

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211810Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211810

Review 1

Drug Name/Dosage Form	Turalio (pexidartinib) capsules
Strength	200 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Daiichi Sankyo
US agent, if applicable	NA

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0002 (2), Original Submission	09/21/2018	Drug Substance (DS), Drug Product (DP), Process, Facilities, Biopharmaceutics, and Microbiology
0003 (3), Quality Amendment	10/26/2018	DP updated stability data
0007 (7), Response to Process IR	12/19/2018	Process
0009 (9), Labeling/Package Insert Draft	12/20/2018	DP Labeling
0014 (14), Response to IR	02/25/2019	Biopharmaceutics
0017 (17), Labeling/Package Insert Draft	03/08/2019	DP Labeling
0019 (18), Response to IR	03/15/2019	DS, DP, Biopharmaceutics
0021 (20), Response to IR	03/18/2019	DP, Process, Microbiology
0027 (27), Labeling/Container-Carton	04/02/2019	DP Labeling
0030 (30), Response to IR	04/11/2019	Process
0032 (32), Labeling/Container-Carton	04/12/2019	DP Labeling

<i>0047 (47), Response to IR</i>	<i>05/08/2019</i>	<i>DP</i>
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Quality Review Team

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Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	Adequate	Information provided in NDA	
	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
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	Type III		Adequate	Information provided in NDA		
	Type III		Adequate	Information provided in NDA		
	Type IV		Adequate	Information provided in NDA		

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	(b) (4) 117332	Initial INDs

2. CONSULTS

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

* The liquid chromatography method for identification and purity was submitted to OPQ/OTR/DPA for method verification. DPA confirmed 29-Mar-18 in Panorama that this method is adequately verified.

Executive Summary

I. Recommendations and Conclusion on Approvability

From the chemistry, manufacturing, and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Based on the provided stability data, a 30-month expiration dating period is granted for Turalio (pexidartinib) capsules, 200 mg when stored at 20 - 25°C (68 - 77°F); with excursions permitted to 15 - 30°C (59 - 86°F) [see USP controlled room temperature].

II. Summary of Quality Assessments

A. Product Overview

Pursuant to 21 CFR 314.50 and section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, Daiichi Sankyo, Inc. (Daiichi Sankyo) submitted NDA 211810 as a rolling submission with the following three parts:

- Part 1/3: Nonclinical section, received on 09/18/2018;
- Part 2/3: CMC section, received on 09/21/2018; and
- Part 3/3: Remaining sections, received on 12/03/2018.

A completed NDA 211810 was received on 12/03/2018 with FDA orphan drug designation (ODD) and breakthrough therapy to support priority review of pexidartinib capsules, 200 mg marketing approval for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

Clinical development data is available in the cross-referenced INDs 117332,

(b) (4)

Pexidartinib hydrochloride (HCl), a kinase inhibitor is a small molecule new molecular entity. Pexidartinib HCl is white to off-white crystalline solid with the melting point at 235°C. The solubility of pexidartinib HCl decreases with increasing pH. Pexidartinib HCl is considered as a Biopharmaceutics Classification System (BCS) Class 2 compound which is a low solubility, high permeability drug. Pexidartinib HCl is very slightly hygroscopic or non-hygroscopic. Pexidartinib HCl has no asymmetric carbon atoms in the molecule.

(b) (4)

Pexidartinib HCl is formulated as immediate-release capsules containing 200 mg of pexidartinib free base for oral administration with the following compendial excipients: poloxamer 407, mannitol, crospovidone, magnesium stearate, and filling into Hypromellose (HPMC) capsules. The capsules are printed with “T10” in white. The drug products are packaged in HDPE bottles containing a desiccant with (b) (4) caps and induction seals in two configurations: 28 capsules in 150 cc bottle and 120 capsules in 200 cc bottle.

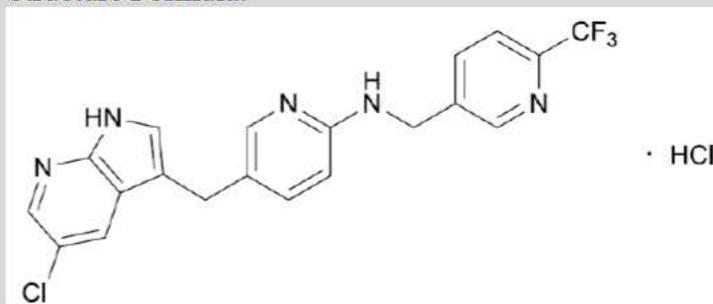
Proposed Indication(s) including Intended Patient Population	For the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.
Duration of Treatment	Continue treatment until disease progression or unacceptable toxicity
Maximum Daily Dose	400 mg orally twice daily
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance [Pexidartinib HCl]

The drug substance (DS) pexidartinib HCl has the following chemical name, structural formula, molecular formula, and molecular weight.

