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RESEARCH**

APPLICATION NUMBER:

219304Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

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

Application Type	505(b)(1) New Drug Application (New Molecular Entity)
Application Number(s)	219304
Priority or Standard	Priority
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 Oncology Drugs
Review Completion Date	See stamp date
Established Name	Vimseltinib
(Proposed) Trade Name	ROMVIMZA
Pharmacologic Class	kinase inhibitor
Code name	DCC-3014
Applicant	Deciphera Pharmaceuticals
Formulation(s)	Capsules: 30 mg, 20 mg, 14 mg
Dosing Regimen	30 mg orally twice weekly
Applicant Proposed Indication(s)/Population(s)	Is a kinase inhibitor indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).
Recommendation on Regulatory Action	Traditional Approval
Recommended Indication(s)/Population(s) (if applicable)	Is a kinase inhibitor indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

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DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GLP	good laboratory practice

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GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event

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SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

Vimseltinib is a new molecular entity (NME), pursuant to regulations under 21 CFR 601. Vimseltinib (ROMVIMZA[®]) is an oral, small molecule kinase inhibitor of colony-stimulating factor 1 receptor (CSF1R). At the time of the New Drug Application (NDA) submission on June 17, 2024, vimseltinib was not approved for any indication in the United States or elsewhere.

The Applicant's proposed indication at the time of the NDA submission was: ROMVIMZA is a kinase inhibitor indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).

1.2 Conclusion on the Substantial Evidence of Effectiveness

The review team concluded that the submitted data provide substantial evidence of efficacy with acceptable safety of vimseltinib for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity. This conclusion is based on the results of Part 1 of Study DCC-3014-03-001 (MOTION), a double-blind, multicenter, randomized (2:1), placebo-controlled study in 123 adult patients with symptomatic TGCT for which surgical resection would potentially cause worsening functional limitation or severe morbidity, as judged by surgical consultation or a multidisciplinary tumor board. Symptomatic disease was defined as experiencing at least moderate pain or moderate stiffness within the screening period. Pain was assessed using the Brief Pain Inventory (BPI) Worst Pain numeric rating scale (NRS); stiffness was assessed using the Worst Stiffness NRS. A score of 4 or more out of 10 (with 10 being the worst condition) on either scale was required to define moderate pain or stiffness for inclusion purposes. Patients received vimseltinib (n=83) 30 mg twice weekly or placebo (n=40) through Week 24 during the double-blind (Part 1) part of the study. During the open-label period (Part 2), patients could continue to receive vimseltinib or crossover from placebo to receive vimseltinib until disease progression or unacceptable toxicity. The primary efficacy endpoint was objective response rate (ORR) at Week 25 as assessed by a blinded independent radiological review (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The ORR in the primary efficacy analysis population of MOTION for the vimseltinib arm was 40% (95% confidence interval [CI]: 29, 51) with 4 (5%) patients experiencing a complete response. Of the 33 patients who experienced an objective response who were followed for an additional 6 months from the time of ORR primary analysis, duration of response (DOR) was ≥ 6 months for 85% of patients and ≥ 9 months for 58% of patients. There were no responders in the placebo arm.

The key secondary endpoints and patient-reported outcome (PRO) endpoints included:

- ORR per tumor volume score (TVS) at Week 25
- change from baseline in active range of motion (ROM) of the affected joint, relative to a reference standard, at Week 25
- change from baseline in the Patient-Reported Outcomes Measurement Information System-Physical Function (PROMIS-PF) score at Week 25
- change from baseline in the Worst Stiffness NRS score at Week 25
- change from baseline in EuroQoL Visual Analogue Scale (EQ-VAS) at Week 25, and
- response of at least a 30% improvement in the mean BPI Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25.

In general, these secondary endpoints supported the primary endpoint results, and the review team included results of the change from baseline in ROM, PROMIS-PF, and BPI analyses in product labeling. Further discussion of these endpoint results are described in the review Sections 8.1.1. and 8.1.2

TGCT is a rare, serious condition that is associated with significant morbidity; patients with TGCT represent a population with a high unmet medical need. The Applicant has demonstrated substantial evidence of effectiveness of vimseltinib in patients with TGCT based on clinically meaningful durable tumor shrinkage accompanied by supportive improvements in clinical outcome assessments including ROM, physical function, and pain. Therefore, the review team recommends granting traditional approval to vimseltinib for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity. The review team modified the indication statement from the Applicant's proposed indication of "treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT)". In addition to requiring patients to have symptomatic disease as described previously, an additional inclusion criterion for patients enrolling in MOTION was that surgical resection would potentially cause worsening functional limitation or severe morbidity. The review team regarded this additional criterion to be essential as part of the indicated patient population given that local treatment with surgery can be effective if feasible, and patients for whom surgery was likely to result in good functional outcomes were not studied in MOTION. As such the review team revised the indication statement accordingly.

1.2. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Tenosynovial giant cell tumors (TGCTs) are a rare, locally aggressive, non-malignant tumor that typically arises from the joints, bursa and tendon sheaths. TGCT is not life-threatening and does not metastasize but may cause significant morbidity impacting a patient's quality of life (Stacchiotti 2023). It exhibits a female predilection (2:1) and primarily affects patients between 20 and 50 years, although it can occur at any age. Because of the rarity of TGCT, there is very limited data in the literature regarding predilection for race or ethnicity. One study conducted in 83 patients with TGCT who received pexidartinib showed that 65% of patients were White, 18% per Other. 8% were Black, and 1.2% were missing. There were no Native Americans or Native Hawaiian or other Pacific Islander reported (Lin 2024). There are two subtypes of TGCT, diffuse and localized. Diffuse TGCT (dTGCT) tends to affect the larger joints, most commonly the knee and tends to be locally aggressive and have a higher recurrence rate of approximately 55%. Localized (lTGCT) disease commonly affects the digits and the wrists and has a recurrence rate of 15% (Ehrenstein 2017). The estimated overall annual incidence in the United States (US) of 11 cases per million; 1.8 cases per million for diffuse-type TGCT and 9.2 cases per million for localized TGCT (Lopez-Bastida 2021). From the largest TCGT registry worldwide, the Danish study reported the prevalence of lTGCT and dTGCT as 44/100,000 and 11/100,000, respectively. The 5-year recurrence-free survival (RFS) for lTGCT is 70–90 % and 30–80 % for dTGCT (Stacchiotti 2023).

Surgery remains the mainstay of treatment for TGCT; however, there is no consensus on the optimal treatment as surgery can lead to joint damage, functional limitations, and recurrence (Stacchiotti 2023). In TGCT, a translocation in CSF1-COL6A3, t(1;2)(p13;q35-37), leads to overexpression of colony stimulating factor 1 (CSF1). In patients with unresectable relapsed and/or recurrent TGCT, agents that inhibit CSF1R, represent a logical therapeutic approach (Tap 2015). Pexidartinib was approved by the US Food and Drug Administration (FDA) for patients with TGCT associated with severe morbidity or functional limitations and not amenable to surgery. However, in the pivotal study to support approval, ENLIVEN, 3 of 61 (5%) patients who received pexidartinib developed signs of serious liver injury. Hepatotoxicity including liver failure and life-threatening vanishing bile duct syndrome, ductopenia, and symptomatic cholestasis can occur. Thus, pexidartinib has a boxed warning for hepatotoxicity and a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU) to mitigate the risk of serious and potentially fatal liver injury. Per the National Comprehensive Cancer Network (NCCN) guidelines for Soft Tissue Sarcoma v1.2023, other systemic treatment options include nilotinib and imatinib in certain circumstances. Radiation therapy may be in used in some certain circumstances including patients with relapsed disease or when surgery results in residual tumor. It has been reported to potentially reduce the risk of recurrence (Griffin 2012 and Stacchiotti 2023).

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The data submitted by the Applicant to support the efficacy of vimseltinib in patients with TGCT come from the MOTION study, an international, multicenter, randomized, double-blind, placebo-controlled study in 123 adult patients with symptomatic TGCT and forms the primary basis on which the Applicant is seeking approval of vimseltinib in the proposed indication. The major efficacy endpoint was ORR assessed by blinded IRC via RECIST v1.1. ORR at Week 25 in patients who received vimseltinib compared to placebo was 40% (95% CI: 29, 51) with 4 (5%) experiencing a complete response for patients on the vimseltinib arm and 0% (95% CI: 0, 9) for patients on the placebo arm (p-value <0.0001). Of the 33 patients who experienced an objective response who were followed for an additional 6 months from the time of ORR primary analysis, duration of response was ≥ 6 months for 85% of patients and ≥ 9 months for 58% of patients. To support an overall favorable risk:benefit based on the effect on ORR, FDA conducted analyses on active ROM and PROs using the PROMIS-PF and BPI-30. The primary endpoint of ORR was supported by statistically significant improvements in active range of motion, patient-reported physical functioning, and patient-reported pain observed in the vimseltinib arm compared to the placebo arm at Week 25.

Safety data supporting the proposed indication reflected exposure to vimseltinib in patients enrolled on the MOTION study (83 patients exposed to vimseltinib and 38 patients exposed to placebo). The most common adverse events for patients treated with vimseltinib included increased aspartate aminotransferase (AST), periorbital edema, fatigue, rash, increased cholesterol, peripheral edema, face edema, decreased neutrophils, decreased leukocytes, pruritus, and increased alanine aminotransferase (ALT).

An additional 135 patients with TGCT or other solid tumors from study DCC-3014-01-001, an open-label, single arm, dose escalation and expansion study evaluating vimseltinib in patients with advanced solid tumors including TGCT were evaluated in the integrated summary of safety.

Both pexidartinib and vimseltinib are kinase inhibitors that inhibit CSF1R. Given the important identified risk of severe hepatotoxicity observed with the use of pexidartinib, FDA performed a comprehensive analysis of the risk of hepatotoxicity associated with vimseltinib. FDA considered the need for a Boxed Warning and REMS based on a possible class effect and the identified risk for hepatotoxicity with use of pexidartinib. However, the safety data from the 253 patients who received at least one dose of vimseltinib in MOTION (including 35 patients who crossed over to receive vimseltinib during the open-label portion) or in the supportive study DCC-3014-01-001 did not identify a risk of serious or significant hepatotoxicity that would require a REMS or a boxed warning. While Grade 1 AST or ALT elevations were common, these did not lead to clinically significant hepatic toxicity or liver injury, with no cases of Hy's law observed. The Applicant argued that the mechanism of action for drug induced liver injury observed with pexidartinib (specifically, cholestatic toxicity) may be due to its unique biomolecular

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characteristics, including metabolites, rather than due to a class effect of agents targeting the CSF1R pathway. While the FDA reviewed the literature and concluded that the presence of unique metabolites might possibly explain pexidartinib-associated hepatotoxicity, the review team concluded that the nonclinical and clinical data could not fully rule out the risk for hepatotoxicity with this class of drugs including vimseltinib. Therefore, the review team included a section 5 warning regarding hepatotoxicity in product labeling (See Sections 5 and 8.2.5 for details). Additionally, a post-marketing requirement (PMR) registry study collecting data on liver function for an additional at least 100 patients dosed with vimseltinib in the postmarketing setting was agreed upon for this application. FDA also instituted an enhanced pharmacovigilance plan to capture hepatotoxicity in the postmarketing setting for patients not enrolled on the registry (See Sections 8.2.5 and 13 for details).

Additional warnings and precautions included in section 5 of product labeling are embryo-fetal toxicity, allergic reactions to FD&C Yellow No.5 and No.6 and increased creatinine without impact on renal function.

A favorable risk:benefit assessment has been established for vimseltinib for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation based on the results of a single study, MOTION. Given the rarity of TGCT and small sample size, there are limited data to draw conclusions regarding subgroup analyses (i.e., race, age, sex, etc.) from this application.

Postmarketing requirements for vimseltinib include the PMR registry study for hepatotoxicity described above, a PMR evaluating vimseltinib in participants with moderate hepatic impairment, a carcinogenicity study, and 3 PMRs to evaluate the potential for drug-drug interactions (with substrates of BCRP, OATP1B1/OATP1B3, and OCT2).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• TGCT is a rare neoplasm, with locally aggressive tumors that do not metastasize. • TGCT manifests as one or more tumors that grow in extra-articular synovial tissues or can be an intra-articular process involving the synovium and bursae. • Tumor mass typically expands in a slowly progressive manner.	TGCT is a serious disease that can result in significant morbidity.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Patients experience pain, stiffness, swelling and reduced ROM that impacts quality of life. • The annual incidence of TGCT in the United States is estimated to be 11 cases per million people. This is based on an estimate that 9.2 cases per million are localized TGCTs and 1.8 cases per million are diffuse-type TGCTs. • Recurrence rates are variable and have been reported to be 15% for localized disease and 55% for diffuse disease. Even higher rates of recurrence have been reported.	
<u>Current Treatment Options</u>	• Excision of tumor is the mainstay of treatment. Patients may require repeated surgical procedures, sometimes leading to loss of function, joint replacement, or amputation. • Pexidartinib is the only FDA-approved systemic therapy in this setting, demonstrating an ORR of 38% (95% CI: 27, 50), with 22/23 responders with ≥ 6 months of follow-up maintaining response for ≥ 6 months. Pexidartinib is available to patients only through implementation of a REMS due to severe and life-threatening liver toxicity, with an associated boxed warning. • Imatinib and nilotinib are listed in the NCCN guidelines for soft tissue sarcoma as useful in certain circumstances. • Radiation therapy may be reserved for those who are not surgical candidates and may reduce the risk of recurrence.	There is an unmet medical need for new effective systemic treatments for patients with TGCT. Due to the nature of TGCT tumors, complete surgical resection is often challenging and the risk of recurrence is variable and has been reported to be as high as 70%. The only approved drug for this condition is not curative and can cause life-threatening hepatotoxicity.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	- The data to support efficacy of vimseltinib was evaluated in the MOTION Study. - The ORR at Week 25 in the vimseltinib arm 40% (95% CI: 29, 51) and 0% (95% CI: 0, 9) for the placebo arm. - Of the 33 patients who treated with vimseltinib who experienced an objective response, duration of response was ≥ 6 months for 85% of patients and ≥ 9 months for 58%. - ROM and PRO data were collected during the conduct of the study to assess PRO measures from baseline over time. Results were supportive of clinical benefit.	MOTION demonstrated a clinically meaningful and durable response in patients who received vimseltinib compared to placebo. Secondary endpoints including ROM and PROs were generally supportive of ORR. ORR is an acceptable endpoint to support approval in this context. ORR results are supported by clinical outcome assessments including improvement in ROM and PROs. The submitted data meets the evidentiary standards for traditional approval in the proposed patient population.
<u>Risk and Risk Management</u>	- The toxicity profile for vimseltinib includes increased AST, periorbital edema, fatigue, rash, increased cholesterol, peripheral edema, face edema, decreased neutrophils, decreased leukocytes, pruritus, and increased ALT. Toxicities were generally manageable with supportive care or dose modifications. - AST/ALT elevations in particular were almost all Grade 1, with no Grade 3 events. - Treatment with another CSF1R targeted drug, pexidartinib, confers a risk of hepatotoxicity. The potential risk of liver injury to patients receiving vimseltinib was thus a major review issue. Although low-	Severe hepatotoxicity was not observed in a total of 253 patients treated with vimseltinib, however hepatotoxicity is seen in patients treated with pexidartinib, another kinase inhibitor that inhibits CSF1R. Though the structure of pexidartinib and resultant metabolites may account for some of the hepatotoxicity (specifically cholestatic hepatotoxicity), nonclinical and clinical data could not fully rule out the risk for hepatotoxicity with vimseltinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	grade transaminase elevations from baseline were common, there were no discontinuations, Hy’s law cases, or other severe hepatotoxicity events that occurred to patients in MOTION, and data from the additional 135 patients from supportive study DCC-3014-01-001, or in the additional 35 patients from the open-label portion of MOTION similarly showed no evidence of severe liver injury.	While there was no clinical safety data consistent with severe liver toxicity, given the similar MOA to pexidartinib and limited clinical safety experience, the review team included a warning about hepatotoxicity in Section 5 of vimseltinib product labeling. Additionally, a PMR registry study will capture additional data on hepatotoxicity, in addition to an enhanced pharmacovigilance plan. (See section 8.2.5 for details).

