CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219304Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 219304
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: A retest period of (b) (4) months is supported for vimseltinib drug substance when stored (b) (4) °C.

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

Drug Product Expiration Dating Period: A shelf life of 24 months will be applied to the drug product ((b) (4) 14 mg, 20 mg, and 30 mg) packaged in oPA-film/aluminum foil/PVC-film(oPA/Alu/PVC) blisters with push-through aluminum foil lidding when stored at controlled room temperature (stored at controlled temperature of 20°C to 25°C with excursions permitted between 15°C and 30°C). Vimseltinib capsules should remain in their original packaging until ready to be taken.

FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions (*Controlled room temperature: 20°–25° (68°–77° F)*).

[Applicant will complete this section.]

Drug Name/Dosage Form	Vimseltinib/Capsules
Strength	(b) (4) 14 mg, 20 mg, 30 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).
Applicant	Deciphera Pharmaceuticals, LLC
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	June 17, 2024
Received Date(s)	June 17, 2024
PDUFA Goal Date	February 17, 2025
Division/Office	Division of Oncology 3/Office of Oncologic Diseases
Review Completion Date	December 18, 2024

All FDA assessment is indicated in colored fonts: Executive Summary, Drug Substance, Drug Product, Environmental Assessment, labeling, Process, Facility, Biopharmaceutics, and Microbiology.

Established Name	Vimseltinib
(Proposed) Trade Name	Romvimza
Pharmacologic Class	colony-stimulating factor 1 receptor (CSF1R) inhibitor
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
NDA	*06/17/2024*	*All*
Quality Amendment	*11/04/2024*	*OPMA*
Quality Amendment	*11/25/2024*	*DS*
Labeling	*12/02/2024*	*DP*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Ray Frankewich	Haripada Sarker
Drug Product	Olen Stephens	Xing Wang
Manufacturing	Quamrul Majumder	Christine Falabella
Biopharmaceutics	Jing Li	Anitha Govada
Regulatory Business Process Manager	Janell Artis	N/A
Application Technical Lead	Xing Wang	N/A
ORA Lead	N/A	
Environmental	Olen Stephens	Xing Wang

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	III		(b) (4)	Adequate	
	III			Adequate	

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

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	131218	Vimseltinib IND

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]

1. EXECUTIVE SUMMARY

[FDA ATL will complete this section.]
The applicant has provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities are deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA219304 for ROMVIMZA (vimseltinib) capsules, for oral use.

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.

A summary of relevant regulatory correspondence with the Agency for vimseltinib under IND 131218 is provided i**n Table 1.**

Table 1: Summary of Key Regulatory Communications

Type of Meeting / Correspondence	Date	Purpose/Summary
Type B pre-IND	September 22, 2016	Discussion on the toxicology package for vimseltinib in support of initiating a human clinical study in patients with advanced cancers.
IND Submission	October 14, 2016	Submitted IND to support the initial development of vimseltinib for the treatment of advanced malignancies (study DCC-3014-01-001).
Study May Proceed letter	November 10, 2016	Clinical study protocol DCC-3014-01-001
Executive CAC	September 17, 2020	ECAC feedback of Deciphera's request for SPA for 26-week carcinogenicity study in HRAS transgenic (CByB6F1-[HRAS]2Jic) mice.
Type C Clinical Meeting (WRO)	March 03, 2020	Preliminary feedback on a registration approach for vimseltinib in TGCT indication. • Trial design including control arm, primary and secondary endpoints, and crossover option
Type C Clinical Meeting	July 22, 2020	Obtained feedback on COA and PRO measures, schedule and methods of assessment, and risk mitigation strategy for missing data for the planned registration study.
Type C Clinical Meeting	August 14, 2020	Meeting objectives included feedback on: • Preliminary design of Phase 3 study • Feedback on dose selection for pivotal trial • Control arm for Phase 3 trial and informed consent