Structure Formula:



International Non-proprietary Name (INN): Pexidartinib

Chemical Name: 5-[(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-N-{{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyridin-2-amine

CAS Registry Number: 1029044-16-3 (as free form) and 2040295-03-0 (as HCl salt)

Mol. Formula: C₂₀H₁₅ClF₃N₅.HCl

Mol. Wt.: 454.28 Daltons (as pexidartinib HCl) and 417.81 Daltons (as pexidartinib)

The characterization, nomenclature, molecular structure, CAS number, and molecular weight of the drug substance (DS) pexidartinib HCl and its free base are accurate. Pexidartinib HCl has low aqueous solubility, and the solubility decreases at increasing pH. According to the USP definition of solubility, pexidartinib HCl is slightly soluble in 0.01 N HCl; very slightly soluble in water (pH ~2.0) and at pH 3.0; and practically insoluble at pH 4.0, 5.0, and 7.5. The solubility data indicated that pexidartinib HCl is generally soluble in organic solvents with high-dielectric constant (≥ 25) and practically insoluble in the solvent with low dielectric constant. The commercial manufacturing process for pexidartinib HCl produces (b) (4)

(b) (4) The particle size distribution of the DS is also controlled (b) (4) in the DS release specification. Pexidartinib HCl is slightly hygroscopic or non-hygroscopic. (b) (4)

(b) (4)
Pexidartinib HCl does not contain any chiral center, and hence the control of the chiral impurity is irrelevant. The partition coefficient and the measured pKa values of its conjugated acid at 2.6 and 5.4 are consistent with the solubility properties provided in the submission.

Pexidartinib HCl is manufactured (b) (4)

(b) (4) A significant level of detail is provided to describe DS manufacturing process. (b) (4)

(b) (4) are justified based on consideration of all principles described in ICH Q11 and accepted by FDA at EOP2, see this review below on the DS section for details.

The source of generation of all potential impurities is understood and demonstrated with many batches of the drug substance. No impurity limit exceeds the ICH Q3A qualification threshold. The (b) (4) meet the acceptance criteria of the particle size distribution in the DS specification. The particle size and proposed limits are justified based on the DS dissolution profile. See the Biopharm review below for details. Adequate justification based on risk assessment for elemental impurities contamination was conducted, and the inclusion of elemental impurities testing is not considered necessary for pexidartinib HCl DS. Adequate assessment for mutagenic impurities was carried out, and there is no significant risk identified per ICH M7. The proposed DS specification is well-justified and acceptable. Any specific tests that are not included in the DS specification are appropriately justified and supported by the trend data of the drug substance analyses, see this review below on DS section for details.

Pexidartinib HCl drug substance (DS) is packaged (b) (4)

(b) (4)
for shipping and handling. The batch analyses data of 23 batches DS are described in the submission including the commercial validation, primary stability, clinical, and toxicological batches. The batch analyses data conform to the proposed DS specification for commercial, primary stability, and late clinical batches, see this review on DS section for details. Stability data on three primary stability batches

supports an initial retest period (b) (4) for pexidartinib HCl DS (b) (4) per ICH Q1E (R2).

Drug Product [Pexidartinib Capsules, 200 mg]

The drug product is formulated as immediate release, Hypromellose (HPMC) size 0 capsules containing 200 mg pexidartinib (equivalent to 217.5 mg pexidartinib HCl) and common compendial pharmaceutical excipients: (b) (4) poloxamer 407 as (b) (4) mannitol (b) (4) crospovidone (b) (4) and (b) (4) magnesium stearate (b) (4). The capsules appear as dark green opaque cap and white opaque body with "T10" in white print. Apart from poloxamer 407, all the ingredients used in the formulation are below the IIG limits based on the maximum daily intake of the proposed product of 800 mg. The maximum daily intake for poloxamer 407 excipient is (b) (4) mg, which is significantly higher than the level present in other approved oral drug products. To support the proposed poloxamer 407 level, the applicant conducted toxicity studies in animals using a placebo containing poloxamer 407 at the same level used in the clinical study and found that there were no toxicological findings. The non-clinical reviewer, Elizabeth Spehalski, Ph. D. was consulted about the level of poloxamer 407 in the drug product and confirmed that there are no safety concerns and thus its level is acceptable.

The manufacturing process of the drug product includes (b) (4) (b) (4)

The drug product specification includes the following CQAs: description by visual inspection; identification by HPCL/UHPLC retention time and UV spectrum; assay by HPLC/UHPLC; uniformity of dosage units by HPLC/UHPLC; related substances by HPLC/UHPLC; dissolution per USP <711> with Q = (b) (4)% in 45 minutes; (b) (4) (b) (4) and microbial control per USP <61> and <62>. The drug product specification is adequate to establish the drug product's identity, strength, quality, and purity. The impurities (b) (4) have acceptance criteria of NMT (b) (4)% and the limits are justified by ICH Q3B for a product that is administered with a

maximum daily dose

(b) (4)

(b) (4)

The applicant provided detailed analytical method validation data. Each method description is also sufficiently detailed. The (b) (4)

(b) (4)

(b) (4) method for release testing and initial testing for stability testing only were submitted to OPQ/OTR/DPA for method verification. DPA confirmed on 05/06/2019 in Panorama that both methods are acceptable with modifications for its intended use.