1.3. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

x	The patient experience data that was submitted as part of the application, include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		
		x	Patient reported outcome (PRO)	Sections 8.1.1 and 8.1.2
		☐	Observer reported outcome (ObsRO)	

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	☒	Clinician reported outcome (ClinRO)	Sections 8.1.1 and 8.1.2
	☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data	
	☐	Natural history studies	
	☐	Patient preference studies (e.g., submitted studies or scientific publications)	
	☐	Other: (Please specify)	
☐		Patient experience data that was not submitted in the application, but was considered in this review.	

Patient-reported outcomes based secondary endpoints were used to assess the overall clinical benefit in support of the marketing application. The following PRO measures were used:

- Patient-reported Outcomes Measurement Information System -Physical Function (PROMIS-PF)
- Change from baseline in the Worst Stiffness numeric rating scale (NRS)
- euroQol visual analogue scale (EQ-VAS) (also known as 5-level EuroQual-5D [EQ-5D-5L] VAS)
- Brief Pain Inventory (BPI) Worst Pain NRS score

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X

Leslie Doros
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Tenosynovial giant cell tumor (TGCT) is a rare tumor arising from the synovium of joints, bursae, and tendon sheaths (de St. Aubain Somerhausen and van de Rijn, 2013) caused by dysregulation of the colony stimulating factor 1 (CSF1) gene which results in overproduction of CSF1 and recruitment of CSF1 receptor (CSF1R)-dependent inflammatory cells into the affected joint (van der Heijden et al, 2023; West et al, 2006). The lesion can either present as a single nodule (localized form) or as multiple nodules (diffuse form) along a synovial layer or tendon sheath. The annual incidence rate of TGCT in the United States (US) is reported as approximately 11 per million (localized: 9.2 per million and diffuse TGCT: 1.8 per million) (Myers and Masi, 1980), with a more recent epidemiological study from the Netherlands reporting a higher worldwide incidence of 43 per million (digits: 29 per million; localized extremities: 10 per million; and diffuse TGCT: 4 per million) (Mastboom et al, 2017). Surgical resection is considered the first treatment option; however, patients may present with inoperable disease or may not be suitable candidates for surgery. Surgery for such patients could cause significant functional limitation or severe morbidity. In addition, relapse rates have been reported for up to 50% of diffuse-type TGCT patients, requiring repetitive surgical treatment that can lead to substantial damage to the affected joint and impaired quality of life (QoL) (Gouin and Noailles, 2016; Staals et al, 2016). As patients are typically diagnosed early in life (35 to 50 years old), limitations from increased morbidity can have a significant impact on QoL (Mastboom et al, 2018, Stacchiotti et al, 2023).

Although TGCT is not life threatening, patients carry the burden of requiring anti-inflammatory and analgesic medications, including opioids, to alleviate the severe pain and debilitation. Additionally, for patients who undergo multiple surgeries, there is also the burden of rehabilitation and recovery after every procedure, which also contributes to associated morbidities. Thus, systemic disease targeted therapy is necessary for patients with inoperable or recurrent TGCT.

The FDA's Assessment:

FDA agrees with applicant's overall assessment. Recurrence rate for patients with localized TGCT is lower than patients with diffuse TGCT (dTGCT), and the reported rate of recurrence for patients with dTGCT has been reported to be as high as 70% (Stacchiotti 2023). In this rare tumor, little data is reported on the race and ethnicity of patients with TGCT. One study conducted in 83 patients with TGCT who received pexidartinib, showed that 65% of patients were White, 18% per Other, 8% were Black, and 1.2% were missing. There were no Native

Americans or Native Hawaiian or other Pacific Islander reported. Most patients (69% of vimseltinib treated, 70% of placebo treated) had diffuse TGCT. In all patients, the most commonly affected joint was knee (68% in both vimseltinib and placebo treated), followed by ankle (11%, 15%) and hip (13%, 2.5%). Mean age at time of enrollment is similar in patients treated with vimseltinib (44, range: 20-78 years old) and placebo (42.5, range: 21-72)

2.2. Analysis of Current Treatment Options

Surgery remains the recommended treatment for all forms of TGCT, when feasible. Localized TGCT can generally be surgically removed, but removal of diffuse TGCT may be challenging because the diffuse nature of the lesions may make full excision difficult ([van der Heijden et al, 2023](#)). Retrospective analysis of patients with newly diagnosed or first relapse TGCT was conducted to understand surgical outcomes and shows most patients (85%) with localized form of TGCT have a complete resection, while only 37% of patients with diffuse type of TGCT have a complete resection ([Palmerini et al, 2015](#)).

Recurrence is observed in both forms of the disease following surgery. In localized TGCT, reported recurrence rate is approximately 10% after surgery ([Gouin and Noailles, 2016](#); [Staals et al, 2016](#); [van der Heijden et al, 2023](#)). Recurrence of localized TGCT is strongly associated with a negative outcome. Approximately 43% of patients who experience a relapse, even after a complete surgical resection, have a subsequent relapse within 5 years ([Palmerini et al, 2015](#)). Recurrence rates are considerably higher for diffuse TGCT, up to 55% ([Ehrenstein et al, 2017](#); [Gouin and Noailles, 2016](#); [Staals et al, 2016](#)) and a relapse-free survival rate of approximately 40% in 10 years ([van der Heijden et al, 2023](#)). Patients with recurring TGCT may require repetitive surgical treatment that can lead to substantial damage to the affected joint and impaired QoL ([Gouin and Noailles, 2016](#); [Staals et al, 2016](#); [Mastboom et al, 2018](#)). Eventually, some patients may require limb amputation for severe complications or present with metastatic disease ([Gouin and Noailles, 2016](#); [Staals et al, 2016](#)). Multiple surgeries owing to recurrence may not be possible for patients who have significant risks associated with open surgery (eg, older patients, patients with comorbidities), or present with inoperable disease. Surgery for such patients could cause significant functional limitation or severe morbidity.

Systemic therapies have been tested in patients with locally advanced or relapsed diffuse TGCT ([Brahmi et al, 2016](#)), including kinase inhibitors that non-selectively target the CSF1/CSF1R axis (eg, imatinib and nilotinib), and monoclonal antibodies targeting CSF1R expression (eg, emactuzumab, and cabiralizumab) ([Stacchiotti et al, 2023](#); [Gronchi et al, 2021](#)). These kinase inhibitors have not been developed for the treatment of TGCT and have been accessed outside of approved labeling for the treatment of TGCT, and monoclonal antibodies are investigational. Best clinical practices have justified the use of systemic therapies in symptomatic TGCT based on the location and extent of the disease, particularly if disease progression or surgical intervention may result in joint damage and affect QoL ([Stacchiotti et al, 2023](#)).

Pexidartinib (TURALIO®), a kinase inhibitor of CSF1R, cellular homolog of the feline sarcoma viral oncogene v-kit (KIT), and FMS-like tyrosine kinase 3 (FLT3), was approved by the Food

and Drug Administration (FDA) in 2019 for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. The approval was based on the results of the placebo-controlled, double-blind Phase 3 study (ENLIVEN) showing an objective response rate (ORR) of 38% for the pexidartinib arm over 0% in the placebo arm at study Week 25. However, pexidartinib can cause serious and potentially fatal liver injury and its use requires frequent liver tests for monitoring of liver toxicity. Pexidartinib's prescribing information includes a black box warning of hepatotoxicity and is only available to patients in the United States through a risk evaluation and mitigation strategy (REMS) program ([TURALIO USPI, 2023](#)).

A high unmet medical need remains for a selective CSF1R inhibitor with a more favorable risk/benefit profile.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of currently available treatments. In many patients, surgery is potentially curative, and surgery is often recommended as first-line treatment in patients for whom surgery would not worsen morbidity of functioning. Surgical options may include marginal excision with synovectomy, debulking surgery, total joint replacement and in rare cases, amputation. In patients for whom surgery is not an option, pexidartinib is the only FDA-approved drug; however, pexidartinib is only available through a REMS program and has a box warning due to risk of serious, potentially irreversible, liver injury, including vanishing bile duct syndrome. Pexidartinib was approved based on a multi-center, double-blind, placebo-controlled study which demonstrated an ORR per RECIST at Week 25 of 38% (95% CI: 27, 50). Twenty-two of the 23 patients who achieved a response and had been followed for at least six months had maintained the response for ≥ 6 months. Additionally, patients who received pexidartinib experienced a statistically significant improvement in range of motion.

Per NCCN guidelines, imatinib and nilotinib are other systemic therapies that are useful in certain circumstances. In certain circumstances, radiation can be considered for patients with diffuse or recurrent TGCT, though data does not currently support inclusion of radiotherapy as a standard treatment. Postsurgical external beam radiation has been shown to improve functional status and provide local control in some patients (Baniel 2023). In all patients with TGCT, active surveillance may be considered, and the risks and benefits of potential treatment must be evaluated for each individual patient. Patients with a low symptom burden and patients for whom surgery would likely not be curative and may increase morbidity may benefit from active surveillance.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Vimseltinib was studied under IND 131218 for the treatment of advanced solid tumors and symptomatic tenosynovial giant cell tumor (TGCT) by Deciphera Pharmaceuticals, LLC.

Vimseltinib is a new molecular entity, and at the time of this application, is currently not approved for marketing in the United States or in any other country.

The FDA's Assessment:

The results of MOTION were used as the main study for the review of the application to assess the overall risk:benefit in the proposed indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

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

Applicant – Summary of Key Regulatory Communications

Table 1 Summary of Key Regulatory Communications

Type of Meeting / Correspondence	Date	Purpose/Summary
Type B pre-IND	22-Sept-2016	Discussion on the toxicology package for vimseltinib in support of initiating a human clinical study in patients with advanced cancers.
IND Submission	14-Oct-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	10-Nov-2016	Clinical study protocol DCC-3014-01-001
Type C Clinical Meeting	03-Mar-2020	Preliminary feedback on a product development/registration approach for vimseltinib in TGCT indication.
Type C Clinical Meeting	22-Jul-2020	Preliminary feedback on COA and PRO measures, schedule and methods of assessment, and risk mitigation strategy for missing data for the planned registration study.

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Type of Meeting / Correspondence	Date	Purpose/Summary
Type C Clinical Meeting	14-Aug-2020	Meeting objectives included preliminary feedback on key elements of the proposed Phase 3 study MOTION, including study endpoints, eligibility criteria, sample size/randomization ratio, study duration, and statistical methodology.
Executive CAC	17-Sep-2020	ECAC feedback of Deciphera's request for SPA for 26-week carcinogenicity study in HRAS transgenic (CByB6F1-[HRAS]2Jic) mice.
Type B EOP meeting	12-Jan-2021	Meeting objectives included feedback on: the design of pivotal Phase 3 study, MOTION, including primary and secondary endpoints, statistical considerations and RP3D, the proposed safety database, the acceptability of the clinical pharmacology program and preliminary feedback on iPSP
Agreed iPSP	26-Jul-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	28-Sep-2021	Granted for the investigation of vimseltinib for the treatment of patients with symptomatic TGCT who are not amenable to surgery.
Executive CAC	05-May-2022	ECAC feedback of Deciphera's request for SPA for a 104-Week carcinogenicity study in Sprague Dawley rats.
Type C CMC meeting	18-Jul-2022	Meeting objective to seek alignment on drug product registration strategy and proposed bridging strategy for three proposed commercial dosage strengths.
Type C CMC meeting	10-May-2023	Meeting objective to discuss starting materials in the synthesis of vimseltinib and the product identifiers for vimseltinib drug product capsules.
Type C Clinical Meeting	22-May-2023	Meeting objectives included feedback on: clinically meaningful thresholds for selected COAs measures, acceptability of data cutoff plan for clinical studies and proposed datasets and safety and efficacy analyses strategy for NDA
Type D CMC	07-Nov-2023	Meeting objective to review biowaiver strategy and provide draft of the biowaiver package.
Type B, pre-NDA	16-Jan-2024	Meeting objectives included feedback on: Pivotal data, content and format of the NDA and regulatory filing strategy
Request for Advice	17-Jan-2024	Request for feedback to IRT on cardiac safety studies and to seek agreement on precluding the need for a dedicated thorough QT (TQT) study.
Proprietary Name Review	30-May-2024	Conditional acceptance of proprietary name ROMVIMZA.

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Abbreviations: COA=clinical outcome assessment; ECAC= Executive Carcinogenicity Advisory Committee; EOP=end of phase; IND=Investigational New Drug; iPSP=initial Pediatric Study Plan; NDA=New Drug Application; PRO=patient-reported outcome; RP3D=recommended phase 3 dose; SPA=special protocol assistance; TGCT=tenosynovial giant cell tumor.

Applicant - Key Regulatory Activities for NDA 219304

Table 2 Key Regulatory Activities for NDA 219304

Submission Type	Date	Purpose/Summary
Part 1 of 2 NDA submission	29-Apr-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.
Part 2 of 2 NDA submission	17-Jun-2024	Second component to complete the NDA submission containing Module 2.2 (introduction), Module 2.5 (clinical overview), and Module 2.7 (clinical summaries); Module 5 (CSRs); Module 2.3 (quality overall summary); Module 3 (quality) and outstanding administrative items in Module 1 including draft USPI and draft carton and container labels.

Abbreviations: CSR=clinical study report; NDA=New Drug Application; USPI=United States product information

The FDA's Assessment:

1. In general, FDA agrees with Applicant's assessment with the following additions noted by the reviewer: Type C Meeting, March 3, 2020: FDA recommended the Applicant consider a study that includes an internal control and stated that FDA was open to a randomized controlled study with a provision for patients crossing over following a limited treatment course for patients randomized to placebo. FDA stated that patients must have surgical consultation prior to enrollment in MOTION, as surgery is potentially curative in some patients.
2. Type C Meeting, July 22, 2020: FDA provided extensive feedback on COA and PRO elements. FDA agreed that proposed concepts of interest (ROM, physical function, pain, stiffness, swelling and joint instability) are important and relevant to the experience of patients with TGCT. FDA requested additional information on the proposed inclusion of qualitative data via the 15 PROMIS-PF measure, which Deciphera provided. FDA agreed with the use of PROMIS-PF and noted that the assessment may bias towards showing less of a response in patients with upper extremity TGCT. FDA agreed that the worst pain NRS was a content-valid item. FDA recommended that interpretation of worst stiffness and worst swelling be done with consideration for potential confounders and noted that qualitative data in RA suggests that patients may not be able to differentiate between stiffness, pain, and swelling. The Applicant proposed removal of the question regarding joint instability, and FDA agreed.