Type of Meeting / Correspondence	Date	Purpose/Summary
Type B EOP meeting	January 12, 2021	Meeting objectives included feedback on: • Design of pivotal Phase 3 study, MOTION, including primary and secondary endpoints, statistical considerations and RP3D • Proposed safety database • Acceptability of the clinical pharmacology program • Preliminary feedback on iPSP.
Agreed iPSP	July 26, 2021	FDA agreement to iPSP for vimseltinib for a full drug-specific waiver in all pediatric subsets (0 to < (b) (4) years).
Fast Track Designation	September 28, 2021	Granted for the investigation of vimseltinib for the treatment of patients with symptomatic TGCT who are not amenable to surgery.
Executive CAC	May 05, 2022	ECAC feedback of Deciphera's request for SPA for a 104-Week carcinogenicity study in Sprague Dawley rats.
Type C CMC meeting	July 18, 2022	Meeting objective: • Seek alignment on drug product registration strategy and proposed bridging strategy for three proposed commercial dosage strengths.
Type C CMC meeting	May 10, 2023	Meeting objective: • Discuss starting materials in the synthesis of vimseltinib and the product identifiers for vimseltinib drug product capsules.
Type C Clinical Meeting	May 22, 2023	Meeting objectives included feedback on: • Plan for determining clinically meaningful thresholds for COAs of ROM, PROMIS-PF), and worst stiffness NRS • Acceptability of proposed data cutoff plan for clinical studies and proposed datasets • Safety and efficacy analyses strategy • Plan for determining clinically meaningful thresholds for selected COA measures
Type D CMC (WRO)	November 07, 2023	Meeting objective: • Review biowaiver strategy and provide draft of the biowaiver package
Type B, pre-NDA	January 16, 2024	Meeting objectives included feedback on: • Pivotal data • Planned content and format of the NDA • Regulatory, CMC, nonclinical, clinical and clinical pharmacology related filing strategy
Request for Advice	January 17, 2024	Deciphera submitted request for comments and advice to the IRT for cardiac safety studies to seek agreement on precluding the need for a dedicated thorough QT (TQT) study and gain agreement that data from the QTc assessment in study DCC-3014-01-002 can be used as a substitute for a thorough QT study.
Proprietary Name Review	May 30,2024	Conditional acceptance of proprietary name ROMVIMZA

Abbreviations: COA=clinical outcome assessment; DOR=durability of response; ECAC= Executive Carcinogenicity Advisory Committee; EOP=end of phase; IND=Investigational New Drug; iPSP=initial Pediatric Study Plan; NDA=New Drug Application; ORR=objective response rate; PRO=patient-reported outcome; RP2D=recommended phase 2 dose; ROM=range of motion; SPA=special protocol assistance; TGCT=tenosynovial giant cell tumor; WRO=written responses only.

Table 2 Key Regulatory Activities for NDA 219304

Submission Type	Date	Purpose/Summary
Part 1 of 2 NDA submission	April 29, 2024	First component containing Module 2.4 (nonclinical overview), Module 2.6 (nonclinical summaries); Module 4 (nonclinical study reports); and related administrative items in Module 1(1.4.2 Statements of Right of Reference).

Abbreviations: NDA=New Drug Application; USPI=United States product information

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

[To the Applicant: Insert text here.] Include CMC meeting dates and any Pre-NDA agreements