Three registration batches of bulk pexidartinib capsules ((b) (4) capsules each) lot # L0600826, L0600827, and L0600828 are packaged (b) (4)

(b) (4) and were placed on stability. All batches were manufactured using commercial process at commercial scale and commercial site.

(b) (4)

The commercial product capsules are white opaque body and dark green opaque cap with white print T10 (b) (4)

(b) (4) This is acceptable as both bands in the cap and body of the capsules for the stability batches represent the worst case in terms of stability. All batches in each bottle configuration met the proposed specification. The 18 months stability studies at long-term support the proposed storage temperature of 20 – 25°C with excursions permitted to 15 – 30°C. No significant chemical or physical changes at accelerated storage conditions are reported in the NDA either. Based on the 18 months available data at long term and 6 months at accelerated storage conditions, 30 months expiration date is granted.

Supportive stability studies include photostability study, stress stability studies at 40°C/75% RH for 12 weeks (open) and at 60°C in amber glass bottles for 4 weeks (closed), freeze-thaw stability studies in both primary configurations, and bulk stability studies for bulk product (b) (4) at long term for 18 months and at accelerated for 6 months. The data show that the drug product is well within the proposed specification for all tested attributes under each test condition. The applicant also confirms (b) (4)

(b) (4)

The applicant's claim for categorical exclusion and request of a waiver from an environmental analysis is granted.

Facility Evaluation

Office of Process and Facilities (OPF/OPQ/CDER) has recommended "Acceptable"

for the following drug substance manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile and previous history.

(b) (4)

Office of Process and Facilities (OPF/OPQ/CDER) has recommended “Acceptable” for the following drug product manufacturers (for manufacture, release testing, stability testing, packaging, and storage) based on Profile and previous history.

(b) (4)

Biopharmaceutics Evaluation

During the development, the applicant implemented the following changes: (b) (4)

(b) (4)

(b) (4) The applicant conducted a bioequivalence (BE) study, PL3397-A-U116 as well as provided a comparative dissolution data to establish a ‘bridge’ between the (b) (4) drug product. The adequacy of the BE study is reviewed by the Office of Clinical Pharmacology (refer to Dr. Burns review). The dissolution profiles of (b) (4) (b) (4) batches are similar with f2 value of 58.63.

Though the drug substance exhibits low solubility profile and polymorphic forms, the applicant provided dissolution data (b) (4)

Additionally, the initial drug product was developed (b) (4)

Based on the overall dissolution data at release and on stability, from a Biopharmaceutics perspective, (b) (4) the risks of dissolution failure during batch release and stability testing deem relatively lower.

Both (b) (4) drug product has been used in the pivotal clinical study. It should also be noted that the (b) (4) drug product is not the commercial drug product. The commercial drug product will have green and white as the color of the HPMC capsule shell without any bands with ‘T10’ logo imprinted. This review team has concluded that the difference in the capsule is considered minor. Therefore, there is no additional information or dissolution data needed to support the minor changes in the capsule shell for the commercial drug product.

The following dissolution method is proposed: USP Apparatus 2 at a paddle speed of 75 rpm in 900 mL 0.01 N HCl with stainless steel helix sinker. The proposed

dissolution exhibits discriminating ability with respect to the PSD of the drug substance ((b) (4) μm), (b) (4)

(b) (4)

The dissolution data also supports the proposed dissolution acceptance criterion of “Q= (b) (4) % in 45 minutes”.

Labeling

The container and carton labels as well as the prescribing information pertinent to the CMC sections (Highlights as well as Section 2, 3, 11, and 16) comply with all regulatory requirements from a CMC perspective after revision (see this review below on labeling section for details).

1. Special Product Quality Labeling Recommendations (NDA only)

NA

2. Final Risk Assessment (see Attachment below)

Attachment - Final Risk Assessment for Pexidartinib Capsules, 200 mg

From Initial Risk Identification			Final 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"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure 	Low	Assessed during development and controlled via specification and container closure	Acceptable	NA
Physical Stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure 	Low	Assessed during development and controlled via specification and container closure	Acceptable	NA
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	Low	Assessed during development and controlled via DS particle size and DP specification	Acceptable	NA
Dissolution	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure 	Medium	Assessed during development and controlled via specification	Acceptable	NA
Microbial Limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure 	Low	Assessed during development with adequate justification provided for not controlling in DP specification	Acceptable	NA
(b) (4)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site • Container closure 	Low	Assessed during development with adequate justification provided for not controlling in DP specification	Acceptable	NA



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LABELING

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Established Name: Pexidartinib Proposed proprietary name: Turalio™
Dosage form, route of administration	Capsules, oral
Controlled drug substance symbol (if applicable)	N/A
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	200 mg capsules

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	400 mg (2x 200 mg capsules) taken twice daily on an empty stomach. It should be swallowed whole.

