not aware of any extraordinary circumstances that exist with the use of this product that would warrant the preparation of an environmental assessment per 21 CFR §25.15(d).

The FDA’s Assessment: **Adequate**

This NDA has a low estimated sales volume and the amount is consistent with the categorical exclusion claim at 21 CFR 25.31(b), therefore, the applicant has submitted a claim of categorical exclusion in accordance with 21 CFR 25.31(b), including a statement of no extraordinary circumstances. The categorical exclusion is appropriate for the estimated amount of drug to be produced. The claim of categorical exclusion is acceptable.

**5 BIOWAIVER REQUEST/BCS DESIGNATION REQUEST (IF APPLICABLE/KNOWN)**The Applicant's Position:

The NDA does not contain a biowaiver request.

The FDA's Assessment:

Since the pharmacokinetic (PK) characteristics of both strengths of the proposed Tucatinib Tablets, 50 mg and 150 mg, have been studied in clinical studies (e.g., ONT-380-004, ONT-380-005, SGNTUC-015), and pivotal safety and efficacy study (ONT-380-206, known as HER2CLIMB), biowaiver request is not needed.

**6 DRUG SUBSTANCE**

(b) (4)

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**LABELING**

**Package Insert**

(a) “Highlights” Section

TUKYSA (tucatinib) tablets, for oral use  
Initial U.S. Approval: 20XX

**Evaluation:**

Item	Comments on the Information Provided in NDA
<b>Drug name (201.57(a)(2))</b>	
Proprietary name and established name	Proprietary name and established name are correctly described. <b>Satisfactory.</b>
Dosage form, route of administration	Tablets, oral <b>Satisfactory.</b>
Controlled drug substance symbol (if applicable)	N/A
<b>Dosage Forms and Strengths (201.57(a)(8))</b>	
Whether the drug product is scored	Tablets, 50 and 150 mg <b>Satisfactory.</b> This drug product is not scored

(b) “Full Prescribing Information” Section

#3. Dosage Form and Strength

**3 DOSAGE FORMS AND STRENGTHS**

50 mg tablets: round, (b)(4) yellow, film-coated, debossed with “TUC” on one side and “50” on the other side.

150 mg tablets: (b)(4) shaped, yellow, film-coated, debossed with “TUC” on one side and “150” on the other side.

**Evaluation:**

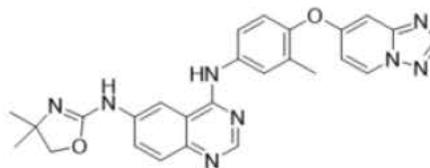
Item	Comments on the Information Provided in NDA
Available dosage forms and strengths: in metric system	The dosage form is tablet with strength of (b)(4)mg. <b>Satisfactory</b>
Active moiety expression of strength with equivalence statement (if applicable)	N/A
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	This section describes the tablets shape, color and marking. <b>Satisfactory</b>

*This section is satisfactory.*

**#11. Description**

**11 DESCRIPTION**

Tucatinib is (b) (4)  
 (b) (4) The chemical name is (N4-(4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)-3-methylphenyl)-N6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine. The molecular formula is C<sub>26</sub>H<sub>24</sub>N<sub>5</sub>O<sub>2</sub> and the molecular weight is 480.52 g/mol. The chemical structure is as follows:



**TUKYSA** (tucatinib) is supplied as 50 mg and 150 mg film-coated tablets for oral (b) (4) and contain the following inactive ingredients:

Tablet core: copovidone, crospovidone, sodium chloride, potassium chloride, sodium bicarbonate, colloidal silicon dioxide, magnesium stearate, and microcrystalline cellulose.

Coating: yellow film coat: polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, and yellow iron oxide non-irradiated.