3. Type C Meeting, August 14, 2020: FDA agreed to the key design elements proposed for MOTION and agreed to the study endpoints, sample size, randomization ratio, study duration and statistical methods. FDA noted that hepatic function criteria in the proposed MOTION study (AST, ALT, bilirubin ≤ 1 times upper limit of normal) are more stringent than in DCC-3014-01-001 (≤ 1.5 times upper limit of normal), the supportive study.
4. Type B Meeting, January 29, 2021: FDA agreed the Phase 3 study design may be appropriate to support future approval of vimseltinib for the treatment of symptomatic TGCT (b) (4) FDA noted that the ability of the proposed study to support a marketing application would depend on the observed ORR and DOR. FDA agreed that the primary and secondary endpoints were appropriate to capture clinically meaningful outcomes. FDA acknowledged the planned safety database size of approximately 400 patients, including 200 oncology patients and 200 patients in clinical pharmacology studies and stated this may be considered adequate to support an NDA provided that no unusual toxicities were identified.
5. Type B, pNDA Meeting, January 16, 2024: FDA additionally noted that efficacy data for the original and the complete NDA should include a minimum of six months of follow-up from the date of the initial confirmed response for all responders. The Applicant agreed to submit updated efficacy data based on a second data cutoff date of February 2024 to provide additional durability and follow-up data. FDA agreed that the additional DOR data would be used to support labeling, but the additional ORR data would not. The Applicant provided information regarding planned safety analyses.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Applicant submitted clinical data from MOTION in support of this NDA. Inspections were performed by OSI for Dr. Gelderblom (site 431), Dr. Blay (Site 402), and the imaging Contract Research Organization (CRO) ((b) (4)). The inspection of the CRO did not reveal any discrepancies, regulatory violations, or Good Clinical Practice noncompliance. The inspections for Drs. Gelderblom and Blay did not find any significant concerns regarding the study conduct, data integrity, GCP, or regulatory compliance. Based on these inspections, MOTION appears to have been conducted adequately by the study sponsor and the data generated by the inspected clinical investigators and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

4.2. Product Quality

The FDA CMC review team determined the application to be acceptable from a product quality review team. The review entered into FDA's DAARTS system on December 19, 2024. FDA will complete this section.

4.3. Clinical Microbiology

The FDA CMC review team determined the application to be acceptable from a product quality review team. The review entered into FDA's DAARTS system on December 19, 2024. FDA will complete this section.

4.4. Devices and Companion Diagnostic Issues

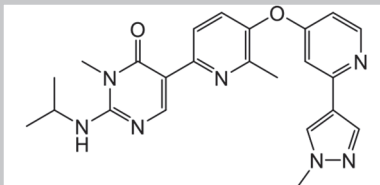
No devices or companion diagnostics were used to support this NDA.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Vimseltinib is a small molecule kinase inhibitor of colony-stimulating factor 1 receptor (CSF1R). The established pharmacologic class is kinase inhibitor.

Figure 1 Chemical Structure of Vimseltinib



(Excerpted from Applicant's Submission)

Target Background

Colony stimulating factor 1 receptor (CSF1R), also known as CD115 (Cluster of Differentiation 115) or macrophage colony-stimulating factor receptor (M-CSFR), is a tyrosine kinase transmembrane receptor encoded by the human CSF1R gene (also known as c-FMS). CSF1R signaling is involved in macrophage and osteoclast development and differentiation. In tenosynovial giant cell tumors, colony stimulating factor 1 (CSF-1) is overexpressed. Overexpression of CSF1 and excess signaling through CSF1R may enhance tumor-associated macrophage (TAM)-mediated tumor growth, angiogenesis, and immunosuppression.

Pharmacology

Vimseltinib inhibited CSF1R with an IC₅₀ of 2.8 nM. In vitro, vimseltinib inhibited autophosphorylation and phosphorylation of CSF1R in THP-1 cells (a cell line used to study monocyte and macrophage function) and ERK signaling in whole blood monocytes. Vimseltinib had anti-tumor activity, inhibiting CSF1R-dependent proliferation in vitro in M-NFS-60 myelogenous leukemia cells. In an in vivo mouse model, administration of vimseltinib reduced levels of CSF1R-dependent cFOS transcription.

ADME/PK

A single IV dose of 1 mg/kg vimseltinib had 73% CNS permeability in Sprague Dawley rats.

General toxicology

Repeat-dose toxicology studies were conducted in rats (4-weeks, 13-weeks, and 26-weeks) and dogs (4-weeks, 13-weeks, and 39-weeks). The indication did not warrant repeat-dose toxicology studies of more than 3 months duration.

Rats exhibited similar findings across studies:

- swollen head and limbs
- decreases in RBC-related parameters (hemocrit, hemoglobin, erythrocytes), lymphocytes, calcium, and phosphate
- increases in AST, ALT, glutamate dehydrogenase (GLDH), fibrinogen, reticulocytes, platelets, and neutrophils
- notable adverse histopathology in the bone, teeth, kidneys (chronic progressive nephropathy), and blood vessel degeneration (fibrinoid necrosis with presence of inflammatory cells) in multiple tissues.
- additional findings in rats relevant to reproductive effects are described below under *Reproductive and Developmental Toxicity*

Rats were more sensitive to the effects of vimseltinib compared to dogs.

Dogs were dosed higher in the 4-week study (up to 25 mg/kg/day) vs. the 13-week and 39-week studies (up to 8 mg/kg/day) and exhibited more severe toxicities at higher doses. Considering all three studies, findings included:

- decreases in phosphate, calcium, and APTT
- increases in AST, ALT, GLDH, creatine kinase, fibrinogen, reticulocytes, and platelets
- edema in the skin, skin de-pigmentation (females only), excessive lacrimation, and epididymal mineralization

The vimseltinib toxicity profile is characterized by inflammation, hematologic, hepatic, renal, bone, and gastrointestinal toxicities, and is generally consistent with CSF1R inhibition. Findings in animals indicate vimseltinib has the potential to cause hepatotoxicity, which may be secondary to inflammation. Another small molecule kinase inhibitor of CSF1R is pexidartinib. Literature (Qin et al., 2023) suggests that the mechanism of action for pexidartinib-mediated liver injury may be due to its unique biomolecular characteristics, including metabolites, rather than due to a class effect alone. While plausible, the totality of the nonclinical data for vimseltinib do not fully rule out the risk for hepatotoxicity in humans.

General toxicology findings reflected in USPI sections 8.4 and 13.2

In a 26-week repeat-dose general toxicology study in rats, chronic progressive nephropathy occurred at vimseltinib doses of ≥ 2.5 mg/kg/day (approximately 6 times the exposure at the recommended dose based on AUC). Degeneration of blood vessels (perivascular inflammation and necrosis of arteries and arteriole walls) occurred in multiple tissues at 5 mg/kg/day vimseltinib (approximately 12 times the exposure at the recommended dose based on AUC).

Rats administered vimseltinib at ≥ 2.5 mg/kg had physeal thickening and decay of the incisors and molars. Bone and tooth toxicities occurred at exposures approximately 8 times the

recommended dose based on AUC. These findings are relevant to pediatric use.

In a 39-week repeat-dose general toxicology study in dogs, skin depigmentation in the head and legs occurred at vimseltinib doses of ≥ 4 mg/kg/day corresponding to exposures lower than the exposure at the recommended dose based on AUC.

Genotoxicity

Vimseltinib was not mutagenic in the bacterial reverse mutation assay (Ames). In an in vitro micronucleus assay, vimseltinib increased micronuclei after a 24-hour incubation in the absence of metabolic activation. In vivo, vimseltinib administered to rats at doses up to 200 mg/kg/day did not increase bone marrow micronucleated polychromatic erythrocytes, nor did vimseltinib increase liver DNA strand breaks. The overall assessment was that vimseltinib was negative for genotoxicity.

Carcinogenicity

In a 6-month transgenic mouse carcinogenicity study at doses up to 12.5 mg/kg/day, vimseltinib was negative for carcinogenic findings. The Applicant is currently conducting a 104-week carcinogenicity study in Sprague Dawley rats to be submitted as a PMR.

Reproductive and Developmental Toxicology

In a rat embryo-fetal development study, pregnant female rats were dosed once daily during the period of organogenesis (gestational days 6 to 17) at doses of 2.5, 5, or 15 mg/kg/day. Structural abnormalities (skeletal variations) occurred at ≥ 2.5 mg/kg/day (approximately 3 times the exposure at the recommended dose based on AUC). Additional structural abnormalities (cardiac malformations) were observed at the highest dose of 15 mg/kg/day (approximately 23 times the exposure at the recommended dose based on AUC).

Based on data from animal studies and its mechanism of action, vimseltinib can cause fetal harm. Females of reproductive potential and males with female partners of reproductive potential are recommended to use effective contraception during treatment with vimseltinib and for 1 month after the last dose. The duration of contraception is based on 5 times the clinical elimination half-life of 6 days.

There are no data on the presence of vimseltinib or its metabolites in either human or animal milk or its effects on a breastfed child or on milk production. Because of the potential for serious adverse reactions in the breastfed child, women are recommended not to breastfeed during treatment with vimseltinib and for 1 month after the last dose.

Based on findings from animal studies, vimseltinib may impair fertility.

In a fertility and early embryonic development study, male rats were administered 1, 2.5, or 5 mg/kg/day of vimseltinib starting 10 weeks before cohabitation, during cohabitation with

untreated females, and at least 2 weeks post-cohabitation. Lower epididymal and testes weights were observed at 5 mg/kg/day (approximately 12 times the exposure at the recommended dose based on AUC). There were no treatment-related effects on mating, fertility, or sperm parameters at any dose tested. Female rats were administered 2.5, 5, or 10 mg/kg/day of vimseltinib 2 weeks prior to cohabitation with untreated males and during cohabitation until gestational day 7. Although there were no treatment-related effects on mating or estrous cycles, vimseltinib administered daily resulted in post-implantation loss at 10 mg/kg/day in female rats (approximately 20 times the exposure at the recommended dose based on AUC).

In a 26-week repeat-dose general toxicology study, recovery male rats that were administered 2.5 or 5 mg/kg/day had moderate to marked reductions in sperm and marked testicular atrophy (1 of 5 and 2 of 5 animals, respectively) corresponding to approximately 6 and 12 times the exposure at the recommended dose based on AUC, respectively. In a 39-week repeat-dose general toxicology study, minimal to moderate epididymal mineralization occurred in male dogs administered ≥ 4 mg/kg/day corresponding to exposures lower than the exposure at the recommended dose based on AUC.

Figure 2 Summary of Nonclinical Exposure Margins for Adverse Findings

Type	Species	Duration	Sex	Dose (mg/kg)	Area Under the Curve (AUC) (ng·h/mL)	Exposure Margin* animal:human	Adverse Findings in Label		
							5/8.1	13.1	13.2
General	SD Rat	26-week	M	1	31100	2.3	-	-	sw
			F		56100	4.2	-	-	sw
			M	2.5	80900	6.0	-	sr, ta	-
			F		115000	8.6	-	-	te
			M	5	166000	12.4	-	-	te, vd, pt
			F		204000	15.2	-	-	vd, pt
	Dog	39-week	M	2	3420	0.3	-	-	-
			F		2130	0.2	-	-	-
			M	4	3670	0.3	-	em	-
			F		4730	0.4	-	-	-
			M	8	8880	0.7	-	-	-
			F		16000	1.2	-	-	-
Gene	SD Rat	3- Day	F	50	37317	2.8	-	-	-
				100	75633	5.6	-	-	-
				200	103217	7.7	-	-	-
Fertility/ Early EFD	SD Rat	D(-70) → D14**	M	1	31100	2.3	-	-	-
		D(-14) → GD7	F	2.5	71000	5.3	-	-	-
		D(-70) → D14**	M	2.5	80900	6.0	-	-	-
		D(-14) → GD7	F	5	143000	10.7	-	-	-
		D(-70) → D14**	M	5	166000	12.4	-	ew	-
		D(-14) → GD7	F	10	269000	20.1	-	pil, uw	-
EFD	SD Rat	GD6 → GD17	F	2.5	40900	3.1	fmal	-	-
			F	5	106000	7.9	fmal	-	-
			F	15	313000	23.4	fmal	-	-

*Exposure margin calculated as AUC.animal/AUC.human; clinical AUC₀₋₂₄ = 13400 ng·h/mL at recommended dose 30 mg Q2W

** dosing began 10 weeks pre cohabitation and ended at least two weeks post, not measured in study, based on General toxicology values
bw - weight loss; em - epididymal mineralization; ew - reduced epididymal weights; fmal - fetal malformations; pil - post-implantation loss; pt -
physis thickness; sr - sperm reduction; sw - swelling (head, limbs); ta - testicular atrophy; te - teeth abnormal; uw - increased uterine weights; vd -
vessel degeneration

There are no approvability issues from a pharmacology/toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced NDAs, BLAs, or DMFs related to nonclinical pharmacology or toxicology for vimseltinib.

5.3. Pharmacology

The Applicant's Position:

Primary pharmacology

Vimseltinib selectively and potently inhibits CSF1R in recombinant kinase assays and in cellular assays with CSF1R-expressing cells, including monocytic cell lines, osteoclast precursors, and monocytes from freshly drawn whole blood samples. In vivo, pharmacokinetic/pharmacodynamic (PK/PD) analysis of vimseltinib inhibition of CSF1R signaling demonstrates potent and durable inhibition of CSF1R. Vimseltinib depletes tumor-associated macrophages (TAMs) in an immunocompetent colorectal cancer model. In a prostate cancer model, wherein primary tumor growth results in bone invasion and osteoclast-mediated bone degradation, vimseltinib treatment demonstrates statistically significant protection of bone degradation. DP-7005, a metabolite of vimseltinib, is an inhibitor of CSF1R kinase in enzyme and cell-based assays.

In Vitro Pharmacology

Vimseltinib is a potent inhibitor of CSF1R kinase in vitro in both recombinant enzyme and cell based assays. Vimseltinib inhibits CSF1-stimulated CSF1R autophosphorylation in a monocytic cell line, inhibits cellular proliferation of a monocytic cell line dependent on CSF1R signaling, inhibits CSF1-stimulated osteoclast differentiation, and decreases macrophage-mediated tumor cell migration. Vimseltinib also inhibits CSF1R signaling in monocytes in an in vitro human whole blood assay.

Table 3 Summary of Key Pharmacologic Properties of Vimseltinib

Assay	
Biochemical Activity	vimseltinib
Inhibition of Recombinant CSF1R Kinase ^a	IC ₅₀ =2.8 nM
Kinetic analysis of CSF1R Kinase assay ^b	K _d =2.3 nM; t _{1/2} =170 min
Cellular Activity	IC ₅₀ vimseltinib
CSF1-stimulated CSF1R autophosphorylation inhibition ^c	18.8 nM
Proliferation inhibition ^d	10.2 nM
Osteoclast differentiation inhibition ^e	9.3 nM
Tumor cell migration inhibition ^f	<100 nM
CSF1R signaling in human whole blood inhibition ^g	310 nM
In Vivo Pharmacodynamics	vimseltinib
Dose-dependent inhibition of CSF1R signaling in PK/PD models ^h	3 mg/kg QD
Prevention of bone degradation ⁱ	10 mg/kg QD
Depletion of tumor-associated macrophages in an immunocompetent mouse tumor model ^j	10 mg/kg QD

Abbreviations: CSF1R=colony stimulating factor 1 receptor; IC₅₀=half maximal inhibitory concentration; PK/PD=pharmacokinetic/pharmacodynamic;

^a Vimseltinib exhibited a preference for CSF1R phosphorylated only on the JM-domain. The IC₅₀ = 2.8 nM for the JM domain phosphorylated CSF1R and IC₅₀ = 290 nM for fully phosphorylated CSF1R. Study DCC-3014-02-0001, eCTD 4.2.1.1.