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	capsules
Strengths: in metric system	200 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not included. The FDA comments to include this information is being sent out during the labeling negotiations.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	White opaque body and dark green opaque cap, with white print "T10".

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Proprietary name: Turalio Established name: Pexidartinib
Dosage form and route of administration	Oral
Active moiety expression of strength with equivalence statement (if applicable)	Each 200 mg capsule contains an equivalent of 217.5 mg of Pexidartinib hydrochloride
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	N/A
Statement of being sterile (if applicable)	N/A
Pharmacological/ therapeutic class	Pexidartinib is a kinase inhibitor for oral use
Chemical name, structural formula, molecular weight	The chemical name of pexidartinib hydrochloride is 5-[(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-N-[[6-(trifluoromethyl)pyridin-3-yl)methyl]pyridin-2-amine monohydrochloride. The empirical molecular formula is C ₂₀ H ₁₅ ClF ₃ N ₅ •HCl The molecular weight is 454.28 gram/mol.
If radioactive, statement of important nuclear characteristics.	N/A
Other important chemical or physical properties (such as pKa or pH)	pKa1: 2.6 pKa2: 5.4

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	200 mg
Available units (e.g., bottles of 100 tablets)	28 capsules per bottle 120 capsules per bottle
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC 65597-402-28, 28 capsules/bottle NDC 65597-402-20, 120 capsules/bottle 200 mg capsules are supplied as white, opaque body and dark green opaque cap with print "T10".
Special handling (e.g., protect from light)	Keep containers closed and do not remove desiccant from bottles
Storage conditions	20°C to 25 °C (68 °F to 77 °F) excursions permitted to 15 °C to 30 °C (59 °C to 86 °C).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Stated under section 17 Daiichi Sankyo, Inc Basking Ridge, NJ 07920

II. Labels:

Container and Carton Labels

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Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Proprietary name: Turalio Established name: Pexidartinib	Proprietary name: Turalio Established name: Pexidartinib
Dosage strength	200 mg	200 mg
Net contents	28 capsules 120 capsules	28 capsules 120 capsules
“Rx only” displayed prominently on the main panel	Provided	Provided
NDC number (21 CFR 207.35(b)(3)(i))	NDC 65597-402-28, 28 capsules/bottle NDC 65597-402-20, 120 capsules/bottle	NDC 65597-402-28, 28 capsules/bottle NDC 65597-402-20, 120 capsules/bottle
Lot number and expiration date (21 CFR 201.17)	Information was provided	Information was provided
Storage conditions	20 °C to 25 °C (68 °C to 77 °F) Excursion permitted to 15 °C to 30 °C (59 °C to 86 °C)	20 °C to 25 °C (68 °C to 77 °F) Excursion permitted to 15 °C to 30 °C (59 °C to 86 °C)
Bar code (21CFR 201.25)	Provided	Provided
Name of manufacturer/distributor	Manufactured for Daiichi-Sankyo Basking Ridge, NJ 07920	Manufactured for Daiichi-Sankyo Basking Ridge, NJ 07920
Must be diluted prior to administration	N/A	N/A
Route of administration	Information was provided	Information was provided
Multi-dose/single dose labeling	N/A	N/A

Reviewer’s Assessment: Adequate with comments

The container and carton labels as well as the prescribing Information complies with all regulatory requirements from a CMC perspective pending revision of the following:

- Under dosage forms and strengths in section 3, the forms and strength should be expressed as “capsules, 200 mg” (b) (4): Pending.

2. Per USP policy salt, the active moiety expression of strength with equivalence statement needs to be included under section 3: Pending
3. Under section 11, where it states “The pKa1 and pKa2 were determined to be 2.6 and 5.4, respectively”, the statement should be replaced with “The pKa1 and pKa2 were determined to be 2.6 and 5.4 respectively for the conjugated acids”: Pending.

Additionally, the following IRs regarding package insert, carton and container labels were sent to the applicant on February 26, 2019.

1. To avoid confusion, replace the phrase (b) (4) with “prescribing information” on the container and carton labels: The applicant updated the PI satisfactorily (see below).
2. Include “for oral use” on container and carton labels if there is space available. The applicant updated the PI satisfactorily (see below).

The applicant responded to the IRs on April 02, 2019

The sponsor replaced (b) (4) with “prescribing information” on the container and carton labels. They have also added “for oral use: on the container and carton labels.

Overall Assessment and Recommendation:

The labels comply with all regulatory requirements and it is recommended for approval from a CMC perspective pending satisfactory update of the USPI for issues raised above.