Each TUKYSA 150 mg tablet contains XX.X mg (X.XXX mEq) of potassium and XX.X mg of sodium (X.XXX mEq). (b) (4)

**Evaluation:**

Item	Comments on the Information Provided in NDA
Proprietary name and established name	TUKYSA (tucatinib) <b>Satisfactory</b>
Dosage form and route of administration	Tablet, oral administration <b>Satisfactory.</b>
Active moiety expression of strength with equivalence statement (if applicable)	N/A
Inactive ingredient information (quantitative, if injectables 21CFR201.100(b)(5)(iii)).	All inactive ingredients are listed. They are not listed in alphabetical order, but since it is not OTC, it is acceptable. <b>Satisfactory.</b>
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	(b) (4) <b>Satisfactory.</b>
Chemical name, structural formula, molecular weight	Chemical name, structural formula and molecular weight are correctly described in this section. <b>Satisfactory.</b>

If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	None
Special labeling	Amount of sodium and potassium that are present in as excipients, are now listed

*The Description section is satisfactory after revision.*

**#16. How Supplied/Storage and Handling**

**16.1 How Supplied**

**TUKYSA** 50 mg tablets are supplied as yellow, film-coated, round (b) (4) tablets containing 50 mg of tucatinib. Each tablet is debossed with “TUC” on one side and “50” on the other side, and is packaged as follows:

50 mg tablets: 60 count in 75 cc bottle: NDC 51144-001-60

**TUKYSA** 150 mg tablets are supplied as yellow, film-coated, (b) (4) shaped tablets containing 150 mg of tucatinib. Each tablet is debossed with “TUC” on one side and “150” on the other side, and is packaged as follows:

150 mg tablets: 60 count in 75 cc bottle: NDC 51144-002-60

150 mg tablets: 120 count in 150 cc bottle: NDC 51144-002-12

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

Dispense to patient in original container only. Store in original container to protect from moisture. Replace cap securely each time after opening. Do not discard desiccant.

Once opened, the product must be used within 3 months. Discard any unused tablets 3 months after opening the bottle.

**Evaluation:**

Item	Comments on the Information Provided in NDA
Strength of dosage form	Strengths are correctly described as 50 and 150 mg per tablet. <b>Satisfactory.</b>
Available units (e.g., bottles of 100 tablets)	Available units are correctly described as 60 count (50 and 150 mg) and 120 count (150 mg) tablets per bottle. <b>Satisfactory</b>
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	The identification of the dosage form is correctly described. NDC Number is stated: <b>Satisfactory.</b>
Special handling (e.g., protect from light)	None
Storage conditions	Storage condition is described as “Store at 20°C to 25°C (68°F -77°F); excursions permitted to 15°F -30°C (59°F -86°F) [See USP Controlled Room Temperature].” <b>Satisfactory</b>
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Stated at the end of the labeling. <b>Satisfactory.</b>

*The “How Supplied/Storage and Handling” section is satisfactory after revision.*

**2. Immediate container label (there are no cartons)**

**A. 50 mg (60 count)**



**B. 150 mg (60 count)**



**C. 150 mg (120 count)**



**Evaluation:** *The expiry analysis shows [redacted] (b) (4)*  
*[redacted] A desiccant is used to protect the drug product from moisture ingress. In our reviews of other products, we had this issue (keep in original bottle and discard the tablets 90 days after opening the bottle) [redacted] (b) (4)*

*[redacted] (b) (4)*  
*Therefore, in consultation with DMEPA reviewer, several inclusions (keep product in original container, discard product if not used in 3 months etc), are made on the container closure and they are implemented. Adequate*