^b Vimseltinib was evaluated for its residence time when bound to CSF1R kinase and exhibited an off-rate of 0.0041 min⁻¹ and an inhibitory residency half-life of nearly 3 hours. Study DCC-3014-02-0021, eCTD 4.2.1.1.

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- c Vimseltinib inhibited CSF1-stimulated CSF1R autophosphorylation in the THP1 human acute monocytic leukemia cell line with $IC_{50} = 18.8$ nM. Study DCC 3014-02-0005, eCTD 4.2.1.1.
- d Vimseltinib inhibited proliferation of M-NFS-60 cells, a CSF1R-dependent mouse myelogenous leukemia cell line, with an average $IC_{50} = 10.2 \pm 3.5$ nM. Study DCC-3014-02-0004, eCTD 4.2.1.1.
- e Human osteoclast precursors are dependent upon CSF1-stimulated CSF1R activity for proliferation and differentiation into osteoclasts. Vimseltinib inhibited osteoclast differentiation with $IC_{50} = 9.3$ nM. Study DCC 3014-02-0008, eCTD 4.2.1.1.
- f Vimseltinib inhibited macrophage-dependent tumor cell migration by >50% at 100 nM, the only concentration tested. Study DCC-3014-02-0022, eCTD 4.2.1.1.
- g Vimseltinib inhibited CSF1R signaling in monocytes in human whole blood with an average $IC_{50} = 310 \pm 84$ nM. Study DCC 3014-02-0007, eCTD 4.2.1.1.
- h Vimseltinib significantly inhibited CSF1 stimulated expression of cFOS mRNA for >24 h post dose at all doses (30, 15, 7.5, and 3.75 mg/kg single dose PO). Study DCC-3014-02-0012, eCTD 4.2.1.1. In a multiple dosing study, after dosing at 10 mg/kg orally for 6 days, vimseltinib inhibited CSF1-stimulated cFOS expression by >80% for >48 h after the last dose. After dosing at 3 mg/kg, vimseltinib inhibited cFOS expression by 90% or greater for 12 h, and ~50% at 24 h and 48 h. After dosing at 1 mg/kg, vimseltinib inhibited cFOS expression by ~80% for 6 h after dosing but did not significantly inhibit at time points >6 h. Study DCC-3014-02-0013, eCTD 4.2.1.1.
- i In the PC3 prostate cancer model (where tumor growth leads to local invasion and bone degradation), treatment with vimseltinib at 30 mg/kg, BID produced statistically significant ($p < 0.0001$) prevention of bone degradation. Study DCC-3014-02-0014, eCTD 4.2.1.1. In a second study, treatment with vimseltinib at 10 mg/kg, administered once or twice daily also led to statistically significant prevention of bone degradation ($p < 0.0001$). Study DCC-3014-02-0033, eCTD 4.2.1.1.
- j

(b) (4)

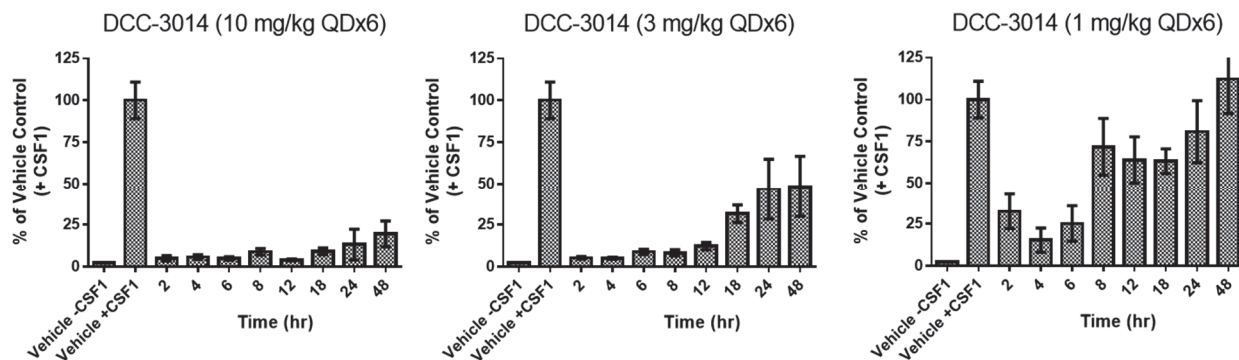
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 at 10 mg/kg PO, QD. Study DCC-3014-02-0015, eCTD 4.2.1.1.

In Vivo Pharmacology

Vimseltinib was well tolerated in all mouse pharmacology studies. In a PK/PD model, vimseltinib significantly inhibited CSF1-stimulated expression of cellular homolog of the Finkel Biskis-Jenkins murine osteogenic sarcoma virus oncogene (cFOS) mRNA for >24 h postdose at all doses, as low as 3.75 mg/kg PO, after a single dose. After dosing at 10 mg/kg orally for 6 days, vimseltinib inhibited CSF1-stimulated cFOS expression by >80% for >48 h after the last dose (Figure 3 and Table 4). After dosing at 3 mg/kg, vimseltinib inhibited cFOS expression by 90% or greater for 12 h, and approximately 50% at 24 h and 48 h. The 24 h area under the concentration time/curve (AUC) for the 3 mg/kg group was 49,314 ng*h/mL (Table 5). The half maximally effective concentration (EC_{50}) was 430 ng/mL and the eighty percent maximally effective concentration (EC_{80}) was 1,700 ng/mL.

Figure 3 Steady-state Inhibition of CSF1-stimulated cFOS Expression by Vimseltinib (DCC-3014) after Six Days of Oral Dosing



Abbreviations: CSF1=colony stimulating factor 1; DCC-3014=vimseltinib; h=hour; QD=once daily
 Source: DCC-3014-02-0013, Figure 1, eCTD 4.2.1.1.

Table 4 Inhibition of CSF1-stimulated cFOS Expression and Plasma PK levels of Vimseltinib after Six Oral Daily Doses in DBA/1 Mice

	%Inhibition of cFOS expression (+CSF1) and Plasma PK							
Vimseltinib	2 h	4 h	6 h	8 h	12 h	18 h	24 h	48 h
10 mg/kg; % Inhibition	95%	94%	95%	91%	96%	91%	87%	81%
Plasma levels (ng/mL)	9,005	8,321	10,738	9,965	9,703	4,798	2,962	712
3 mg/kg; % Inhibition	95%	95%	91%	92%	88%	69%	53%	52%
Plasma levels (ng/mL)	3,025	2,705	3,226	2,815	3,139	1,035	752	107
1 mg/kg; % Inhibition	68%	85%	75%	28%	36%	37%	19%	-12%
Plasma levels (ng/mL)	1,121	553	994	875	827	357	228	36

Abbreviations: cFOS=cellular homolog of the Finkel-Biskis-Jenkins murine osteogenic sarcoma virus oncogene; CSF1=colony stimulating factor 1; h=hour; PK=pharmacokinetics
Source: DCC-3014-02-0013, Table 4 and Table 5, eCTD 4.2.1.1.

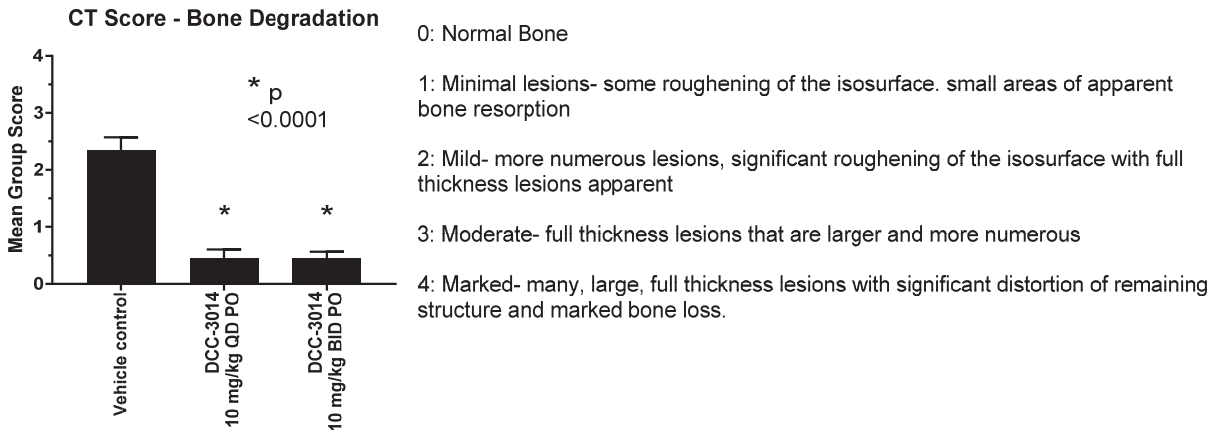
Table 5 Pharmacokinetic Parameters for Vimseltinib after Six Oral Daily Doses in DBA/1 Mice

Pharmacokinetic Parameter	10 mg/kg	3 mg/kg	1 mg/kg
C _{max} (ng/mL)	10738	3226	1121
t _{max} (h)	6	6	2
AUC ₀₋₂₄ (ng*h/mL)	170035	49314	14625
AUC _{0-t} (ng*h/mL)	207,922	57,244	17,125
AUC _{inf} (ng*h/mL)	219339	58622	17599
t _{1/2} (h)	11.11	8.96	9.07
Vz _{obs} (L/kg)	0.731	0.661	0.744
Cl _{obs} (L/h/kg)	0.046	0.051	0.057

Abbreviations: AUC_{0-t}=area under the plasma concentration curve from time zero to the last quantifiable concentration; AUC_{inf}=area under the plasma concentration curve from zero to infinity; C_{max}=maximum drug concentration; Cl_{obs}=observed clearance; h=hours; t_{1/2}=half-life; t_{max}=time to maximum drug concentration; Vz_{obs}=observed volume of distribution
Source: DCC-3014-02-0013, Table 6, eCTD 4.2.1.1.

In the PC3 prostate cancer model, treatment with vimseltinib at 10 mg/kg, administered once or twice daily led to statistically significant prevention of bone degradation (p<0.0001; Figure 4).

Figure 4 Vimseltinib (DCC-3014) Inhibition of Bone Degradation in the PC3 Xenograft Model



Abbreviations: BID=twice daily; DCC-3014=vimseltinib; CT=computed tomography; PO=orally; QD=once daily
Source: DCC-3014-02-0033, Figure 2, eCTD 4.2.1.1.

In the MC38 syngeneic colon cancer model,

(b) (4)

(Figure 5Figure 6).

Figure 5

(b) (4)

Abbreviation: DCC-3014=vimseltinib

Source: DCC-3014-02-0015, Figure 1, eCTD 4.2.1.1.

Figure 6



Abbreviation: DCC-3014=vimseltinib

Source: DCC-3014-02-0015, Figure 2, eCTD 4.2.1.1.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position; however, FDA disagrees with interpretation of Study DCC-3014-02-0015 as described in footnote *j* of Table 3 and Figure 5 and Figure 6. (b) (4)

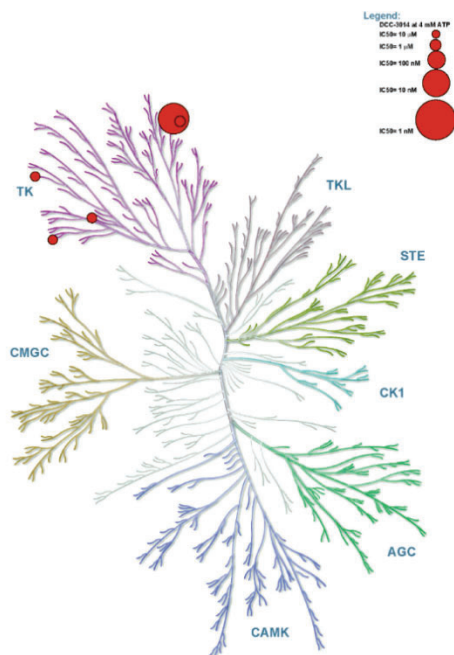
Secondary Pharmacology

The Applicant's Position:

In a large panel of kinase activity assays, vimseltinib exhibits >100-fold selectivity for CSF1R kinase versus 298 other human kinases, including its closely related family members KIT, platelet-derived growth factor receptor alpha (PDGFR α), PDGFR beta (PDGFR β), and FLT3 (DCC-3014-02-0002, DCC-3014-02-0003, and DCC-3014-02-0031, eCTD 4.2.1.2; Figure 7). Vimseltinib was evaluated versus a battery of 135 receptors, ion channels, and enzymes (DCC-3014-02-0010, eCTD 4.2.1.2). Among the battery of 104 receptor binding assays profiled, vimseltinib inhibited MT3 (ML2) (agonist radioligand) by 68.2% when evaluated at 10 μ M concentration. All other receptor binding assays were inhibited <25% by vimseltinib. Among the battery of 31 enzyme and uptake assays, vimseltinib exhibited 86.2% inhibition of ABL kinase, 42.8% inhibition of FYN kinase, and 90.6% inhibition of LYN kinase when evaluated at 10 μ M concentration. These kinases were further tested, wherein IC₅₀ values of 2,200 nM, >3,300 nM,

and >3,300 nM were determined, respectively, all of which are >500-fold weaker than the IC₅₀ for inhibition of CSF1R (DCC-3014-02-0002, DCC-3014-02-0003, and DCC-3014-02-0031, eCTD 4.2.1.2).

Figure 7 Kinome Selectivity of Vimseltinib (DCC-3014) when Tested at 4 mM ATP



Abbreviations: AGC=protein kinase A, protein kinase G, protein kinase C; ATP=adenosine triphosphate; CAMK=calcium/calmodulin-dependent protein kinases; CK1=casein kinase 1; CMGC=family of CDK, MAPK, GSK, and CLK kinases; IC₅₀=half maximal inhibitory concentration; STE=serine/threonine protein kinase; TK=tyrosine kinase; TKL=tyrosine kinase-like; vimseltinib=DCC-3014
Source: DCC-3014-02-0031, Figure 2, eCTD. 4.2.1.2.

The FDA's Assessment:

The FDA agrees with the Applicant's position. Vimseltinib mainly inhibits CSF1R.

Assay	IC ₅₀ (nM)
CSF1R	2.8
ABL	2,250
AKT1	>3,300
BRAF	>10,000
CRAF	>10,000
FGFR1	>3,300
FGR	>3,300
FLT3	>3,300
FYN	>3,300
HCK	>3,300
HER1	>3,300
IRK	>3,300
JAK2	>3,300
KDR	>3,300
KIT	476
LCK	1,110
LYN	>3,300
MEK1	>3,300
MET	>5,000
MK2	>3,300
PDGFR α	436
PDGFR β	2,290
pKIT	>10,000
TRKC	1,970

Source: Excerpted from Applicant's Submission

Safety Pharmacology

The Applicant's Position:

Vimseltinib was assessed in nonclinical safety pharmacology studies including evaluation of neurobehavioral effects and evaluation of impact on cardiovascular parameters and respiratory function. There were no effects of vimseltinib on central nervous system (CNS) function in rats at single doses up to 30 mg/kg, the highest dose tested. A mildly higher tidal volume was noted in rats given 30 mg/kg in the respiratory safety pharmacology study, without an effect on respiratory rate or minute volume. The 30 mg/kg/day dose exceeds the severely toxic dose in 10% of the evaluation cohort (STD₁₀) determined in the definitive Good Laboratory Practice (GLP) compliant 28-day rat study. In the dog cardiovascular (CV) safety pharmacology study, no vimseltinib-related qualitative electrocardiogram (ECG) effects or quantitative changes in PR interval, QRS duration, QT interval, QT interval corrected by Fridericia's formula (QTcF) interval, heart rate (HR), arterial pressure, or body temperature were seen at doses up to 15 mg/kg. In the in vitro human ether-à-go-go-related gene (hERG) study, the half maximal inhibitory concentration (IC₅₀) values for inhibition of the hERG potassium current by vimseltinib and DP-7005 could not be calculated due to 17% or less inhibition at the maximum concentrations that could be tested at the solubility limits of the two compounds (30 μ M). Based

on these results, vimseltinib appears unlikely to have significant CNS, respiratory, or cardiovascular safety pharmacology liabilities in humans. Comprehensive data from Deciphera clinical trials support the nonclinical data and conclusions indicating no safety concerns related to CNS, respiratory, or cardiovascular effects.