Table 3: Summary of Key CMC Presubmission Agreements

Type of Meeting / Correspondence	Date	Agreements
Type C CMC meeting	July 18, 2022	Type C Meeting Minutes: CMC (Ref ID: 5015519, 19-Jul-2022) • The drug product registration campaign will include three batches of the 14 mg dosage strength, three batches of the 30 mg dosage strength and one batch of the 20 mg dosage strength and will utilize at least two unique drug substance batches. The proposed blister container closure system will be child resistant and will comply with the standards set by the Consumer Product Safety Commission (CPSC) in 16 CFR 1700. The final container closure will be presented in the initial NDA. • FDA acknowledged the biowaiver request for the proposed commercial vimseltinib drug products (14, 20 and 30 mg capsules) is feasible. The proposed strategy to support the biowaiver appears reasonable. FDA has the following additional comments: • (i) Provide justification/reasons of using combined drug product batches in dissolution testing (i.e., 3x10 mg vs. 1x30 mg capsules, 1x10 mg + 2x2 mg vs. 1x14 mg); • (ii) Provide comparative dissolution profile data of all proposed commercial drug products (i.e., 14, 20 and 30 mg) vs. clinical drug product (i.e., 2 and 10 mg) by using appropriate dissolution method(s); • (iii) Provide data to demonstrate if the proposed dissolution method (USP Apparatus II Paddle, 75 rpm, 900 mL of 200 mM sodium citrate buffer, pH 2.9, 37°C) will be able to discriminate/reject drug product batches with larger drug substance particle size distribution (DS PSD) compared to the clinical batches A and B (Table 26) and commercial batch (Table 28 and 29); • (iv) The dissolution profile data of the commercial drug products using one capsule per each strength in one dissolution vessel are required for setting the dissolution quality control specification for batch release and stability testing.
Type C CMC meeting	May 10, 2023 (meeting canceled by Sponsor based	Type C Meeting Preliminary Comments: CMC (Reference ID: 5161884, 21-Apr-2023) • Based on the information in the meeting package, the Agency agrees to the proposed designated regulatory starting materials (b) (4)

Type of Meeting / Correspondence	Date	Agreements
	on preliminary comments)	(b) (4)) for the commercial synthesis of vimseltinib. At the time of NDA submission, provide detailed information on the spike, fate, and purge studies conducted to support the acceptance criteria for each specified impurity in the starting material specifications. The final determination regarding acceptability of starting materials specifications and relevant control strategies will be made at the time of NDA review • The three dosages of vimseltinib capsules are manufactured using varying text, capsule size and capsule color. The FDA agreed that the proposed text, size, and colors for the vimseltinib commercial capsules appear reasonable.
Type D CMC (WRO)	November 07, 2023	Type D Meeting Request- Written Response (Reference ID: 5273889) • Your proposed overall strategy to support the biowaiver request for the to-be-marketed 14, 20, and 30 mg vimseltinib capsules is adequate. However, we cannot address your question at this time because your response to our Advice/Information Request communication dated 09/29/2023, regarding the dissolution method development report for your drug product, is pending.
Type B, pre-NDA	January 16, 2024	CMC Feedback on Concurrent Validation for Drug Product: • At the time of NDA submission, Deciphera intends on submitting a proposal for concurrent release of PPQ batches describing the circumstances and rationale. • At the meeting, the FDA said they may be able to provide feedback on the concurrent release proposal of PPQ batches during the mid-cycle communication meeting, if there is enough information on this product's designations and rationale provided in the proposal.

Abbreviations: IND=Investigational New Drug; NDA=New Drug Application; WRO=written responses only.

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 statement or environmental assessment (EA) is made under 21 Code of Federal Regulations (CFR) Section 25.31 (b) on the basis that estimated concentration of the active moiety into the aquatic environment is less than 1 part per billion (ppb).

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

The applicant confirmed that to the best of their knowledge, no extraordinary circumstances exist that would require an environmental assessment. The applicant also

estimates the concentration of the substance at the point of entry to an aquatic environment to be below 1 ppb. Representative calculations are provided.

5. FACILITIES

[Applicant will complete this section.]
Drug substance manufacturing, packaging and testing facilities are listed below:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)			Approve - Based on Previous History
			Approve - Based on Previous History
			Approve - Based on Previous History

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

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)			Approve - Based on Previous History
			No Evaluation Necessary

(b) (4)

No Evaluation Necessary

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

The DP manufacturer has prior CHG manufacturing experience.
The DS and DP manufacturing and DS/DP testing facilities were deemed adequate based on their current cGMP compliance and past inspectional history.

(b) (4)

133 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

8. BIOPHARMACEUTICS

a. BCS Classification

Applicant to fill:	FDA assessment (FDA to fill):
BCS Classification: BCS II	Choose an item.