Item	Comments on the Information Provided in NDA
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The established name is presented correctly. The font size of established name is greater than 50% of the proprietary name. <b>Satisfactory</b>
Dosage strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Strengths (50 and 150 mg) are correctly expressed. <b>Satisfactory</b>
Net contents (21 CFR 201.51(a))	The net content is 60 or 120 tablets described <b>Not satisfactory</b>
“Rx only” displayed prominently on the main panel	The statement is prominently displayed. <b>Satisfactory</b>
NDC number (21 CFR 201.2; 21 CFR 207.35(b)(3)(i))	NDC number is indicated. <b>Satisfactory</b>
Lot number and expiration date (21 CFR 201.17)	There is a space allocated for this information. <b>Satisfactory</b>
Storage conditions	Storage condition is correctly described. Store at 20°C to 25°C (68°F -77°F); excursions permitted to 15°F -30°C (59°F - 86°F) [See USP Controlled Room Temperature].” <b>Satisfactory</b>
Bar code (21CFR 201.25)	Barcode is indicated. <b>Satisfactory</b>
Name of manufacturer/distributor per	The name of manufacturer is correctly

21CFR 201.1.

described

And others, if space is available

**Satisfactory**

N/A

*Immediate container labels are satisfactory.*

## Final Risk Assessments

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, Stability	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	(b) (4)	L	The assay shows little change on stability. No trends observed.
Physical stability (solid state)	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	(b) (4)	M	(b) (4)
Content uniformity	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	(b) (4)	L	
Moisture content	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipment</li> <li>• Site</li> </ul>	M	(b) (4)	L	Change in container closure system should be evaluated carefully. Adequate instructions in USPI
Microbial limits	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	L	(b) (4)	L	
Dissolution – BCS Class II & IV	<ul style="list-style-type: none"> <li>• Formulation</li> <li>• Container closure</li> <li>• Raw materials</li> <li>• Process parameters</li> <li>• Scale/equipments</li> <li>• Site</li> </ul>	M	(b) (4)	L	Method has limited (b) (4)

					(b) (4)
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**ATTACHMENT 1 BIOPHARMACEUTICS REVIEW**

**EXECUTIVE SUMMARY**

Tucatinib is a selective, adenosine triphosphate (ATP) competitive small molecule inhibitor of the tyrosine kinase human epidermal growth factor receptor-2 (ErbB2/HER2) for the treatment of patients with locally advanced unresectable or metastatic HER2-positive breast cancer, including patients with brain metastases. The drug substance (DS), tucatinib (b) (4) (b) (4)

The proposed finished drug product (DP), Tucatinib Tablets, are immediate release film-coated tablets supplied with two strengths, 50 mg and 150 mg. The proposed dose is 300 mg taken orally twice daily.

The Biopharmaceutics Review focuses on the evaluation of (i) the in vitro dissolution method and acceptance criterion as a quality control (QC) test for the proposed drug product, Tucatinib Tablets, 50 mg and 150 mg; (ii) the need of in vitro formulation bridging studies between the clinical and the commercial formulation.

Since the plasma pharmacokinetic (PK) characteristics of both strengths of the proposed Tucatinib Tablets, 50 mg and 150 mg, have been studied in clinical studies (e.g., ONT-380-004, ONT-380-005, SGNTUC-015), and pivotal safety and efficacy study (ONT-380-206, known as HER2CLIMB), biowaiver request is not needed.

*In Vitro Dissolution Testing of the Finished Product:*

The dissolution method parameters have been evaluated and found acceptable. The proposed dissolution method showed acceptable discriminating ability with regards to material variables (b) (4). Therefore, the proposed dissolution method is **acceptable** as a quality control (QC) test for the proposed drug product for batch release and stability testing. The overall dissolution data support the proposed acceptance criterion of Q = (b) (4)% 30 minutes.

The final approved in vitro dissolution method and acceptance criterion for the proposed Tucatinib Tablets, 50 mg and 150 mg, are presented below:

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Dissolution Medium	900 mL of 0.1 M citrate buffer, pH 3.4, containing 0.05% Brij 35
Temperature	37°C±0.5°C
Sampling Time	10, 15, 20, 30, 45, 60 minutes
Acceptance Criterion	Q = (b) (4)% in 30 minutes

*The In Vitro Formulation Bridging:*

The in vivo clinical studies to bridge the early development formulation [e.g., powder in capsule (PiC)] and the to-be-market/commercial formulation (tucatinib tablets) will be assessed by the Office of Clinical Pharmacology (OCP).