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Table 6 Safety Pharmacology

Organ Systems Evaluated	Test System	Method of Admin.	Doses (mg/kg)	and No. per Group	Noteworthy Findings	GLP	Study Number
Cardiovascular	In vitro human hERG binding assay	In vitro	Vimseltinib (0.1 μ M to 25 μ M)	N/A	The average hERG EC ₅₀ was greater than 25 μ M and the EC ₂₀ = 19.4 $\pm$ 7.1 μ M for vimseltinib.	No	DCC-3014-02-0011 eCTD 4.2.1.3
Cardiovascular	In vitro HEK-293 cell line transfected with hERG cDNA	In vitro	Vimseltinib (10 μ M, 30 μ M) DP-7005 (10 μ M, 30 μ M)	N/A	The IC ₅₀ for the inhibitory effect of vimseltinib on hERG potassium current was greater than 30 μ M. The IC ₅₀ for the inhibitory effect of DP-7005 on hERG potassium current was greater than 30 μ M.	Yes	DCC-3014-02-0034 eCTD 4.2.1.3
Central Nervous System	Rat/ Hsd:Sprague Dawley	Oral Gavage	0 (Control) 5 (Low) 15 (Mid) 30 (High)	Male/8 Male/8 Male/8 Male/8	None	Yes	DCC-3014-02-0026 eCTD 4.2.1.3
Respiratory	Rat/ Hsd:Sprague Dawley	Oral Gavage	0 (Control) 5 (Low) 15 (Mid) 30 (High)	Male/8 Male/8 Male/8 Male/8	Higher tidal volume (up to +0.27 mL or +17%) at 30 mg/kg	Yes	DCC-3014-02-0027 eCTD 4.2.1.3
Cardiovascular	Dog / Beagle	Oral Gavage	0 (Control) 2.5 (Low) 7.5 (Mid) 15 (High)	Male/4	None	Yes	DCC-3014-02-0028 eCTD 4.2.1.3

Abbreviations: cps=centipoise; cDNA=complementary DNA; GLP=Good Laboratory Practice; EC₂₀=twenty percent maximally effective concentration; EC₅₀= half maximally effective concentration HEK-293= human embryonic kidney 293 cells; hERG=human ether-à-go-go-related gene; IC₅₀=half maximal inhibitory concentration; Hsd=Harlan Sprague Dawley; N/A=not applicable; w=weight; V=volume.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

5.4. ADME/PK

The Applicant's Position:

The absorption, distribution, metabolism, and excretion (ADME) of vimseltinib and its active metabolite, DP-7005, were characterized in a range of in vitro and in vivo studies to support the proposed clinical indication and dosing regimen. The absorption of vimseltinib has been characterized in an extensive program of single-dose PK studies and repeated-dose toxicokinetic (TK) studies in mouse, rat, dog, and monkey. The distribution of vimseltinib was evaluated in a quantitative whole-body autoradiography study and vimseltinib's ability to penetrate the CNS was assessed in rats. Plasma protein binding was evaluated in mouse, rat, dog, monkey, and humans. The characterization of vimseltinib's metabolites were assessed in vitro with mouse, rat, dog, monkey, and human hepatocytes and in vivo in dogs and bile duct-cannulated (BDC) rats. Metabolic stability was evaluated in mouse, rat, dog, monkey, and human liver microsomes and hepatocytes while cytochrome P450 enzyme (CYP) reaction phenotyping was assessed in human liver microsomes and recombinant human CYP enzymes. CYP induction and inhibition were evaluated using human hepatocytes and liver microsomes, respectively. The excretion of vimseltinib was evaluated in dogs and in bile-duct cannulated rats. The potential for vimseltinib to affect transporter activity was evaluated in vitro.

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Absorption

The PK parameters of vimseltinib following oral and IV administration of vimseltinib in male Sprague Dawley rats (DCC-3014-03-0012) and male beagle dogs (DCC-3014-03-0014) are provided in Table 7. PK parameters in rats following oral administration were similar to IV, with the exception that T_{max} occurred at 2.67-24 hours, depending on dose level, instead of immediately after infusion. The PK of DP-7005 was evaluated in dog studies in addition to vimseltinib after dog microsomal studies indicated substantial formation of the metabolite DP-7005.

A key finding from the single dose oral PK studies in rats (Table 8) was a plateau in vimseltinib exposures between 100 and 300 mg/kg, which was used to inform dose selection in repeat-dose toxicology studies.

Table 7 Mean PK Parameter Values of Vimseltinib and DP-7005 Following Single-Dose Administration

Species (Strain)	Sex/N	Compound Dosed (mg/kg)	Route	Analyte	C_{max} (ng/mL)	T_{max} (h)	$t_{1/2}$ (h)	AUC_{0-t} (ng*h/mL)	AUC_{0-inf} (ng*h/mL)	Cl_{obs} (L/h/kg)	Vz_{obs} (L/kg)	F (%)
Rat (Sprague Dawley) ^a	3M	Vimseltinib 10	Oral	Vimseltinib	16,115	2.67	19.83 ^b	164,004	277,667	0.04 ^b	1.02 ^b	76.38
	3M	Vimseltinib 1	IV	Vimseltinib	2906	0.08	14.19	21,473	29,605	0.03	0.69	NA
	3M	Vimseltinib 1	IV	DP-7005	2363	0.08	3.30	2927	2957	0.34	1.64	NA
Dog (Beagle) ^c	3M	Vimseltinib 10	Oral	Vimseltinib	1676	1.67	6.91	11,263	11,324	1.39	14.05	61
				DP-7005	904	4.00	15.15 ^d	14,724	22,153 ^d	NA ^d	NA ^d	
	3M	Vimseltinib 1	IV	Vimseltinib	1503	0.08	7.84 ^d	4233	4567 ^d	0.22 ^d	2.48 ^d	NA
				DP-7005	367	4.00	19.75 ^d	4590	5307 ^d	NA ^d	NA ^d	NA
	3M	DP-7005 1	IV	DP-7005	2017	0.08	11.04 ^d	7532	7584 ^d	0.13 ^d	2.10 ^d	NA

Abbreviations: AUC_{0-t} =area under the plasma concentration versus time-curve from time zero to the last measurable (nonzero) time point; AUC_{0-inf} =area under the plasma concentration versus time-curve from time zero to infinity; Cl_{obs} =observed clearance; C_{max} =maximum plasma concentration; F (%)=bioavailability; h=hour; IV=intravenous; M=male; N=number per group; NA=not available/not determined; $t_{1/2}$ =terminal elimination half-life; T_{max} =time to maximum plasma concentration; Vz_{obs} =volume of distribution.

^a Study DCC-3014-03-0012, eCTD 4.2.2.2

^b The 24 h sample from rat 3 was excluded from the elimination phase as it appears to be an anomalous outlier.

^c Study DCC-3014-03-0014, eCTD 4.2.2.2

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^d The elimination phases of Dogs 1 (DP-7005) and 3 (vimseltinib) of the vimseltinib IV administration group, Dog 3 of the DP-7005 administration group, and Dog 2 (DP-7005) of the oral administration group were not reportable due to the elimination phase being undefined and therefore not included in the calculations in the AUC_{0-inf}, t_{1/2}, V_z, and Cl.

Table 8 Mean PK Parameter Values of Vimseltinib in Male Rats Following Single-Dose Administration

Parameter (units)	10 mg/kg PO	30 mg/kg PO	100 mg/kg PO	300 mg/kg PO	500 mg/kg PO
C _{max} (ng/mL)	5360	18,500	48,000	64,500	58,500
T _{max} (h)	8.00	6.67	24.00	24.00	17.3
AUC ₀₋₂₄ (ng*h/mL)	103,000	344,000	942,000	1,150,000	1,060,000

Abbreviations: AUC₀₋₂₄=area under the concentration-time curve from hour 0 to hour 24, estimated by the linear trapezoidal rule; C_{max}=maximum plasma concentration; h=hour; PO=oral; T_{max}=time to maximum plasma concentration.

Source: Study DCC-3014-03-0011, eCTD 4.2.2.2

Distribution

Plasma Protein Binding	An in vitro distribution study characterized the plasma protein binding of vimseltinib in mouse, rat, dog, monkey, and human plasma. Percent bound values ranged from 95.4% in monkey, 96.4% in dogs and 99.3% in rat plasma. Percent bound in human plasma was determined to be 96.5 (DCC-3014-03-0002, eCTD 4.2.2.3).
CNS Penetrability	An in vivo distribution study to assess CNS penetrability was performed in rats. Vimseltinib exhibited a brain:plasma ratio of 0.73, indicating a significant 73% CNS penetrability after systemic IV dosing (DCC-3014-03-0015, eCTD 4.2.2.3).
Tissue Distribution	After oral dosing to male Sprague Dawley and Long Evans rats, [¹⁴ C]-vimseltinib-derived radioactivity was widely distributed to almost all tissues by the first collection time point (0.5 hours postdose). Radioactivity was cleared from most tissues by 168 hours postdose, but still quantifiable in the meninges, eye uveal tract, eye(s), and eye vitreous humor at 672 hours(DCC-3014-03-0022, eCTD 4.2.2.4).

Metabolism

Metabolite Profile	The metabolite profiles of [¹⁴ C]-vimseltinib were evaluated in vitro using mouse, rat, dog, monkey, and human hepatocytes and microsomes (DCC-3014-03-0008 and DCC-3014-03-0023, both eCTD 4.2.2.4). Metabolism was species-dependent. [¹⁴ C]-vimseltinib was metabolized in mouse, rat, dog, monkey, and human hepatocytes and microsomes via oxidation, N-dealkylation, and dehydrogenation. No Phase II metabolites were detected. Up to 7 metabolites were tentatively identified/characterized in hepatocytes and microsomes, in addition to unchanged vimseltinib. Metabolites detected in human hepatocytes and microsomes were also found in other species. Metabolic profiling as part of the human AME
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	study (DCC-3014-01-003, eCTD 5.3.3.1) determined that primary metabolism occurred by oxidation, N-demethylation, and N-dealkylation; secondary biotransformation pathways included N-demethylation, dehydrogenation, and oxidation. Metabolite identification studies in hepatocytes were also completed (DCC-3014-03-0008). Of the 24 identified metabolites observed across all species (mouse, rat, dog, monkey, human), only four were present at levels high enough for UV detection in the hepatocyte incubations, and only one (C6, DP-7005) was observed by UV in the human hepatocyte incubations. No human-specific metabolites were observed in the study, but neither mouse rat, dog, nor monkey formed all the vimseltinib metabolites observed in human hepatocyte incubations. The rat and dog hepatocytes between them provided coverage of all the observed human metabolites except component C19. This metabolite coverage supported the use of rats and dogs as appropriate toxicological species. The metabolism of [¹⁴C]-vimseltinib after a single IV bolus or oral administration was evaluated in dogs (DCC-3014-03-0021, eCTD 4.2.2.4). Vimseltinib and DP-7005 were the major circulating components in plasma after an IV or oral dose. Vimseltinib underwent biotransformation and was primarily metabolized via N-dealkylation to yield the major metabolite DP-7005 after both oral and IV administration (DCC-3014-03-0022, eCTD 4.2.2.4). Minor biotransformation pathways included oxidation, dehydrogenation, and glucuronidation. While the metabolite DP-7005 was minimally formed in rat and human hepatocytes, it was formed to a much greater extent in dog and monkey hepatocytes (DCC-3014-03-0008). Metabolite DP-7005 was experimentally measured in the plasma of both rats and dogs after single or multiple oral dose vimseltinib PK studies, although its appearance in rat plasma was minimal (approximately 2% compared to exposure of parent vimseltinib) consistent with its minimal formation in microsomal preparations. The minimal appearance of DP-7005 in rat contrasts with the proportion formed in dogs after oral administration of vimseltinib, wherein metabolite DP-7005 exposure dominated by up to approximately 5-fold compared to parent vimseltinib in multiple dose studies (DCC-3014-04-0005, eCTD 4.2.3.2). Metabolite DP-7005, like vimseltinib, is a CSF1R inhibitor (IC₅₀ = 65 nM). In the human AME study, the metabolite-to-parent molar AUC ratio for DP-7005 was 0.05 confirming minimal formation of DP-7005 in humans after a single oral dose (DCC-3014-01-003 CSR).
Metabolic Stability	The overall extent of vimseltinib stability in hepatocytes from highest to lowest followed the rank order mouse~rat~dog~human>monkey. Half-lives in human and mouse hepatocyte preparations were equal or greater than 4 hours, as no substrate loss was observed after 240 minutes of incubation with mouse and human hepatocytes (DCC-3014-03-0003, eCTD 4.2.2.4).
Excretion	
	The excretion of [¹⁴C]-vimseltinib was evaluated after a single administration to rats via oral gavage. Most of the [¹⁴C]-vimseltinib-derived radioactivity after oral administration to both intact males and females was excreted primarily in feces within 96 hours after dosing. Excretion profiles were similar between males and females, suggesting no sex differences. Following oral dosing to BDC male rats, a significant percentage of radioactivity was eliminated in the bile after oral dosing, indicating the biliary excretion was a significant route of elimination of absorbed [¹⁴C]vimseltinib-derived radioactivity. Fecal excretion was the major pathway for elimination of [¹⁴C]-vimseltinib-derived radioactivity in intact and BDC rats after oral dosing (DCC-3014-03-0022).