Information to support the BCS Class I designation request, if applicable.
Link: ***Not applicable*** Page#: NA

b. Dissolution Test

[Applicant to fill]

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
2 (Paddles)*	75 rpm	900 mL	37°C ± 0.5°C	200 mM citrate buffer at pH 2.9#	Q = (b) (4)% in 30 minutes

*Note from FDA: with sinker

#Note from FDA: In addition to the above QC dissolution method, the Applicant proposed the following Tier-2 testing method:

Apparatus	USP Apparatus II (rotating paddles) with 1L vessel
Sinker	Appropriate size, e.g. QLAACAPWHT-2S and QLAACAPWHT-02
Initial media	200 mM Citrate buffer, pH 2.90 w/ 75,000 U/L pepsin
Initial Media Volume	250 mL
Final Media	200 mM Citrate Buffer, pH 2.9 w/ 20,833 U/L pepsin
Final Media Volume	900 mL
Speed	75 rpm
Temperature	37 °C ± 0.5 °C

Biopharmaceutics Figure 1: Dissolution Profiles as a function of:

a. Impact of medium pH on dissolution

Applicant to insert figure here:

A dissolution parameter sensitivity analysis study was conducted to probe the impact of changes to dissolution medium pH and citrate buffer concentration on drug substance particle size discrimination. See Section 3.2.3 of Module 3.2.R.2. Dissolution Method Development Report.

Applicant's comments:

(b) (4)

	(b) (4) Collectively, these observations support the appropriateness of the selected conditions of 200 mM sodium citrate buffer at pH 2.9 as a good compromise of method discrimination, method precision, and suitable release rates for the dissolution method

FDA Comment:

The Applicant previously submitted the proposed dissolution method to IND 131218 (SDN# 176[1]), and FDA has conveyed a few minor deficiency comments[2] regarding the method development studies through an advice letter on 09/29/2023[3].

In the NDA submission, the Applicant updated the method development report[4] to address the FDA comments conveyed under IND 131218 regarding the originally proposed QC dissolution method. In addition, the Applicant is proposing to include a Tier-2 dissolution test due to cross-linking of the gelatin capsules that was observed (b) (4) (b) (4). The following briefly summarizes the assessment of the originally proposed QC dissolution method and the newly proposed Tier-2 testing.

[1] Dissolution method development report submitted under IND 131218.
\\CDSESUB1\EVSPROD\ind131218\0172\m3\32-body-data\32r-reg-info\dissolution-dev-rpt.pdf
[2] Biopharmaceutics review for IND 131218-SDN#176.
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806f8b28
[3] CMC advice letter dated 09/29/2023.
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af806f888c
[4] Dissolution method development report submitted to NDA 219304.
\\CDSESUB1\EVSPROD\nda219304\0002\m3\32-body-data\32r-reg-info\disso-dev-report-v3.pdf

- **QC Dissolution Method:**

The development studies for the proposed QC dissolution method (Table 8-1) have been assessed under IND131218.

Table 8-1. Proposed QC Dissolution Method Testing Parameters

Apparatus:	USP Apparatus II (Rotating Paddles) with 1 L vessel
Sinker:	Appropriate size, e.g. QLAACAPWHT-2S and QLAACAPWHT-02
Media:	200 mM Citrate Buffer, pH 2.9
Media Volume:	900 mL
Temperature:	37 °C ± 0.5°C
Sampling Volume:	3 mL
Discard Volume:	2 mL
Speed:	75 rpm
Sampling Times:	5, 10, 15, 30, 45, 60 and 90 minutes
Filter:	0.45 µm PVDF

Briefly,

- Vimseltinib exhibits pH dependent solubility, with high solubility at pH 1.0 and 3.0, and low solubility at higher pH range. Based on the 30 mg strength, the solubility of the drug substance is low overall.