The clinical formulation is same as the commercial formulation, with same manufacturing process and manufacturing site. Therefore, no additional in vivo or in vitro bridging studies are needed between the clinical and the commercial formulations (tucatinib tablets).

**RECOMMENDATION**

**From the Biopharmaceutics perspective, NDA 213411 for the proposed Tukysa™ (Tucatinib) Tablets, 50 mg and 150 mg, is recommended for APPROVAL.**

**BIOPHARMACEUTICS REVIEW**

**1. In Vitro Dissolution Method**

Dissolution is one of the critical quality attributes (CQAs) of the proposed drug product. The proposed dissolution method and acceptance criterion are listed as below, while the dissolution method development is provided in M.3.2.P.2.

USP Apparatus	II (Paddle)
Rotation Speed	75 rpm
Dissolution Medium	900 mL of 0.1 M citrate buffer, pH 3.4, containing 0.05% Brij 35
Temperature	37°C±0.5°C
Sampling Time	10, 15, 20, 30, 45, 60 minutes
Acceptance Criterion	Q = <sup>(b)</sup> <sub>(4)</sub> % in 30 minutes

The following drug substance characteristics and dissolution parameters have been evaluated for determining the proposed dissolution method, summarized as:

(1) Drug substance <sup>(b)</sup><sub>(4)</sub> solubility and permeability

Per the Applicant, Tucatinib is a BCS class 2 compound. The drug substance (DS), tucatinib <sup>(b)</sup><sub>(4)</sub> <sup>(b)</sup><sub>(4)</sub>

<sup>(b)</sup><sub>(4)</sub>

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(b) (4)

(b) (4)

Overall, this Reviewer considers that the dissolution method parameters have been evaluated and acceptable. The proposed dissolution method (USP Apparatus II Paddle, 75 rpm, 900 mL of 0.1 M Citrate Buffer, pH 3.4 containing 0.05% Brij 35) showed acceptable discriminating ability with regards to in process variable  (b) (4)

that are outside of established in-process control. Therefore, the proposed dissolution method is acceptable as a quality control (QC) test for the proposed drug product.

**2. Dissolution Data and Acceptance Criterion**

The dissolution profiles of the proposed Tucatinib Tablets 50 mg (primary stability lots KH18/0224, KH18/0225, and KH18/0226) and 150 mg (primary stability lots KH18/0227, KH18/0228, and KH18/0229) are presented in the following Figures 9 and 10, respectively. Both strengths products exhibit rapid dissolution (> (b) (4) % dissolution in 30 minutes).