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	The excretion of [^{14}C]-vimseltinib was evaluated after a single IV or oral administration to dogs. Fecal and/or biliary excretion were the major pathway for elimination of [^{14}C]-vimseltinib-derived radioactivity in male and female dogs (DCC-3014-03-0021). Elimination of vimseltinib in humans occurred by metabolism and urinary and fecal excretions. In human AME study DCC-3014-01-003, when extrapolated to infinity, 37.5% of the administered ^{14}C-vimseltinib dose was excreted in urine and 42.9% in feces.
Drug-Drug Interaction	
CYP Reaction Phenotyping	In reaction phenotyping studies (time course studies in microsomal preparations and recombinant human CYP enzyme incubations; DCC-3014-03-0007, eCTD 4.2.2.4) vimseltinib disappearance ranged from zero to 10% over a 120 minute incubation period when human liver microsomes were incubated with vimseltinib at various concentrations (0.1, 1 and 10 μM). Substrate loss was 6% or less in the absence of microsomal protein, and no loss occurred in the absence of the NADPH-generating system at all three concentrations of vimseltinib (Module 2.6.5, Table 39). Incubations of vimseltinib (0.1 and 1 μM) were performed in a panel of recombinant human CYP enzymes (20 pmol CYP/mL; 30 minutes) (Module 2.6.5, Table 39). Loss of vimseltinib (0.1 μM) ranged from 2.8 to 22.3% in incubations with the panel of recombinant human CYP enzymes. The negative control incubations, control bacosomes and reductase control, resulted in 0.6 and 3.9% substrate loss, respectively. Loss of vimseltinib (1.0 μM) ranged from zero to 18.6% in incubations with the panel of recombinant human CYP enzymes. The negative control incubations (control bacosomes and reductase control) resulted in 3.1 and 7.5% substrate loss, respectively..
CYP Induction and Inhibition	In vitro, both vimseltinib and DP-7005 exhibited IC_{50} values $>40 \mu\text{M}$ for all CYP isoforms studied (40 μM was the highest concentration studied for DP-7005), and IC_{50} values $>100 \mu\text{M}$ were exhibited by vimseltinib for five out of seven CYP isoforms (DCC-3014-03-0001, eCTD 4.2.2.4). Additionally, neither vimseltinib nor DP-7005 exhibited time-dependent or metabolism-dependent inhibition of any CYP isoform, demonstrating little to no risk for time- or metabolism-dependent inhibition of CYP isoforms. Vimseltinib demonstrated low to minimal risk for CYP3A4 or CYP1A2 enzyme induction, and a slight risk for CYP2B6 induction at anticipated clinical exposures ($<10 \mu\text{M}$; DCC-3014-03-0009, eCTD 4.2.2.4).
Transporters	Vimseltinib is a moderate to weak inhibitor of various human efflux transporters (IC_{50} values from 4.35 to 51.5) (DCC-3014-03-0006, eCTD 4.2.2.6). Two transporters, BCRP and OCT2, were inhibited by vimseltinib with IC_{50} values of less than 1 μM (0.556 and 0.456 μM, respectively).. The efflux ratio of vimseltinib across MDCKII-MDR1 (P-gp) cells was 2.62 and decreased to 1.48 in the presence of a P-gp inhibitor (valsopodar). Vimseltinib was not a substrate of BCRP, BSEP, OATP1B1, OATP1B3 OAT1, OAT3, OCT2, MATE1, and MATE-2K. DP-7005 was also not a substrate of MATE1 or MATE2-K.
Toxicology	
General Toxicology	Refer to Section 5.5.1, Table 9 and Table 10

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Reproductive Toxicology	Refer to Section 5.5.4
Carcinogenicity	Refer to Section 5.5.3
Tabulation of any exposure margins used in proposed labeling	Refer to Section 5.5.6

Abbreviations: AUC=area under the curve; AME=absorption, metabolism, excretion; BCRP=breast cancer resistance protein; BDC=bile duct cannulated; BSEP=bile salt export pump CNS=central nervous system; CYP=cytochrome P450 enzyme; CYP1A2=cytochrome P450 1A2; CYP3A4=cytochrome P450 3A4; IV=intravenous; MATE1=multidrug and toxin extrusion protein 1; MDCKII-MDR1=Madin-Darby canine kidney type II cells overexpressing the human MDR1 gene; MATE2-K=multidrug and toxin extrusion protein 2-K; MDR1=multi-drug resistance 1; OAT=organic anion transporter; OAT1=organic anion transporter 1; OAT3=organic anion transporter 3; OATP1B1=organic anion-transporting polypeptide 1B1; OATP1B3=organic anion-transporting polypeptide 1B3; OCT2=organic cation transporter 2; P-gp=permeability glycoprotein; UV=ultraviolet; PK=pharmacokinetic; CSF1R=colony stimulating factor 1 receptor; CSR=clinical study report.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

The toxicological profile of vimseltinib has been characterized in an extensive program of repeated-dose toxicity studies of up to 26 weeks in rats and 39 weeks in dogs, a standard battery of genetic toxicity studies, carcinogenicity studies in transgenic mice and rats (ongoing), and reproductive and development toxicity studies in rats and rabbits. In addition, an in vitro assessment of the potential for vimseltinib to produce phototoxicity was performed. Pivotal toxicology studies were conducted in compliance with current International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines, generally accepted procedures for the testing of pharmaceutical compounds, and in concordance with the United States FDA GLP regulations, 21 CFR Part 58.

In repeat dose toxicity studies of up to 26 weeks in rats, there were findings of swollen head and/or limbs, and abnormal teeth at doses of 1 mg/kg/day. The dental effects at doses of 5 mg/kg/day in male rats were associated with lower food consumption and reduced body weight. Chronic progressive nephropathy occurred in animals receiving ≥ 2.5 mg/kg/day. Degeneration of blood vessels in multiple tissues and increased physis thickness was observed in rats receiving 5 mg/kg/day.

In repeat dose toxicity studies of up to 39 weeks in dogs, there were findings of periocular swelling, epiphora, excessive lacrimation and discolored and depigmented skin on the head and legs (which were swollen and wrinkled [head only]) were observed for animals administered 4 and 8 mg/kg/day. All observations showed complete or partial recovery by the end of the recovery phase at 4 mg/kg/day, while observations of wrinkled skin, excessive lacrimation, and skin de-pigmentation (females only) persisted throughout the recovery phase at 8 mg/kg/day. Vimseltinib-related increased body weight and body weight gain were noted during the dosing phase for animals administered 8 mg/kg/day; however, during the recovery phase, animals previously administered 8 mg/kg/day were observed with body weight loss and clinical observations of decreased activity, thin appearance, fever, and hunched posture (which necessitated veterinary examination and/or treatment). Microscopic findings included slight to moderate edema in the skin collected from the head of animals administered 8 mg/kg/day, which correlated with macroscopic observations of swollen head and subcutaneous tissue having a gelatinous appearance. Based on the veterinary intervention and body weight loss noted during the recovery phase for animals administered 8 mg/kg/day, this dose level was considered adverse.

Table 9 26-Week Rat Study

Study Number: DCC-3014-04-0012, eCTD 4.2.3.2								
Study Title: A 26-Week Oral Gavage Toxicity and Toxicokinetic Study with DCC-3014 in Sprague Dawley Rats with a 4 Week Recovery Phase								
Key Study Findings:								
- Daily administration of 1.0, 2.5, or 5.0 mg/kg/day vimseltinib to rats for 26 weeks resulted in observations of swollen head and/or limbs and abnormal teeth (discolored, broken, or thickened), noted either clinically or at necropsy at all dose levels. The broken and discolored teeth in males at 5.0 mg/kg/day were associated with decreased body weight gain and lower food consumption. - Degeneration/necrosis of vessels in multiple tissues and increased physis thickness were observed in rats administered 5.0 mg/kg/day, while CPN observed in rats administered ≥ 2.5 mg/kg/day, and degeneration/necrosis and dental dysplasia of molar teeth in animals administered ≥ 1.0 mg/kg/day.								
GLP compliance: Yes								
Dose and frequency of dosing:	0, 1.0, 2.5, or 5.0 mg/kg/day for 26 weeks							
Route of administration:	Oral gavage							
Formulation/Vehicle:	0.4% (w/v) hydroxypropyl methylcellulose (80 to 120 cps) in reverse osmosis water							
Species/Strain:	Rat/Sprague Dawley							
Number/Sex/Group:	Main: 15/sex/group, Recovery: 4/sex/group							
Age:	6 to 7 weeks							
Satellite groups/Unique design:	Toxicokinetic group: 4 rats/sex (control), 7 rats/sex (vimseltinib-treated group)							
Toxicokinetics - vimseltinib								
Sex	Male				Female			
Daily Dose (mg/kg/day)	0	1.0	2.5	5.0	0	1.0	2.5	5.0
Number of Toxicity Animals at Study Start	15	15	15	15	15	15	15	15
Number of TK Animals	4	7	7	7	4	7	7	7
Day 1								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	12,000	39,500	70,800	BLQ	15,700	37,500	86,400
C _{max} (ng/mL)	BLQ	823	4020	5630	BLQ	1220	2160	5960
Day 91								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	26,100	63,600	151,000	BLQ	35,300	89,300	199,000
C _{max} (ng/mL)	BLQ	2030	5170	10,100	BLQ	1950	5380	10,500
Day 182								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	31,100	80,900	166,000	BLQ	56,100	115,000	204,000
C _{max} (ng/mL)	BLQ	1780	3860	11,500	BLQ	2880	5800	10,900
Findings								

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Died or Sacrificed Moribund	One toxicity male administered 2.5 mg/kg/day, a toxicity female administered 5.0 mg/kg/day, and a toxicokinetic female administered 5.0 mg/kg/day were sacrificed in a moribund condition on Days 166, 162, or 142 of the dosing phase, due to vimseltinib-related clinical observations of foot/footpad inflammation, skin findings (epidermal acanthosis and serocellular crust), decreased activity, and poor, unkempt haircoat and piloerection. One toxicity female administered 5.0 mg/kg/day died due to a procedural error while trimming overgrown lower incisors; this death was not vimseltinib-related.
Body Weight and Food Consumption	Reversible, increased body weight and body weight gain were noted in males administered ≤ 2.5 mg/kg/day and females administered ≥ 2.5 mg/kg/day.
Ophthalmoscopy	No significant treatment-related findings
Hematology	• Non-reversible, mildly to moderately, dose independent, higher WBC and absolute neutrophil count and globulin concentration and lower A:G ratio, accompanied by higher total protein concentration (reversible) was observed in animals administered ≥ 1.0 mg/kg/day. • Reversible, lower calcium concentration (protein bound) was observed in rats administered ≥ 2.5 mg/kg/day (attributed to lower albumin concentrations). • Reversible, minimally to mildly lower red blood cell count was observed in rats administered ≥ 2.5 mg/kg/day. • Reversible, minimally to mildly lower indicators of red cell mass and absolute reticulocyte counts was observed in rats administered ≥ 1.0 mg/kg/day. • Minimally higher MCV and RDW with minimally lower MCHC was observed in rats administered 5.0 mg/kg/day; minimally and dose-dependent higher RDW in rats administered ≥ 2.5 mg/kg/day. • Reversible and minimally to mildly higher platelet counts were observed in rats administered 5.0 mg/kg/day. • Reversible, mildly lower lymphocyte counts was observed in rats administered ≥ 1.0 mg/kg/day.
Clinical Chemistry	• Non-reversible, minimally to mildly lower albumin concentration was observed in rats administered ≥ 2.5 mg/kg/day or 5.0 mg/kg/day. • Non-reversible, dose-dependent, minimally to mildly higher globulin concentration and A:G ratio was observed in rats administered ≥ 1.0 mg/kg/day • Reversible, minimally to mildly higher total protein concentrations was observed in rats administered ≥ 1.0 mg/kg/day. • Reversible, minimally to mildly lower calcium concentrations was observed in rats administered ≥ 1.0 mg/kg/day • Reversible, dose-dependent, mildly to moderately higher ALT and AST aminotransferase was observed in rats administered ≥ 1.0 mg/kg/day. • Reversible, minimally lower inorganic phosphorus concentrations was observed in rats administered ≥ 1.0 mg/kg/day and higher cholesterol concentration observed in females administered ≥ 1.0 mg/kg/day and 5.0 mg/kg/day.
Urinalysis	• Reversible, minimally higher urine specific gravity was observed in rats administered ≥ 2.5 mg/kg/day associated with minimally lower urine volume noted in rats administered 5.0 mg/kg/day.

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	• Non-reversible and higher incidence and magnitude of positive protein reactions was observed in females administered ≥ 1.0 mg/kg/day. • Reversible, hyaline casts was observed in one male and three females administered 5.0 mg/kg/day and one female administered 1.0 mg/kg/day.
Organ Weight	• Reversible, mean organ weight effects included increased thyroid and parathyroid weights in rats administered ≥ 1.0 mg/kg/day; and increased adrenal gland and liver weights in females administered ≥ 2.5 mg/kg/day and decreased thymus weights in males administered 5.0 mg/kg/day. Higher mean spleen weights persisted in a few individual males and females administered ≥ 2.5 mg/kg/day and ≥ 5.0 mg/kg/day, respectively.
Microscopic Observations	• Vimseltinib-related microscopic findings of degeneration/necrosis of vessels (at slight to moderate severity) in multiple tissues and increased physis thickness (moderate severity) were observed in rats administered 5.0 mg/kg/day, while CPN (moderate to severe severity) occurred in animals administered ≥ 2.5 mg/kg/day, and degeneration/necrosis and dental dysplasia (minimal to slight) of molar teeth occurred in animals administered ≥ 1.0 mg/kg/day; these microscopic findings were all considered adverse. • Partial reversibility of degeneration/necrosis of vessels and dental dysplasia and degeneration/necrosis of molars at recovery. • Observations of increased physis thickness and mixed cell inflammation in the swollen foot/footpad persisted at a similar severity following recovery.

Abbreviations: A:G=albumin/globulin ratio; AUC₀₋₂₄=area under the concentration versus time curve from 0 to 24 hours; ALT=alanine; AST=aspartate; BLQ=below the limit of quantitation; C_{max}=maximum drug concentration; CPN= chronic progressive nephropathy; MCHC=mean cell corpuscular hemoglobin concentration; MCV=mean cell volume; RDW=red cell distribution width; TK=toxicokinetic; WBC=white blood cell.

The FDA's Assessment:

In the 28-day repeat-dose rat toxicology study (Study No. 8332976), vimseltinib was administered once daily by oral gavage at 0, 5, 15, or 30 mg/kg/day. Findings included:

- decreases in RBC mass, lymphocytes, calcium, and phosphate
- increases in AST (up to a 230%), ALT (up to a 500%), glutamate dehydrogenase (GLDH) (up to a 180%), total protein, globulin, fibrinogen, platelets, and neutrophils.

Vimseltinib-related microscopic findings included:

- hypocellularity in bone marrow, necrosis/apoptosis in lymphoid tissues (lymph nodes, spleen)
- hypertrophy of zonal fasciculate and individual cell necrosis in adrenal
- acute inflammation in kidney, apoptosis/necrosis with infiltrating neutrophils in pylorus
- individual cell apoptosis/necrosis in stomach, individual cell apoptosis/necrosis in lamina propria of duodenum

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- hypertrophy of the physis and primary spongiosa in femur
- no liver pathology was noted

Overall, the 28-day study identified signals for inflammation, hematologic, hepatic, renal, bone, and gastrointestinal toxicities.

In the 13-week repeat-dose rat toxicology study (Study No. 8403647-1) with a 4-week recovery phase, vimseltinib was administered once daily by oral gavage at 0, 1.876, 3.75, or 7.5 mg/kg/day. Findings were similar to the 28-day repeat-dose toxicology study and included increases in AST, ALT, fibrinogen, platelets, and neutrophils and decreases in red cell mass, calcium, phosphate, and reticulocytes. Histopathology data are tabulated in Section 19.3.

In the 26-week repeat-dose rat toxicology study (Study No. 8413878) with a 4-week recovery phase, vimseltinib was administered once daily by oral gavage at 0, 1, 2.5, or 5 mg/kg/day. Findings were similar to the 28-day and 13-week repeat-dose toxicology study.

Clinical pathology findings are supportive of an inflammatory state, as well as risk for hepatotoxicity and bone-related findings.