Table 8-2. Aqueous pH solubility data of Vimseltinib at 37 °C

Aqueous pH Solubility Data (mg/mL)	
pH 1 (HCl buffer) @37°C	134
pH 3 (citrate buffer) @37°C	0.566
pH 5 (citrate buffer) @37°C	<0.004
pH 6.8 (phosphate buffer) @37°C	<0.004
FaSSIF (pH 6.5)	0.0012
FeSSIF (pH 5.0)	0.015

- The development studies supported the selection of the testing apparatus and dissolution media, but did not provide sufficiency justifications for the selection of the paddle speed of 75 rpm.
- The Applicant demonstrated limited discriminating ability of the proposed method towards particle size of the drug substance.
- Though the method validation reports were not assessed under the IND, the robustness studies suggest the dissolution method is sensitive to changes in testing parameters, including pH of the medium.

In the NDA submission, in addition to the information submitted to the IND, the Applicant addressed the FDA comments regarding the selection of paddle speed and method robustness.

(b) (4)

[redacted]

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

Complete dissolution profile data are available for all registration batches at release and registration and clinical combinations used for the strength dependent biowaiver in Module 5.3.1.3. All	See Module 3.2.P.5.6, Section 6.2.6 for full evaluation of all data available. In summary,

[7] Drug substance specifications. \\CDSESUB1\EVSPROD\nda219304\0002\m3\32-body-data\32s-drug-sub\vimseltinib-all\32s4-contr-drug-sub\32s41-spec\specification.pdf

multipoint dissolution profiles in graphical format for the registration and clinical batches are provided in Module 3.2.P.5.6. Furthermore, graphical trend plots are provided in 3.2.P.8.1 that show no meaningful trends were observed on stability.	the average release rate of the registration drug product batches on stability at 25°C/60% RH up to 12 months demonstrate nominally greater than (b)(4)% release by the 30-minute time point. The individual vessel data for some of the batches and stability time points at the 30 minute time interval is observed below (b)(4)% but marginally equal or higher than (b)(4)%. Approximately, 10% of the batches/time point required S-2 testing at the proposed specification with all the batches meeting the requirement of Q= (b)(4)% at 30 minutes.

FDA Comment:

The figure below shows the dissolution profiles for the clinical and registration lots based on the individual vessel data submitted to Module 5.3.1.3. The dissolution data support the proposed dissolution acceptance criterion of "Q= (b)(4)% in 30 min".

(b) (4)

Figure 8-5. dissolution profiles for the clinical and registration lots

The dissolution method is discriminating for:	Applicant to fill:	FDA assessment:
i) Particle size distribution (PSD) Link[1]: Module 3.2.P.5.6	Discriminating	Choose an item. Page#: 20 Section 6.2.6
ii) Polymorph/solid state form Link[1]: 3.2.R.2 Dissolution Method Development Report	Not discrimitating	Choose an item. Page#: 94 Section 3.2.7.1.1
iii) Formulation variations Link[1]:	Not applicable	Choose an item. Page#:
iv) Manufacturing process variations Link[1]:	Not applicable	Choose an item. Page#:
v) Gelatin Capsule Cross-linking Link[1]: 3.2.R.2 Dissolution Method Development Report	Discriminating	Choose an item. Page#: 105 Section 3.2.7.2

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

c. Bridging Throughout Drug Product Development (Formulation, Process, or Site Change)

[To the Applicant: Include a schematic representation of the development of your proposed drug product from initial IND-product to the to-be-marketed product. Include all the formulation/manufacturing/process/etc. changes that occurred throughout development, the studies (in vitro or in vivo) bridging those products, and the PK, clinical, stability-registration studies in which those products were used. Applicant provide supporting data/Figure(s) here:]

Link: ***Not applicable*** Page#: NA

[To the Applicant: Insert text here]

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

[FDA will complete this section.]
Vimseltinib drug product for clinical studies is supplied as powder-filled, hard gelatin capsules in active strengths of 2 mg and 10 mg for oral administration. Deciphera intends to commercialize the 14 mg, 20 mg and 30 mg capsules products in the US. (b) (4)

The proposed commercial-process drug product capsule formulations are compositionally identical to the 10 mg capsule formulation currently being dosed in the pivotal

registration clinical study, [redacted] The hard gelatin capsules are [redacted] Size 4 orange/white (14 mg) and Size 2 yellow/white (20 mg) and Size 1 [redacted] white (30 mg).