Figure 9: Dissolution profiles of the proposed Tucatinib Tablets, 50 mg

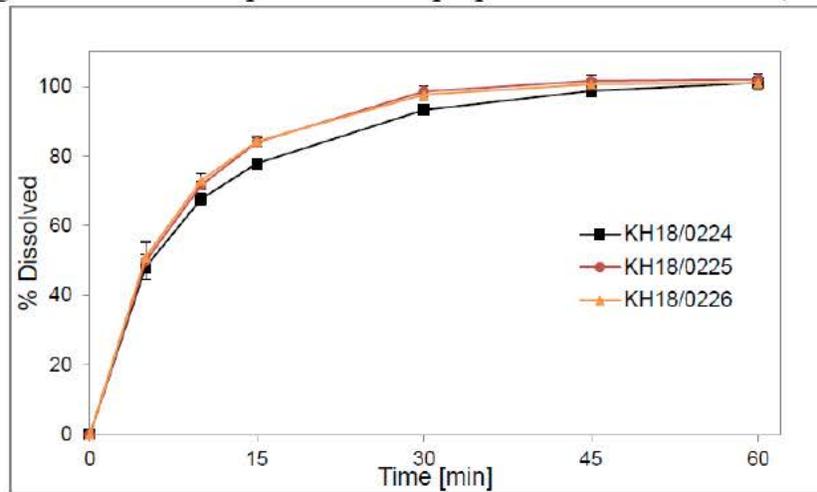
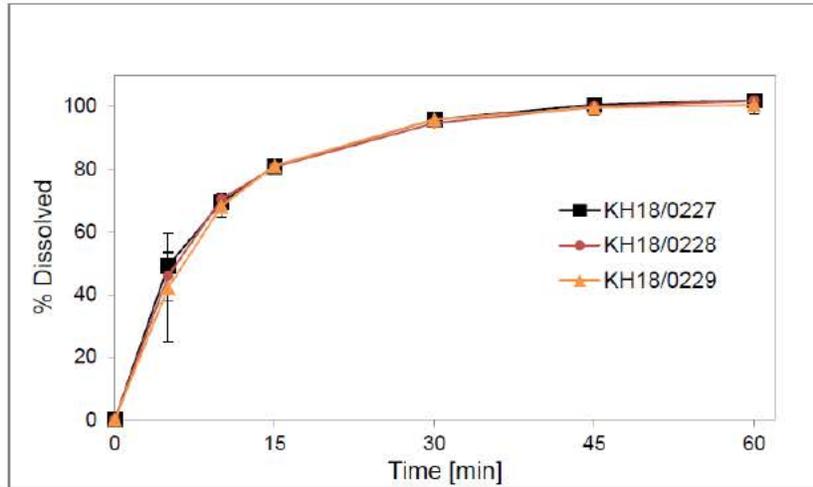


Figure 10: Dissolution profiles of the proposed Tucatinib Tablets, 150 mg



The mean dissolution data of the above six primary stability batches are >92% for 50 mg, and >93% for 150 mg, respectively, at single time point of 30 minutes up to 12 months at long-term (25°C/60% RH) stability conditions. There were no significant changes or trends in various stability conditions that were observed, as data showed in Figure 11 below.

Figure 11: Percent dissolved (in 30 minutes), tucatinib tablets lots at 25°C/60% RH

(b) (4)

Overall, this Reviewer considers the proposed dissolution acceptance criterion of “Q= (b) (4) % in 30 minutes” is supported by the data then is acceptable.

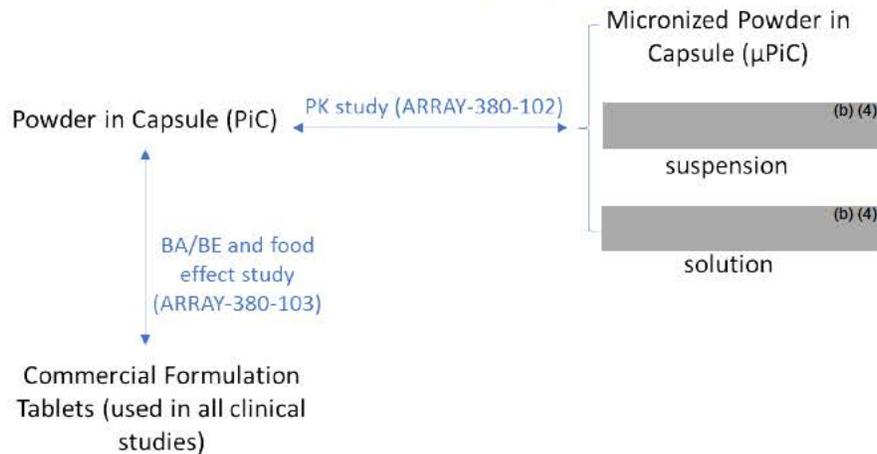
**3. In vitro formulation bridging**

The early development formulations included powder in capsule (PiC), micronized powder in capsule ( $\mu$ PiC), (b) (4) suspension, and (b) (4) solution. The to-be-market/commercial formulation is the tucatinib tablets. The formulations that have been used in clinical development are summarized in the following Table 4 and Figure 12.