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Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	2.5	5	0	1	2.5	5
Number of Animals								
Toxicity	15	15	15	15	15	15	15	15
Toxicokinetics	0	6	6	6	0	6	6	7
DOSING Day 183								
CLINICAL CHEMISTRY / SERUM								
Albumin (g/dL)	4.59	0	-7	-12	5.31	3	-7	-19
Alanine Aminotransferase (U/L)	46.9	120	190	222	36.6	145	205	227
Aspartate Aminotransferase (U/L)	104.7	73	155	169	94.2	113	186	207
Calcium (mg/dL)	10.37	-1	-11	-17	10.47	0	-14	-18
Phosphate (mg/dL)	6.01	-15	-42	-42	5.07	-18	-35	-27
COAGULATION / PLASMA								
Activated Partial Thromboplastin Time (sec)	17.11	-6	-8	-11	16.4	2	-7	-13
Fibrinogen (mg/dL)	162.2	8	6	9	122.6	14	14	23
HEMATOLOGY / WHOLE BLOOD								
Hematocrit (%)	49.37	-2	-6	-10	46.64	-4	-5	-15
Hemoglobin (g/dL)	16.11	-3	-7	-12	15.31	-4	-6	-18
Neutrophils (10 ⁹ /L)	2.767	56	62	62	0.908	127	263	293
Platelets (10 ⁹ /L)	905.3	8	12	35	926.7	15	14	29
Erythrocytes (10 ¹² /L)	9.405	-1	-7	-14	8.352	-2	-7	-23
Reticulocytes (10 ⁹ /L)	197.75	1	13	25	171.45	-8	0	43
Leukocytes (10 ⁹ /L)	8.03	1	1	1	4.529	15	50	40
ORGAN WEIGHTS								
KIDNEY								
Organ to Body Weight Ratio (%)	0.52497	2	3	12	0.57376	6	8	14
RECOVERY Day 211								
CLINICAL CHEMISTRY / SERUM								
Albumin (g/dL)	4.5	-6	-10	-10	5.2	-6	-8	-12
ORGAN WEIGHTS								
KIDNEY								
Organ to Body Weight Ratio (%)	0.55538	3	5	16	0.59336	5	12	14

Administration of vimseltinib was associated with decreased calcium and phosphate. The Applicant suggests that the decreased calcium is a result of reduced serum albumin levels as most serum calcium is bound to albumin; however, the levels of calcium and phosphate return to that of the controls during recovery while serum albumin does not.

The bone, kidney, and small intestine play a role in serum calcium and phosphate homeostasis. Administration of vimseltinib was associated with chronic progressive nephropathy and physcal thickening of the sternum and femur. Taken together these data suggest that the observed decreases in calcium are unlikely due to reduced serum albumin.

In the following histopathology tables, the findings of degeneration/necrosis largely correspond to vessel findings. Vimseltinib-related degeneration/necrosis of vessels occurred in multiple tissues/organs of animals administered ≥ 2.5 mg/kg/day. Vessel findings were characterized by fibrinoid necrosis of variably sized vessel (primarily artery or arteriole) walls, often with cellular debris and/or variable numbers of inflammatory cells within the wall and perivascular inflammatory cell infiltrates.

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ROMVIMZA (vimseltinib)

Study No. 8413878 (DCC-3014-04-0012): A 26-Week Oral Gavage Toxicity and Toxicokinetic Study in Rats with a 4-Week Recovery Phase									
Sex		M				F			
Group #		1	2	3	4	1	2	3	4
Dose (mg/kg/day)		0	1	2.5	5	0	1	2.5	5
Number of Animals									
TERMINAL/MORIBUND/ACCIDENTAL									
VESSEL DEGENERATION/NECROSIS									
minimal slight moderate marked severe									
ADIPOSE TISSUE									
	4 OF 5	0	0	0	0	0	0	0	1
BONE, STERNUM									
	1 OF 5	0	0	0	3	0	0	1	0
CERVIX									
	1 OF 5	0	0	0	0	0	0	1	0
	2 OF 5	0	0	0	0	0	0	0	2
EPIDIDYMIS									
	1 OF 5	0	0	1	1	0	0	0	0
	2 OF 5	0	0	0	2	0	0	0	0
	3 OF 5	0	0	0	1	0	0	0	0
ESOPHAGUS									
	1 OF 5	0	0	0	0	0	0	0	1
GLAND, THYROID									
	1 OF 5	0	0	0	0	0	0	0	1
HEART									
	1 OF 5	0	0	0	1	0	0	0	1
LARGE INTESTINE, CECUM									
	3 OF 5	0	0	0	0	0	0	0	1
LARGE INTESTINE, COLON									
	2 OF 5	0	0	0	0	0	0	0	1
LARGE INTESTINE, RECTUM									
	1 OF 5	0	0	2	0	0	0	0	0
	3 OF 5	0	0	0	0	0	0	0	1
LYMPH NODE, MESENTERIC									
	2 OF 5	0	0	0	0	0	0	0	1
MUSCLE, BICEPS FEMORIS									
	1 OF 5	0	0	0	0	0	0	0	1
PANCREAS									
	2 OF 5	0	0	0	0	0	0	0	1
SKIN/SUBCUTIS									
	1 OF 5	0	0	0	1	0	0	0	0
SMALL INTESTINE, DUODENUM									
	3 OF 5	0	0	0	0	0	0	0	1
SMALL INTESTINE, ILEUM									
	3 OF 5	0	0	0	0	0	0	0	1
SMALL INTESTINE, JEJUNUM									
	3 OF 5	0	0	0	0	0	0	0	1
STOMACH, GLANDULAR									
	2 OF 5	0	0	0	0	0	0	0	1
THYMUS									
	1 OF 5	0	0	0	0	0	0	0	1
TOOTH, INCISORS, LEFT & RIGHT									
	1 OF 5	0	0	3	0	0	0	0	2
URINARY BLADDER									
	1 OF 5	0	0	0	0	0	0	1	0
VAGINA									

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study No. 8413878 (DCC-3014-04-0012): A 26-Week Oral Gavage Toxicity and Toxicokinetic Study in Rats with a 4-Week Recovery Phase									
Sex		M				F			
Group #		1	2	3	4	1	2	3	4
Dose (mg/kg/day)		0	1	2.5	5	0	1	2.5	5
RECOVERY SACRIFICE EPIDIDYMIS HEART LARGE INTESTINE, RECTUM PANCREAS TESTIS TONGUE TOOTH, INCISORS, RIGHT	1 OF 5	0	0	0	0	0	0	0	1
	2 OF 5	0	0	1	2	0	0	0	0
	1 OF 5	0	0	0	1	0	0	0	1
	1 OF 5	0	0	1	0	0	0	1	0
	1 OF 5	0	0	0	1	0	0	0	0
	1 OF 5	0	0	0	1	0	0	0	0
	2 OF 5	0	0	0	1	0	0	0	0
	1 OF 5	0	0	1	1	0	0	1	1
	2 OF 5	0	0	0	0	0	0	0	1

Additional notable vimseltinib-related histopathological changes included bone physéal thickening, chronic progressive nephropathy, and tooth decay.

Sex		M				F			
Group #		1	2	3	4	1	2	3	4
Dose (mg/kg/day)		0	1	2.5	5	0	1	2.5	5
HISTOPATHOLOGY									
minimal slight moderate marked severe other									
BONE, FEMUR PHYSIS THICKNESS, INCREASED BONE, STERNUM PHYSIS THICKNESS, INCREASED BRAIN INFILTRATE EYELID HYPERPLASIA FOOT INFLAMMATION GLAND, MAMMARY	1 OF 5	0	1	2	0	0	0	3	0
	2 OF 5	0	0	4	1	0	0	6	0
	3 OF 5	0	0	0	9	0	0	1	11
	1 OF 5	0	0	3	3	0	0	2	8
	1 OF 5	0	0	0	1	0	0	0	0
	1 OF 5	0	0	2	7	0	0	3	3
	2 OF 5	0	0	0	1	0	0	0	0
	0	0	0	1	0	0	0	0	2
	3 OF 5	0	0	0	0	0	0	0	1
	4 OF 5	0	0	1	0	0	0	0	1

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Sex		M				F			
Group #		1	2	3	4	1	2	3	4
Dose (mg/kg/day)		0	1	2.5	5	0	1	2.5	5
CARCINOMA, MALIGNANT		0	0	0	0	0	0	0	1
	GLAND, PITUITARY								
	HYPERPLASIA								
	1 OF 5	0	0	0	1	0	0	0	0
	HYPERTROPHY								
	1 OF 5	1	3	1	3	0	0	0	0
HEART									
	INFLAMMATION								
	2 OF 5	0	0	0	0	1	0	0	0
KIDNEY									
	CHRONIC PROGRESSIVE NEPHROPATHY								
	1 OF 5	7	4	3	4	1	6	4	5
	2 OF 5	2	2	3	4	0	3	4	4
	3 OF 5	0	0	1	1	0	0	0	1
	4 OF 5	0	0	0	1	0	0	0	1
	5 OF 5	0	0	0	0	0	0	1	0
OVARY									
	INFILTRATE								
	2 OF 5	0	0	0	0	0	0	1	0
SKIN/SUBCUTIS									
	CRUST								
	1 OF 5	0	0	0	0	0	0	1	1
	3 OF 5	0	1	0	0	0	0	0	0
	EROSION/ULCER								
	1 OF 5	0	0	0	0	0	0	0	1
	HYPERPLASIA								
	1 OF 5	0	0	0	0	0	0	0	1
	2 OF 5	0	0	0	0	0	0	0	1
	NECROSIS								
	3 OF 5	0	1	0	0	0	0	0	0
STOMACH, GLANDULAR									
	EROSION/ULCER								
	2 OF 5	0	0	0	0	0	0	0	1
	INFILTRATE								
	2 OF 5	0	0	0	0	0	0	1	0
THYMUS									
	APOPTOSIS, INCREASED								
	1 OF 5	0	0	0	4	0	1	4	2
	2 OF 5	0	0	1	0	0	0	0	1
	CELLULARITY, DECREASED								
	1 OF 5	0	1	3	1	0	1	0	2
	2 OF 5	0	0	0	1	0	0	0	0
	HYPERPLASIA								
	2 OF 5	0	0	0	0	0	0	1	3
TEETH, INCISOR/MOLARS, LEFT & RIGHT									
	DEGENERATION/NECROSIS								
	1 OF 5	0	2	2	20	0	3	7	9

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	2.5	5	0	1	2.5	5
2 OF 5	0	0	0	7	0	0	0	3
DENTAL DYSPLASIA								
1 OF 5	3	5	9	9	0	1	7	8
2 OF 5	0	4	2	9	0	0	0	4
3 OF 5	0	0	0	3	0	0	0	0
4 OF 5	0	0	0	0	0	0	0	1
DENTIN MATRIX ALTERATION								
1 OF 5	0	0	0	2	0	0	0	0
2 OF 5	0	0	0	1	0	0	0	1
EDEMA								
1 OF 5	0	17	16	17	0	19	16	16
2 OF 5	0	0	1	1	0	1	4	0
INFILTRATE								
1 OF 5	0	1	6	5	1	1	4	3
2 OF 5	0	2	1	1	0	0	0	5
INFLAMMATION								
3 OF 5	0	1	0	0	0	0	0	0
PERIODONTAL POCKET								
1 OF 5	1	1	1	8	3	1	2	2
2 OF 5	0	0	1	7	0	0	1	1
UTERUS								
INFLAMMATION								
2 OF 5	0	0	0	0	0	1	0	0
METAPLASIA								
1 OF 5	0	0	0	0	1	6	3	1

In addition to the terminal sacrifice findings that did not resolve during recovery in both sexes, recovery males also had testicular atrophy and reduced sperm.

Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1	2.5	5	0	1	2.5	5
HISTOPATHOLOGY								
minimal slight moderate marked severe								
RECOVERY SACRIFICE								
BONE, FEMUR								
PHYSIS THICKNESS, INCREASED								
1 OF 5	0	0	2	2	0	0	1	0
2 OF 5	0	0	0	1	0	0	4	0
3 OF 5	0	0	0	2	0	0	0	4
EPIDIDYMIS								
INFILTRATE								
1 OF 5	2	2	3	4	0	0	0	0
2 OF 5	0	0	1	0	0	0	0	0
SPERM, DECREASED								
3 OF 5	0	0	1	1	0	0	0	0
4 OF 5	0	0	0	1	0	0	0	0
EYELID								

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Sex		M				F			
Group #		1	2	3	4	1	2	3	4
Dose (mg/kg/day)		0	1	2.5	5	0	1	2.5	5
FOOT	CRUST								
	1 OF 5	0	0	0	1	0	0	0	0
	2 OF 5	0	0	0	0	0	0	0	1
	HYPERPLASIA								
	1 OF 5	0	0	1	2	0	0	1	0
	2 OF 5	0	0	0	1	0	0	0	1
	INFLAMMATION								
	3 OF 5	0	0	0	0	0	0	0	1
	KIDNEY								
	CHRONIC PROGRESSIVE NEPHROPATHY								
	1 OF 5	4	3	3	4	1	3	2	3
	2 OF 5	1	2	2	1	0	0	2	1
	5 OF 5	0	0	0	0	0	0	1	0
	HYPERPLASIA								
	2 OF 5	0	0	0	0	0	0	1	0
	TESTIS								
	DEGENERATION/ATROPHY								
	4 OF 5	0	0	1	2	0	0	0	0
	DEGENERATION/NECROSIS								
	1 OF 5	0	0	0	1	0	0	0	0
	SPERM GRANULOMA								
	2 OF 5	0	0	1	0	0	0	0	0
	TEETH, INCISOR/MOLARS, LEFT & RIGHT								
	DEGENERATION/NECROSIS								
	1 OF 5	0	2	2	7	0	2	5	1
	2 OF 5	0	1	1	2	0	0	2	3
	3 OF 5	0	0	0	1	0	0	0	0
	DENTAL DYSPLASIA								
	1 OF 5	1	6	13	7	1	6	5	7
	2 OF 5	0	0	0	3	0	0	0	1
	3 OF 5	0	0	0	4	0	0	0	0
	DENTIN MATRIX ALTERATION								
	2 OF 5	0	0	0	1	0	0	0	0
	INFILTRATE								
	1 OF 5	0	0	5	3	0	1	4	2
	2 OF 5	0	0	1	0	0	0	3	0
	PERIODONTAL POCKET								
	1 OF 5	9	10	13	12	10	4	7	7
	2 OF 5	1	0	2	2	0	0	2	2
	3 OF 5	0	0	0	0	0	0	1	0
	UTERUS								
	METAPLASIA								
	1 OF 5	0	0	0	0	1	1	1	2
	2 OF 5	0	0	0	0	0	2	0	0

Source: Data tabulated from Study No. 8413878 (DCC-3014-04-0012)

The Applicant's Position:

Table 10 39-Week Dog Study

Study Number: DCC-3014-04-0013, eCTD 4.2.3.2								
Study Title: A 39-Week Oral Gavage Toxicity and Toxicokinetic Study with DCC-3014 in Beagle Dogs with a 4-Week Recovery Phase								
Key Study Findings:								
- Vimseltinib was well tolerated during the dosing phase of 2, 4, or 8 mg/kg/day. The NOAEL for vimseltinib was 4 mg/kg/day. - Beagle dogs showed periocular swelling, epiphora, excessive lacrimation and discolored and depigmented skin on the head and legs (≥4 mg/kg/day). All observations showed complete or partial recovery at ≥4 mg/kg/day while observations of wrinkled skin, excessive lacrimation, and skin de-pigmentation (females only) persisted throughout the recovery phase at 8 mg/kg/day.								
GLP compliance: Yes								
Dose and frequency of dosing:	0, 2, 4 or 8 mg/kg/day for 39 weeks							
Route of administration:	Oral gavage							
Formulation/Vehicle:	0.4% (w/v) hydroxypropyl methylcellulose (80 to 120 cps) in reverse osmosis water							
Species/Strain:	Dog/Beagle							
Number/Sex/Group:	Main: 6/sex/group for 0, 4, and 8 mg/kg/day groups; Recovery: 3/sex for 2 mg/kg/day							
Age:	5 to 6 months							
Satellite groups/Unique design:	Not applicable							
Toxicokinetics - vimseltinib								
Sex	Male				Female			
Daily Dose (mg/kg/day)	0	2	4	8	0	2	4	8
Number of Toxicity Animals at Study Start	6	3	6	6	6	3	6	6
Day 1								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	4140	4240	16,100	BLQ	1380	7350	15,700
C _{max} (ng/mL)	BLQ	313	464	1730	BLQ	187	721	1420
Day 89								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	3270	2060	13,300	BLQ	837	7420	17,400
C _{max} (ng/mL)	BLQ	448	172	1450	BLQ	64.4	681	1670
Day 180								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	3230	4460	13,300	BLQ	1830	6190	18,700
C _{max} (ng/mL)	BLQ	372	403	1310	BLQ	209	728	2060
Day 271								
AUC ₀₋₂₄ (h*ng/mL)	BLQ	3420	3670	8880	BLQ	2130	4730	16,000
C _{max} (ng/mL)	BLQ	402	398	999	BLQ	217	487	1350