There is a manufacturing site change from the clinical DP to the proposed commercial DP. The proposed vimseltinib commercial-process capsules will be manufactured at [redacted]

The to-be-marketed vimseltinib capsules are manufactured using the same manufacturing process used for the 10 mg clinical vimseltinib drug product. This manufacturing process differs slightly from the process used to manufacture the 2 mg clinical vimseltinib drug product.

Table 8-8. Dose Proportional Formulations of Vimseltinib Capsules

Component	Function	Grade	Composition								
			Formulation Used During Clinical Development				Intended Commercial Formulation				
			2 mg		10 mg		[redacted]		14 mg	20 mg	30 mg
			% (w/w)	mg/unit	% (w/w)	mg/unit	% (w/w)	mg/unit	mg/unit	mg/unit	mg/unit
Vimseltinib (as dihydrate)	Active	Module 3.2.S.4.1	[redacted]						15.18	21.68	32.52
Excipients											
Lactose monohydrate [redacted]	[redacted]	NF, Ph. Eur.									
Crospovidone, [redacted]		NF, Ph. Eur.									
Magnesium stearate [redacted]		NF, Ph. Eur.									
Empty hard gelatin capsule		Manuf.							Size 4 Orange/ White	Size 2 Yellow/ White	Size 1 Light Blue/ White
Total											

Abbreviations: manuf.=manufacturer; N/A=not applicable; NF=National Formulary; Ph. Eur.=European Pharmacopoeia; w/w=weight per weight.

The clinical drug product and the proposed commercial drug products are bridged through comparative in vitro dissolution testing, as discussed in section **d. Biowaiver**.

d. Biowaiver Request

The Applicant's Position:

The NDA does contain a biowaiver request.

[To the Applicant: Explain the reasons why biowaiver is not needed for the proposed drug product. If biowaiver request is made, provide information to support the biowaiver

request, if applicable (compositional proportionality, PK linearity, comparative dissolution profiles with f2 analysis)]

Link: ***Module 1.12.15 Request for waiver of in vivo bioavailability studies*** Page#: All

[To the Applicant: Insert text here]

Deciphera is requesting a biowaiver of their 14 mg, 20 mg, and 30 mg to-be-marketed capsules under **21 CFR** § 320.22(d)(2). This request is supported by *FDA Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs — General Considerations*, *Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation* and *EMA Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*. The comparison to support the biowaiver will be based on the 2 mg and 10 mg capsules dosed in the pivotal clinical trial to the 14 mg, 20 mg, and 30 mg to-be-marketed capsules. The biowaiver requirements investigated are:

- The applicant submits evidence showing that both drug products are manufactured by the same manufacturing process/dosage form and are proportionally similar in their active and inactive ingredients.
- The bioavailability of this other drug product has been measured.
- Both drug products meet an appropriate in vitro test.
- Appropriate in vitro dissolution data should confirm the adequacy of waiving additional in vivo bioequivalence testing.

Additionally, as noted in the *FDA Guidance for Industry: Bioavailability Studies Submitted in NDAs or INDs — General Considerations*, a biowaiver may be obtained for higher strengths if linear pharmacokinetics are demonstrated over the therapeutic dose range. A summary of data demonstrating the pharmacokinetic linearity of the vimseltinib capsules over a 6 mg to 50 mg dose range is provided.

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

[FDA will complete this section.]
The Applicant proposed biowaiver request of 14 mg, 20 mg, and 30 mg to-be-marketed capsules is found acceptable based on the following justifications:

- Composition proportionality between the 14 mg, 20 mg, 30 mg (commercial) and the 10 mg (clinical) strengths, as shown in Table 8-8.
- Comparable in vitro dissolution profiles between the 14 mg, 20 mg, 30 mg (commercial) and the 10 mg (clinical) strengths, obtained using the QC

dissolution method and multi-unit samples (f2>50). The approach of using multi-unit of different strengths to achieve the same dosing regimen for the dissolution testing is acceptable. A representative comparative dissolution profiles for the 30mg regimen is provided in Figure 8-6.