Table 4: Tucatinib development formulations that have been used in clinical development

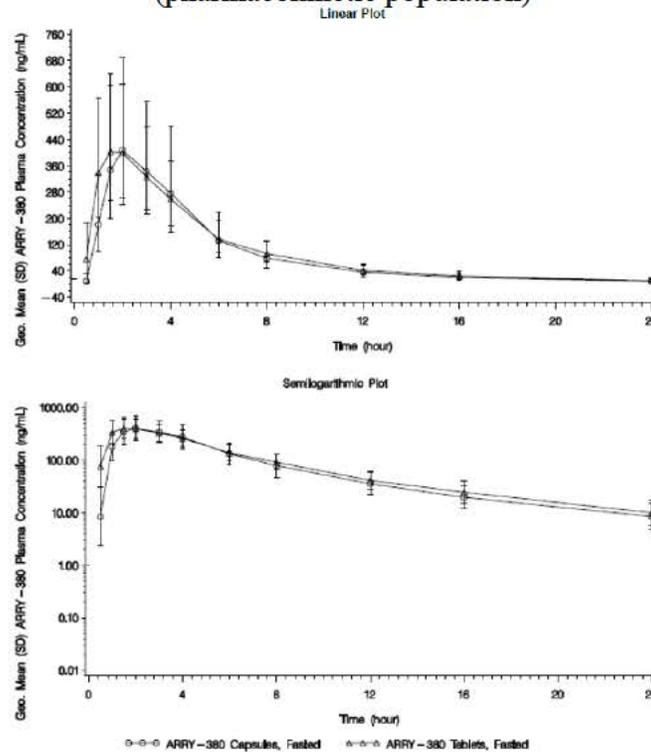
Formulation Description (Abbreviated)	Formulation Description (b) (4)	Clinical Study Number
Powder in capsule (PiC)	(b) (4)	ARRAY-380-101
Micronized powder in capsule ( $\mu$ PiC)		ARRAY-380-102
(b) (4) suspension		ARRAY-380-102
(b) (4) solution		ARRAY-380-102
Powder in capsule		<u>ARRAY-380-103</u>
Tucatinib tablet	Proposed commercial formulation	<u>ARRAY-380-103</u> and all subsequent studies

Figure 12: In vivo clinical studies to bridge the development formulations (diagramed by this Reviewer)



The in vivo bioavailability (BA) study (ARRAY-380-103) is under purview by the Office of Clinical Pharmacology (OCP). On face, the study results (as shown in the following Figure 13, Tables 5 and 6) showed that 90% CI of AUC between tucatinib PiC and commercial tucatinib tablets are out of (b) (4) % range, however, the adequacy of the in vivo formulation bridging will be assessed by OCP.

Figure 13: Geometric mean (geometric SD) plasma concentrations of tucatinib versus time (tablet versus capsule) linear and semilogarithmic scales (pharmacokinetic population)



Source: ARRAY-380-103, CSR, Figure 2

Table 5: Summary of plasma pharmacokinetic parameters of tucatinib in study ARRAY-380-103

Formulation <sup>a</sup>	Treatment	N	C <sub>max</sub> <sup>b</sup> (ng/mL)	T <sub>max</sub> <sup>c</sup> (hr)	AUC <sub>last</sub> <sup>b</sup> (hr*ng/mL)	AUC <sub>inf</sub> <sup>b</sup> (hr*ng/mL)	t <sub>1/2</sub> <sup>c</sup> (hr)
PIC	Fasted	12	428 (55.4)	2.00 (1.00, 4.00)	2130 (49.2)	2200 (49.4)	5.30 (4.07, 7.00)
Tablet	Fasted	12	429 (47.8)	1.51 (1.50, 2.00)	2330 (36.2)	2410 (36.2)	5.58 (4.17, 6.84)
Tablet	Fed	11	479 (40.3)	4.00 (2.00, 6.02)	3510 (32.9)	3660 (32.9)	5.07 (4.07, 6.03)
Tablet	Fasted/ Omeprazole	9	379 (42.8)	2.00 (1.50, 3.00)	2040 (33.4)	2120 (33.1)	5.46 (4.34, 6.58)