Primary Labeling Reviewer Name and Date: Tefsit Bekele April 04/04/2019

Secondary Labeling Reviewer Name and Date: Anamitro Banerjee April 22, 2019



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BIOPHARMACEUTICS

Application No: NDA 211810

Drug Product Name / Strength: Turalio™ (pexidartinib hydrochloride capsules), 200 mg

Route of Administration: Oral

Applicant Name: Daiichi Sankyo, Inc.

Primary Reviewer: Parnali Chatterjee, Ph.D.

Secondary Reviewer: Banu Zolnik, Ph.D.

Background:

The Applicant is seeking approval for Turalio™ (pexidartinib hydrochloride capsules, PLX3397), 200 mg to be administered twice daily for the treatment of adult patients with giant cell tumor of the tendon sheath (GCT-TS) that is associated with severe morbidity or functional limitations, and for which surgery is not recommended *via* the 505 (b)(1) regulatory pathway. The recommended daily dose is 400 mg (2×200 mg) capsules taken twice daily on an empty stomach atleast 1 hour before or 2 hours after a meal.

Turalio™, 200 mg received Breakthrough Therapy Designation (BTD) for the treatment of patients with GCT-TS in whom surgical intervention is associated with potentially worsening functional limitation or severe morbidity. The Applicant conducted a pivotal Phase III clinical study PLX108-10 to support safety and efficacy of the proposed drug product in addition to other clinical studies. During the development, the Applicant implemented changes (b)(4) (b)(4) and conducted a bioequivalence (BE) study, PL3397-A-U116, to establish a ‘bridge’ between the (b)(4) drug product J-3397-AF. Both (b)(4) drug product has been used in the pivotal clinical study.

It should be noted that the (b)(4) drug product is not the commercial drug product. The commercial drug product will have green and white as the color of the HPMC capsule shell with ‘T10’ logo imprinted. During a discussion with the Review Team, it was concluded that the change in the capsule color is a minor change. Therefore, no additional information was needed to support the change in the capsule shell for the commercial drug product.

REVIEW SUMMARY:

This Biopharmaceutics Review evaluated 1) the proposed dissolution acceptance criterion, and 2) the need for bridging the different formulations and manufacturing processes throughout the product development stage. It should be noted that the dissolution method has been found acceptable during the IND stage. See the Biopharmaceutics review attached in Appendix 1.

➤ ***Dissolution Method:***

The dissolution profile data for various testing parameters and discriminating ability of the proposed dissolution method was assessed by Dr. Ta-Chen Wu on 09/08/2016 under the IND 117332 (SN0069/SDN 70).

Pexidartinib is a low aqueous soluble drug substance, therefore particle size of the drug substance may have an impact on the dissolution profile of the drug product. A three-tier particle size distribution ($D_{10}=NMT$ (b) (4) μm , $D_{50}=NMT$ (b) (4) μm , $D_{90}=NMT$ (b) (4) μm) was proposed refer to Drug Substance review for more information).

The proposed dissolution method was found **ACCEPTABLE** for batch release and stability testing of the proposed drug product and conveyed to the Applicant in an Advice letter on 09/28/2016 (refer to the following link for the Advice letter: <https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af80405f03>).

Parameters	ACCEPTABLE Dissolution Method
<i>Apparatus</i>	USP Apparatus 2 (paddle)
<i>Speed</i>	75 rpm
<i>Sinkers</i>	Helix stainless-steel sinkers
<i>Media/Volume</i>	0.01 N HCl/900 mL
<i>Bath temperature</i>	37.0±0.5 C

➤ ***Dissolution Acceptance Criterion:***

The Applicant proposed “ $Q=(b) (4) \%$ in 45 minutes” as the acceptance criterion at release and on stability for the proposed drug product in the current submission. However, the dissolution profile data for the bio-batch, batches used in clinical studies, and on stability support a dissolution acceptance criterion of “ $Q=(b) (4) \%$ in 45 minutes” for the proposed drug product. In response to an Information Request comment, the Applicant agreed to implement “ $Q=(b) (4) \%$ in 45 minutes” as the dissolution acceptance criterion for batch release and stability testing of Turalio™ containing 200 mg of pexidartinib.

➤ ***Bridging of the Batches:***

- *Bridging of batches due to formulation and manufacturing process changes:*

During the pivotal Phase III clinical study (PLX108-10), the applicant implemented the following changes to the drug product: (b) (4)

(b) (4)
 (b) (4) The Applicant used both (b) (4)
 (b) (4) in the in the pivotal Phase III clinical study, PLX108-10.

The Applicant conducted a bioequivalence (BE) study, PL3397-A-U116, and provided a comparative dissolution data to establish a ‘bridge’ between the (b) (4) drug product. The adequacy of the BE study is reviewed by the Office of Clinical Pharmacology (refer to Dr. Burns review). The dissolution profiles of (b) (4) batches are

similar with f_2' value=58.63. Figure below shows the schematic overview of the drug product development and bridging strategy.