- Comparable in vitro dissolution profiles between the 14 mg, 20 mg, 30 mg (commercial) and the 10 mg (clinical) strengths, obtained using the QC dissolution method and single-unit samples (f2>50).
- Comparative dissolution data between the 14 mg, 20 mg, 30 mg (commercial) and the 10 mg (clinical) strengths in multi-media testing conditions (pH 1.2, pH 4.5, and pH 6.8), which provided additional supportive information.
- PK Linearity. Vimseltinib exhibits PK linearity over the 6 mg and 50 mg range, based on Dr. Sarah Kim-McOlash's Clinical Pharmacology Assessment.

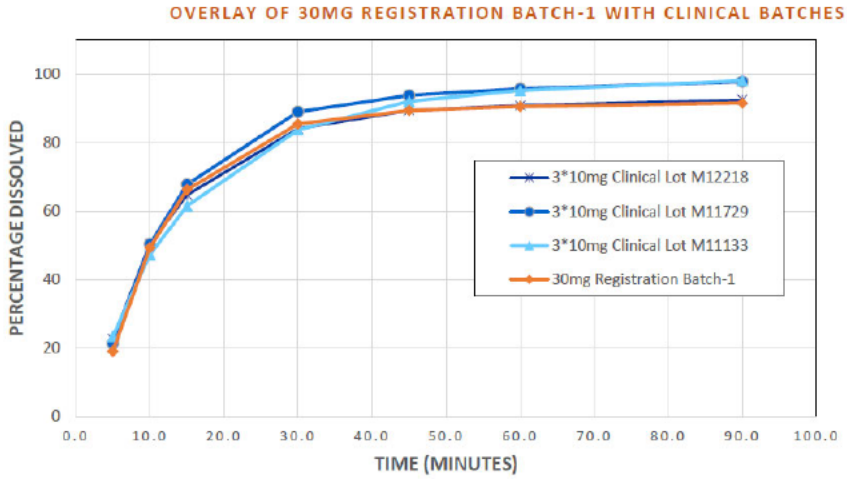


Figure 8-6. Comparative Dissolution Profiles (n=12) for 30 mg Registration Batch-1 (026133) vs 3*10 mg Clinical Batches

Overall, the biowaiver request for the to-be-marketed 14 mg, 20 mg, and 30 mg capsules is granted.

e. Data to Support IVIVC and/or PBBM Modeling, If Applicable.

[To the Applicant: Provide summary of the objective of the model, model development and validation, and outcome. Insert additional text, graphs, and table here to support the information provided above as necessary]

Link: ***Not applicable*** Page#:

[To the Applicant: Insert text here]

The FDA's Assessment: Choose an item.

[FDA will complete this section.]

9. LABELING

USPI

Highlights: ***Adequate***

Capsules: 30 mg, 20 mg, 14 mg

The 20 mg capsule includes FD&C Yellow 5 (tartrazine), so a warning statement, is necessary for potential allergic reactions. This will be coordinated with the DMEPA reviewer. Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) and No. 6 (Sunset Yellow FCF): Contains FD&C Yellow No. 5 (tartrazine) and No. 6 (sunset yellow FCF) as color additives, which may cause allergic reactions (including bronchial asthma) in certain susceptible patients. (5.11) This change was made in coordination with DMEPA.

Section 2 (if relevant): ***Not Applicable***

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

30 mg capsule
Light blue cap, white body size 1 capsule imprinted with "DCV30" in black ink.
20 mg capsule
Yellow cap, white body size 2 capsule imprinted with "DCV20" in black ink.
14 mg capsule
Orange cap, white body size 4 capsule imprinted with "DCV14" in black ink.