Abbreviations: AUC<sub>0-last</sub>=area under the plasma concentration-time curve from time 0 to the last measurable concentration; hr=hour(s); t<sub>1/2</sub>=apparent terminal half-life; T<sub>max</sub>=time of maximum observed plasma concentration.

a Dose was 300 mg, single dose

b Geometric mean (%CV)

c Median (minimum, maximum)

Source: ARRAY-380-103, CSR, Table 7

Table 6: Statistical analysis of plasma pharmacokinetic parameters of tucatinib (relative bioavailability)

	Treatment <sup>a</sup>	N	Geometric Mean	Ratio (%) of Geometric Means (Test/Reference)	90% CI of Ratio	Intersubject Variability	Intrasubject Variability	P value <sup>b</sup>
AUC <sub>last</sub> (hr*ng/mL)	B	12	2325.49	109.35	90.19–132.58	11.65	34.02	0.2766
	A	12	2126.69			0.00	49.16	
AUC <sub>inf</sub> (hr*ng/mL)	B	12	2410.82	109.68	90.51–132.91	36.24	0.00	0.2709
	A	12	2198.09			19.95	44.27	
C <sub>max</sub> (ng/mL)	B	12	429.26	100.40	81.12–124.25	18.93	43.17	0.5965
	A	12	427.57			0.00	55.43	

CI=confidence interval; N=number of subjects

Note: A repeated measures analysis of variance was performed on the natural logarithms of the parameters with treatment as a fixed, repeated effect and subject as a random effect to allow both inter- and intrasubject variance to be estimated. Point estimates and 90% CIs for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

a A=tucatinib capsules 300 mg, fasted; B=tucatinib tablets 300 mg, fasted

b Pitman-Morgan test

Source: ARRAY-380-103, CSR, Table 8

The clinical formulation (tucatinib tablets) is same as the commercial formulation (tucatinib tablets), while they have same manufacturing process and manufacturing site. Therefore, no additional in vivo or in vitro bridging studies are needed between the clinical and the commercial formulations.

#### 4. Biowaiver

Since both the proposed Tucatinib Tablets, 50 mg and 150 mg, have been used in multiple clinical studies (e.g., ONT-380-004, ONT-380-005, SGNTUC-015), and pivotal safety and efficacy study (ONT-380-206, also known as HER2CLIMB), the plasma pharmacokinetics (PK) characteristics of both strengths products have been evaluated. Therefore, no biowaiver is needed nor submitted for review.

## Recommendation Page

### *Drug Substance: Approval*

*Primary Reviewer:* Rajan Pragani      Date: 04/07/2020  
*Secondary Reviewer:* Ali Al-Hakim      Date: 04/07/2020

### *Drug Product: Approval*

*Primary Reviewer:* Rajiv Agarwal      Date: 04/14/2020  
*Secondary Reviewer:* Anamitro Banerjee      Date: 04/14/2020

### *Process and Facility: Approval*

*Primary Reviewer:* Feiyan Jin, Haitao Li      Date: 04/16/2020  
*Secondary Reviewer:* Steve Rhieu      Date: 04/16/2020

### *Biopharmaceutics: Approval*

*Primary Reviewer:* Mei Ou      Date: 04/15/2020  
*Secondary Reviewer:* Banu Zolnik      Date: 04/15/2020

### *Application Technical Lead: Approval*

Xiao Hong Chen      Date: 04/16/2020

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**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.**  
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/s/  
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