Figure. Schematic Diagram of Batches Used in Clinical Development and Bridging Strategy



➤ ***Biopharmaceutics Risk Assessment:***

Though the drug substance exhibits low solubility profile and polymorphic forms, the Applicant provided dissolution data (b) (4)

(b) (4) Additionally, the initial drug product was developed (b) (4)

(b) (4) Based on the overall dissolution data at release and on stability, from a Biopharmaceutics perspective, (b) (4) (b) (4) the risk of dissolution failure during batch release and stability testing is relatively lower.

➤ ***OVERALL REVIEW RECOMMENDATION:***

From the Biopharmaceutics perspective, NDA 211810 for Turalio™ containing 200 mg of pexidartinib (PLX3397) is recommended for **APPROVAL**.

BIOPHARMACEUTICS ASSESSMENT

➤ **LIST OF SUBMISSIONS REVIEWED:**

Submissions Reviewed	Reference ID
Original NDA Submission 211810	Dated 09/21/2018, SDN 1 (\\cdsesub1\evsprod\nda211810\0002\m2\23-qos\23p-drug-product.pdf)
Dissolution Method Development Report, IND 117332	Dated 08/02/2016, SDN 70 (\\cdsesub1\evsprod\ind117332\0069\m3\32-body-data\32p-drug-prod\plx3397-capsules-(b)(4)\32p2-pharm-dev\diss-meth-devel-rpt.pdf)
Advice Letter, IND 117332	Dated 09/28/2016 (https://darrrts.fda.gov/darrrts/ViewDocument?documentId=090140af80405f03)
Response to Information Request Comment #1	Dated 02/25/2019, SDN 14 (\\cdsesub1\evsprod\nda211810\0014\m1\us\1111-quality.pdf)
Response to Information Request Comment #2	Dated 03/15/2019, SDN 18 (\\cdsesub1\evsprod\nda211810\0019\m1\us\1111-quality-amend-2019-mar-05.pdf)

➤ **DRUG SUBSTANCE**

The active ingredient in the proposed drug product is pexidartinib hydrochloride (molecular weight 454.28 grams/mole), which is a white to off-white crystalline drug substance. The drug substance exhibits (b) (4)

(b) (4) and is used in the proposed drug product. Pexidartinib hydrochloride exhibits two pka values, $pK_{a1} = 2.6$ and $pK_{a2} = 5.4$. The log D for pexidartinib hydrochloride is 5.1 at 20 C.

- **Solubility:**

The apparent solubility profile of pexidartinib was determined in buffer solutions across the physiological pH range 1.2-6.8 at 37 C, following two hours of incubation with the drug substance (see **Table 1a**).

Table 1a. Apparent solubility of pexidartinib (PLX3397) drug substance in buffer solutions across the physiological pH range 1.2-6.8 at 37 C for 2 hours

Test media	pH of medium		Apparent solubility (Cs, µg/mL) ^a	Ratio of Cs to Cd ^b
	Initial	After equilibrium		
0.1N HCl	1.1	1.1	2451	10.1 (≥3)
0.01N HCl	2.0	2.1	2164	8.9 (≥3)
Diluted McIlivaine buffer (pH 2.5)	2.5	2.3	533	2.2
Diluted McIlivaine buffer (pH 3.0)	3.0	2.8	166	0.7
Diluted McIlivaine buffer (pH 4.0)	4.0	3.7	22	0.1
USP, Phosphate buffer (pH 6.8)	6.8	6.6	0	0
Distilled water	5.8	2.4	347	1.4

^a as pexidartinib HCl

^b Cd is defined as a nominal concentration when 217.5 mg of the drug substance as the HCl salt is completely dissolved in 900 mL of medium (217.5 mg/900 mL=242 µg/mL)

(b) (4)

Reviewer’s Assessment of Drug Substance Solubility:

Pexidartinib (PLX3397) drug substance exhibits pH-dependent solubility profile in buffer solutions across the physiological pH range 1.1-6.8 at 37 C (see **Table 1a**). Additionally, the drug substance exhibits buffering capacity in water, as a shift in the pH of water (to acidic pH) is observed at 37 C. Highest solubility of pexidartinib is in 0.1N-0.01N HCl, pH 1.1-2.1 (~2164-2451 µg/mL), with low solubility in phosphate buffer, pH 6.8. Therefore, the highest dose of pexidartinib i.e., 200 mg will not be soluble in 250 mL buffer solution across the physiological

pH range 1.2-6.8 at 37 C. Consequently, pexidartinib is categorized as a ‘low’ soluble drug substance per BCS.

(b) (4)

- **Permeability/Absorption:**

An exploratory MDR-1 permeability study PLX-008 was conducted with pexidartinib HCl drug substance (see **Table 1c**). The Papp (A-B) was determined to be 21.8×10^{-6} cm/sec in the Study PLX-008.