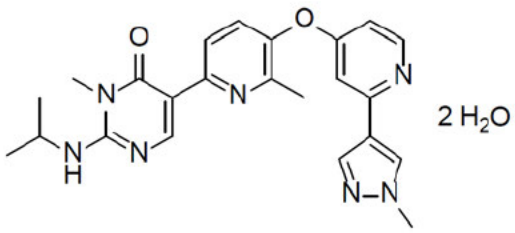
Section 11 Description: ***Not Adequate***

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

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

Vimseltinib is a kinase inhibitor (b) (4) (b) (4). The chemical name of vimseltinib dihydrate is

The molecular formula for vimseltinib dihydrate is C23H25N7O2 • 2 H2O, and the molecular weight is 467.52 g/mol. The chemical structure is:



ROMVIMZA (vimseltinib) capsules are supplied as printed hard (b) (4) capsules containing 14 mg, 20 mg, or 30 mg of vimseltinib (equivalent to 15.18 mg, 21.68 mg, or 32.52 mg of vimseltinib dihydrate, respectively). The capsule contains the following inactive ingredients: lactose monohydrate, crospovidone, and magnesium stearate. The capsule shell contains gelatin, titanium dioxide, Brilliant Blue FCF (30 mg strength), erythrosine (30 mg strength), Sunset Yellow FCF (14 mg and 20 mg strengths), and tartrazine (20 mg).

The applicant was asked to include chemical and physical description of the drug substance, which were incorporated into the label.

Section 16 How Supplied/Storage and Handling: Choose an item.
ROMVIMZA 30 mg capsules (b) (4) size 1 hard gelatin capsules with white body and light blue cap with black print "DCV30", packed in oPA-film/aluminum foil/PVC-film blisters with push-through aluminum foil lidding. (b) (4) (b) (4)

ROMVIMZA 20 mg capsules (b) (4) size 2 hard gelatin capsule with white body and yellow cap with black print "DCV20", packed in oPA-film/ aluminum foil /PVC-film blisters with push-through aluminum foil lidding. (b) (4) (b) (4)

ROMVIMZA 14 mg capsules (b) (4) size 4 hard gelatin capsule with white body and orange cap with black print "DCV14", packed in oPA-film/ aluminum foil /PVC-film blisters with push-through aluminum foil lidding. (b) (4) (b) (4)

Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
Do not (b) (4) ROMVIMZA in another container. (b) (4) (b) (4)

The (b) (4) *was removed* (b) (4).

Manufacturer Information (Name and Address): ***Not Provided: Not Adequate***
The applicant was instructed to add this information and it is present in the current label.

In the patient labeling, the storage conditions was reversed to list Fahrenheit before Celsius and is correct in the current label.

Carton/Container Label ***Adequate***

No substantive, information based changes are needed for the current container closures.

(b) (4)

[redacted]

4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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	
Moisture content	• Formulation • Container closure • Process parameters • Scale/equipment • Site	Low		Low	
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	Low		Low	

Recommendation Page

[FDA will complete this section.]

Drug Substance: Approval

Primary Reviewer: Raymond P. Frankewich, Ph.D. Date: December 16, 2024
Secondary Reviewer: Haripada Sarker, Ph.D. Date: December 17, 2024

Drug Product: Approval

Primary Reviewer: Olen Stephens Date: December 3, 2024
Secondary Reviewer: Xing Wang Date: December 18, 2024

Manufacturing: Approval

Primary Reviewer: Quamrul Majumder Date: December 3, 2024
Secondary Reviewer: Christine Falabella Date: December 18, 2024

Biopharmaceutics: Approval

Primary Reviewer: Jing Li Date: November 21, 2024
Secondary Reviewer: Anitha Govada Date: December 18, 2024

Application Technical Lead: Approval

Xing Wang Date: December 18, 2024

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
12/18/2024 11:25:52 AM

RAYMOND P FRANKEWICH
12/18/2024 12:14:44 PM

HARIPADA SARKER
12/18/2024 10:36:49 PM
DS review for IQA.

OLEN M STEPHENS
12/19/2024 07:26:47 AM

QUAMRUL MAJUMDER
12/19/2024 10:13:53 AM

CHRISTINE A FALABELLA
12/19/2024 10:53:00 AM

ANITHA P GOVADA
12/19/2024 10:59:11 AM