Table 1c. Permeability of pexidartinib (PLX3397) drug substance in MDR-1 cells from Study PLX-008

Test Substance	$P_{e(AP \rightarrow BL)}$ ($\times 10^{-6}$ cm/sec)	Mass Balance (%)	$P_{e(BL \rightarrow AP)}$ ($\times 10^{-6}$ cm/sec)	Mass Balance (%)
Pexidartinib	21.8	90	23.3	85
Propranolol ^a	49.6 ^b	74 ^b	51.4 ^b	82 ^b

Source: Module 5.3.2.2, Study **PLX-008**.

^a Propranolol is classified as a high-permeability drug in FDA Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (Aug 2000).¹

^b Data from Polli et al, 2001.²

AP = apical; BL = basolateral; FDA = Food and Drug Administration; Pe = permeability.

Additionally, a Caco-2 permeability study GE-1430-G was conducted with ¹⁴C-pexidartinib HCl drug substance (see **Table 1d**). The Papp (A-B) was determined to be 18.4×10^{-6} cm/sec in the Study GE-1430-G. The Papp ratio (Papp (B-A)/Papp (A-B)) was determined to be 1.4-1.76 in the Study GE-1430-G indicating that pexidartinib HCl exhibits low-moderate permeability as compared to propranolol, a highly permeable drug substance.

Table 1d. Apparent permeability of pexidartinib (PLX3397) drug substance in Caco-2 cells from Study GE-1430-G

Test Substance	$P_{app(AP \rightarrow BL)}$ ($\times 10^{-6}$ cm/sec)	$P_{app(BL \rightarrow AP)}$ ($\times 10^{-6}$ cm/sec)	P_{app} Ratio
¹⁴ C-Pexidartinib	18.1 ± 0.4	31.9 ± 1.1	1.76

Source: Module 5.3.2.2, Study **GE-1430-G**.

AP = apical; BL = basolateral; Caco-2 = colorectal adenocarcinoma-2 cell line; FDA = Food and Drug Administration; P_{app} = apparent permeability.

Reviewer’s Assessment of Permeability/Absorption:

Based on the overall information provided by the Applicant, pexidartinib HCl can be categorized as a ‘moderately’ permeable drug substance.

Particle Size Distribution:

Pexidartinib exhibits low aqueous solubility in buffer solutions across the physiological pH range 1.2-6.8. Particle size of the drug substance could alter the dissolution profile of the drug product. Therefore, particle size distribution (PSD) of the drug substance in the drug product was evaluated under “*Discriminatory Power of the Dissolution Method*” (see Dr. Ta-Chen Wu’s assessment dated 09/08/2016 under the IND 117332 (SN0069/SDN 70). According to Dr. Wu’s assessment, the proposed dissolution method exhibits discriminating power to differentiate drug products with different particle size of the drug substance (see Section: *Dissolution Method*).

The Applicant proposed the following three-tier PSD for the drug substance in all batches of the drug product (see **Table 2**).

Table 2. Particle size distribution (PSD) for the drug substance in the proposed drug product

Specification/Test	Acceptance Criteria	Range of batch results ^a
Particle size distribution	X ₁₀ : NMT (b) (4) μm	(b) (4) μm to (b) (4) μm
Laser diffractometry (b) (4)	X ₅₀ : NMT μm	μm to μm
	X ₉₀ : NMT μm	μm to μm

^a All batches manufactured since 2016 (includes primary stability batches, commercial-scale and commercial validation batches)

➤ ***DRUG PRODUCT:***

The to-be-marketed (TBM) 200 mg strength drug product (J-3397-AF) will be an immediate-release, green and white, size 0, hydroxypropyl methylcellulose (HPMC) (b) (4) capsule with ‘T10’ logo imprinted and containing 200 mg pexidartinib as free base.. The TBM drug product will include a change in the capsule color (b) (4) (b) (4). During a discussion with the Review Team, it is concluded that the change in the capsule color for the TBM product is a minor change. Therefore, there is no additional information needed for change in capsule color for the commercial drug product

The composition of the 200 mg proposed TBM drug product is provided in **Table 3**.

Table 3. Composition of Turalio™ containing 200 mg of pexidartinib (PLX3397) formulation J-3397-AF

Ingredient	Function	Quality standard	Weight/Unit (mg)	% w/w
Pexidartinib HCl (as pexidartinib free form)	Drug substance	Section 3.2.S.4.1	217.5 (200)	(b) (4)
Poloxamer 407				(b) (4)
Mannitol				
Crospovidone				
Magnesium stearate				
Total fill weight				
Hypromellose capsule ^a				

^a Size 0 capsule

➤ **DISSOLUTION INFORMATION:**

Dissolution testing was identified as a critical quality attribute (CQA) for the proposed drug product (b) (4) for the batches used in the pivotal clinical PK studies, and for batches on stability. The dissolution method was also utilized to select the final drug product formulation, the final manufacturing process, to bridge different batches used in the pivotal clinical study, and for the ‘waiver’ of in vivo bioequivalence studies for the commercial drug product.

➤ **DISSOLUTION METHOD:**

The dissolution method was found **ACCEPTABLE** by Dr. Ta-Chen Wu on 09/08/2016 for routine quality control testing of the proposed drug product (see in **Table 4a**). (Refer to: <https://darrts.fda.gov/darrts/ViewDocument?documentId=090140af80405f03> and **Appendix II**).

Table 4a. **ACCEPTABLE** dissolution method for Turalio™ containing 200 mg of pexidartinib (PLX3397)

Parameters	Method
<i>Apparatus/Speed</i>	USP Apparatus 2 (paddle)/75 rpm
<i>Sinkers</i>	Helix, stainless-steel
<i>Media/Volume</i>	0.01 N HCl/900 mL
<i>Bath temperature</i>	37.0±0.5 C

Selection of Dissolution Apparatus and Agitation Speed:

USP Apparatus (b) (4) and USP Apparatus 2 at (b) (4) 75 rpm paddle speed with sinkers in 900 mL 0.01N HCl was evaluated for dissolution testing of the proposed capsule product (see **Figure 1a**).

(b) (4)

(b) (4) Therefore, USP Apparatus 2 at 75 rpm paddle speed was proposed for dissolution testing of the proposed product.

Selection of Dissolution Medium:

Pexidartinib exhibits pH-dependent solubility profile

(b) (4)

(b) (4)

➤ **BIOPHARMACEUTICS RISK ASSESSMENT:**

Though the drug substance exhibits low solubility profile and polymorphic forms, the Applicant provided dissolution data [REDACTED] (b) (4) [REDACTED] (see Dr. Ta-Chen Wu's review). Additionally, the initial drug product was developed [REDACTED] (b) (4) [REDACTED]

[REDACTED] Based on the overall dissolution data at release and on stability, from a Biopharmaceutics perspective, [REDACTED] (b) (4) [REDACTED] (b) (4) the risk of dissolution failure during batch release and stability testing is relatively low.

➤ **POST-APPROVAL COMMITMENTS:** None

➤ **LIST OF DEFICIENCIES:** None

➤ **OVERALL REVIEW RECOMMENDATION:**

From the Biopharmaceutics perspective, NDA 211810 for Turalio™ containing 200 mg of pexidartinib (PLX3397) is recommended for **APPROVAL**.

APPENDIX I

Dissolution Method Development Review_IND 117332, Dr. Ta-Chen Wu (2016)



Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of New Drug Products
Division of Biopharmaceutics

BIOPHARMACEUTICS REVIEW

Division of Biopharmaceutics/Office of New Drug Products/Office of Pharmaceutical Quality

IND No (SN/SDN):	117,332 (SN0069/SDN70)
Drug Product:	Pexidartinib (PLX3397)
Dosage Form/ Strength:	Immediate-Release Oral Capsules (200 mg)
Indication:	Tenosynovial giant cell tumour (TGCT), localized and diffuse type
Type of Submission:	IND Amendment (Dissolution Method Development Report)
Applicant/Sponsor:	Daiichi Sankyo, Inc.
Date of Submission:	August 02, 2016
Date of Review:	September 08, 2016
OND Division:	Division of Oncology Products 2
Primary Reviewer:	Ta-Chen Wu, Ph.D., Biopharmaceutics Reviewer
Secondary Reviewer:	Gerlie Gieser, Ph.D., Biopharmaceutics Reviewer
Tertiary Reviewer:	Okpo Eradiri, Ph.D., Act. Biopharmaceutics Lead
Biopharmaceutics Branch Chief (Acting):	Angelica Dorantes, PhD

EXECUTIVE SUMMARY

The proposed QC dissolution method [USP Apparatus 2 (paddle) at 75 rpm with sinker, 900 mL of 0.01 N HCl solution at 37 °C ± 0.5 °C] for the routine QC of pexidartinib oral capsules during batch release and during stability testing is ACCEPTABLE. The proposed dissolution method was shown to have discriminating power for drug substance particle size, and critical formulation changes (b) (4)

(b) (4) Additionally, the chosen method parameters were shown to achieve and maintain (b) (4) conditions, and the analytical method (HPLC with UV detection) was satisfactorily validated.

The interim dissolution acceptance criterion is "Q = (b) (4)% at (b) (4) min". Full *in vitro* dissolution profile data are being collected to support the approval of a final dissolution acceptance criterion for the NDA.

BACKGROUND

The current submission contains a full Dissolution Method Development report in order to obtain the FDA'S feedback, per FDA recommendation at the Type B End-of-Phase 2 (EoP2) CMC specific meeting held on March 29, 2016.



Parnali
Chatterjee

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