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ROMVIMZA (vimseltinib)

Findings	
Died or Sacrificed Moribund	All animals survived to scheduled necropsy.
Body Weight and Food Consumption	Reversible, increased body weight and body weight gain were observed in dogs administered 8 mg/kg/day. No vimseltinib-related alterations in food consumption were noted at any dose level.
Ophthalmoscopy	Reversible, periocular swelling and epiphora (partially reversible) were observed in dogs administered 8 mg/kg/day.
ECG	No significant treatment-related findings
Hematology	Hematologic findings were mild in magnitude, generally non-progressive, lacked microscopic correlates, with reversibility during recovery.
Clinical Chemistry	Clinical chemistry findings were mild in magnitude, generally non-progressive, lacked microscopic correlates, and exhibited evidence of reversibility during recovery. Reversible, mildly increased AST and CK activities were observed in dogs administered 8 mg/kg/day, which likely resulted from vimseltinib mediated inhibition of CSF1R function in macrophages, which has been reported to promote increased AST and CK activities without muscle injury (Radi et al., 2011; Wang et al., 2011).
Urinalysis	No significant treatment-related findings
Organ Weight	No significant treatment-related findings
Microscopic Observations	Microscopic findings included slight to moderate edema in the skin in animals administered 8 mg/kg/day, which correlated with macroscopic observations of swollen head and subcutaneous tissue having a gelatinous appearance. Non-reversible, minimal to moderate mineralization of the epithelium was observed in males administered ≥ 4 mg/kg/day. No noteworthy microscopic findings occurred in other tissues, including the liver.

Abbreviations: AUC₀₋₂₄=area under the concentration versus time curve from 0 to 24 hours; AST=aspartate; BLQ=below the limit of quantitation; CK=creatinine kinase; C_{max}=maximum drug concentration; CSF1R=colony-stimulating factor 1 receptor; NOAEL=no observed adverse effect level.

The FDA's Assessment:

In the 28-day repeat-dose dog toxicology study (Study No. 8332977), vimseltinib was administered once daily by oral gavage at 0, 2.5, 7.5, 15, or 25 mg/kg/day. Vimseltinib-related moribund euthanasia occurred in all dogs at 15 mg/kg (on Day 24) and 25 mg/kg (on Day 8) during the dosing phase due to poor food consumption, significant body weight loss, and clinical signs of toxicity. Findings in the study included:

- decreases in phosphate, calcium, and APTT
- increases in creatine kinase (up to 207%), AST (up to 159%), ALT (up to 40%), GLDH, fibrinogen, and platelets

Vimseltinib-related microscopic findings included:

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ROMVIMZA (vimseltinib)

- decreases in zymogen granules and acinar cell degeneration/necrosis in exocrine pancreas
- atrophy, single-cell necrosis, inflammation with infiltrating neutrophils and mucosal hemorrhage in gastrointestinal tract and associated lymphoid tissues (GALT/Peyer's patch)
- infiltrating neutrophils in multiple tissues including liver and heart.

In the 13-week repeat-dose dog toxicology study (Study No. 8403702) with a 4-week recovery phase, vimseltinib was administered once daily by oral gavage at 0, 2, 4, or 8 mg/kg/day. Findings were similar to the 28-day repeat-dose toxicology study but less severe. Clinical pathology and histopathology data are tabulated in Section 19.3.

In the 39-week repeat-dose dog toxicology study (Study No. 8413879) with a 4-week recovery phase, vimseltinib was administered once daily by oral gavage at 0, 2, 4, or 8 mg/kg/day. Findings were similar to the 13-week repeat-dose toxicology study, and there were fewer microscopic findings in the 39-week study when compared to 4-week dog study with higher doses. In dogs, skin findings included a gelatinous appearance, edema, and immune cell infiltration. Dose-dependent epididymal mineralization in dogs receiving ≥ 4 mg/kg/day persisted into recovery.

Study No. DCC-3014-04-0013: A 39-Week Oral Gavage Toxicity and Toxicokinetic Study with DCC-3014 in Beagle Dogs with a 4-Week Recovery Phase								
Sex	M				F			
Dose (mg/kg/day)	0	2	4	8	0	2	4	8
DOSING PHASE								
CLINICAL CHEMISTRY / SERUM								
Alanine Aminotransferase (U/L)	43.7	+3	+18	+23	41.8	+3	+22	+23
Aspartate Aminotransferase (U/L)	32.8	+20	+58	+155	33.5	+11	+46	+167
Creatine Kinase (U/L)	153.0	+56	+115	+320	201.2	-4	+21	+223
Glutamate Dehydrogenase (U/L)	5.0	-20	-20	+14	3.0	-	+27	+193
COAGULATION / PLASMA								
Activated Partial Thromboplastin Time (sec)	13.95	-4	-8	-10	13.98	+2	+4	-14
Fibrinogen (mg/dL)	237.5	+31	+30	+22	267.0	-15	-1	+8
HEMATOLOGY / WHOLE BLOOD								
Platelets ($10^9/L$)	278.7	+13	+56	+37	322.3	-3	+28	+60
Reticulocytes ($10^9/L$)	52.32	+10	+15	+39	51.62	+26	+13	+39
URINALYSIS/URINE CHEMISTRY / URINE								
Volume (mL)	22.25	+188	+346	+275	72.18	+127	+79	+18
ORGAN WEIGHTS								
Organ to Body Weight Ratio (%)								
BRAIN	0.6883	-9	-5	-16	0.7250	+2	-4	-16
LIVER	2.5235	-1	+5	-5	2.9073	-17	-15	-15
SPLEEN	0.2663	+18	+14	+122	0.5635	+21	-9	-17
TESTIS	0.1438	-1	-21	-15	-	-	-	-

Sex	M				F			
Dose (mg/kg/day)	0	2	4	8	0	2	4	8
GROSS PATHOLOGY								
SKIN/SUBCUTIS, Site A								

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ROMVIMZA (vimseltinib)

Sex		M				F			
Dose (mg/kg/day)		0	2	4	8	0	2	4	8
gelatinous		0	0	0	3	0	0	0	2
HISTOPATHOLOGY									
1 = minimal; 2 = slight; 3 = moderate; 4 = marked; 5 = severe									
BRAIN	MINERALIZATION								
	1 OF 5	0	0	0	1	0	0	0	0
EPIDIDYMIS	CONGESTION								
	2 OF 5	0	0	0	2	0	0	0	0
	MINERALIZATION								
	1 OF 5	0	0	2	0	0	0	0	0
	2 OF 5	0	0	0	3	0	0	0	0
	3 OF 5	0	0	0	1	0	0	0	0
LARGE INTESTINE, CECUM	APOPTOSIS								
	1 OF 5	1	3	0	0	1	3	4	3
	2 OF 5	0	0	0	0	0	0	0	1
OVARY	HYPERPLASIA								
	3 OF 5	0	0	0	0	0	0	0	1
PANCREAS	DEGENERATION/NECROSIS								
	2 OF 5	0	0	0	0	0	0	0	1
	FIBROSIS								
	2 OF 5	0	0	0	0	0	0	0	1
SKIN/SUBCUTIS	EDEMA								
	1 OF 5	0	0	1	1	0	0	0	0
	INFILTRATE								
	1 OF 5	0	0	1	0	0	0	1	0
	3 OF 5	0	0	1	0	0	0	0	0
	MINERALIZATION								
	1 OF 5	0	0	0	1	0	0	0	0
SKIN/SUBCUTIS, Site A	EDEMA								
	2 OF 5	0	0	0	2	0	0	0	0
	3 OF 5	0	0	0	0	0	0	0	1
	INFILTRATE								
	1 OF 5	0	1	0	0	0	1	1	0
URINARY BLADDER	HEMORRHAGE								
	1 OF 5	0	0	1	0	0	0	0	0
UTERUS	HYPERPLASIA								
	1 OF 5	0	0	0	0	0	0	1	0
	2 OF 5	0	0	0	0	0	0	1	0

Sex		M				F			
Group #		1	2	3	4	1	2	3	4
Dose (mg/kg/day)		0	2	4	8	0	2	4	8
RECOVERY									

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	2	4	8	0	2	4	8
CLINICAL CHEMISTRY / SERUM								
Alanine Aminotransferase (U/L)	47.5	-	-4	-6	41.5	-	+17	+8
Aspartate Aminotransferase (U/L)	30.0	-	+35	+25	37.0	-	-20	-15
Creatine Kinase (U/L)	118.5	-	+228	+105	283.5	-	-52	-47
COAGULATION / PLASMA								
Activated Partial Thromboplastin Time (sec)	14.60	-	-2	-3	14.15	-	+2	-2
Fibrinogen (mg/dL)	214.5	-	-13	+32	262.0	-	-29	+16
HEMATOLOGY / WHOLE BLOOD								
Platelets (10 ⁹ /L)	211.5	-	+58	+40	294.5	-	-22	-2
Reticulocytes (10 ⁹ /L)	42.85	-	+87	+53	45.80	-	-3	+28
URINALYSIS/URINE CHEMISTRY / URINE								
Volume (mL)	40.40	-	+373	+756	52.75	-	+190	+394
ORGAN WEIGHTS								
Organ to Body Weight Ratio (%)								
BRAIN	0.6440	-	+12	+7	0.7825	-	-0	+1
LIVER	2.3575	-	+17	+17	2.8450	-	-17	-0
SPLEEN	0.2715	-	+13	+9	0.5170	-	-14	-28
TESTIS	0.1570	-	-24	-12	-	-	-	-

Sex	M				F			
Dose (mg/kg/day)	0	2	4	8	0	2	4	8
Number of Animals	2	0	2	2	2	0	2	2
POSTDOSE EVALUATION								
HISTOPATHOLOGY								
1 = minimal; 2 = slight; 3 = moderate; 4 = marked; 5 = severe								
EPIDIDYMIS								
INFILTRATE								
1 OF 5	0	0	0	1	0	0	0	0
MINERALIZATION								
1 OF 5	0	0	1	0	0	0	0	0
2 OF 5	0	0	1	1	0	0	0	0
3 OF 5	0	0	0	1	0	0	0	0
URINARY BLADDER								
INFILTRATE								
1 OF 5	0	0	0	0	0	0	1	0
MINERALIZATION								
1 OF 5	0	0	0	1	0	0	0	0

Source: Data tabulated from Study No. DCC-3014-04-0013

5.5.2. Genetic Toxicology

The Applicant's Position:

The genotoxic potential for vimseltinib to induce DNA mutations, micronuclei, or unrepaired DNA breaks has been investigated. Vimseltinib tested negative for mutagenicity in a GLP Ames assay, but positive for in vitro micronuclei formation in the absence of metabolic activation when incubated with human lymphocytes for 24 hours at $\geq 16 \mu\text{g/mL}$. In accordance with ICH S2(R1), the genotoxic potential for vimseltinib was further evaluated in vivo in rats, testing negative for both micronuclei formation in bone marrow and unrepaired DNA breaks in the liver. Based on

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the results of the in vivo rat micronucleus and alkaline comet study, together with the demonstrated lack of mutagenicity, no additional genetic toxicology studies were conducted.

GLP genotoxicity studies conducted with vimseltinib are summarized in Table 11Table 11.

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Table 11 GLP Genotoxicity Studies

Type of Test	Study Number	Test System	Metabolic Activation	Dose/Concentration	Results
Bacterial Reverse Mutation Assay	DCC-3014-04-0014 eCTD 4.2.3.3.1	<i>Salmonella typhimurium</i> (TA98, TA100, TA1535, TA1537), <i>Escherichia coli</i> (WP2 <i>uvrA</i>)	With and without S9 activation	5, 16, 50, 160, 500, 1600, and 5000 µg/plate	Cytotoxic Effects: Evidence of toxicity was observed at 5000 µg/plate in strain TA1537 in the presence of S9. Genotoxic Effects: None.
In Vitro Human Lymphocyte Micronucleus Assay	DCC-3014-04-0015 eCTD 4.2.3.3.1	Human lymphocytes (prepared from pooled blood of two male donors)	With and without S9 activation	16, 18, 20, and 30 µg/mL	Cytotoxic Effects: Cells treated with 16, 18, 20, and 30 µg/mL vimseltinib for 48 hours in the absence of S9 resulted in 38, 46, 48, and 51% cytotoxicity. Genotoxic Effects: Vimseltinib induced micronuclei in cultured human peripheral blood lymphocytes following 48 hours of treatment in the absence of S9 at 16 to 30 µg/mL. In the same test system, vimseltinib did not induce micronuclei following 24 hour treatments in the absence and presence of S9 when analyzed up to cytotoxic concentrations and/or the limit of solubility in the test system (lowest precipitating concentration observed at the end of treatment incubation) of 150 to 160 µg/mL.
Rat Micronucleus and Alkaline Comet Assay	DCC-3014-04-0019 eCTD 4.2.3.3.2	Sprague Dawley rats	N/A	50, 100, or 200 mg/kg/day	Toxic/Cytotoxic Effects: None Genotoxic Effects: None Evidence of Exposure: Systemic exposure to vimseltinib was confirmed at 50, 100, and 200 mg/kg/day in plasma derived from whole blood samples collected at necropsy (6 hours post final dose)

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Vimseltinib induced micronuclei in cultured human peripheral blood lymphocytes following 24 hours of treatment in the absence of S9.

5.5.3. Carcinogenicity

The Applicant's Position:

The Applicant conducted a 26-week carcinogenicity study in 001178-T (hemizygous) RasH2 transgenic mice (DCC-3014-04-0018, eCTD 4.2.3.3.2). Male and female mice were administered vehicle control or 1.0, 4.0, or 12.5 mg/kg/day vimseltinib via oral gavage once daily for up to 26 weeks; or positive control article (MNU) once on Day 1. Dose levels of vimseltinib evaluated in this study were consistent with feedback on the study design provided by the Agency Executive Carcinogenicity Advisory Committee ([ECAC](#)). Vimseltinib was well tolerated, and no vimseltinib-related carcinogenic potential was noted for animals administered up to 12.5 mg/kg/day, the highest dose tested. This dose level corresponded to mean C_{max} and AUC₀₋₂₄ values of 7320 ng/mL and 102,000 h*ng/mL, respectively, for vimseltinib and 207 ng/mL and 3380 h*ng/mL, respectively, for DP-7005 (metabolite) on Day 182 of the dosing phase.

- No vimseltinib-related mortality or effects on survival were noted. A clear carcinogenic response was noted for positive control animals. The increased mortality for the positive control group was attributed primarily to the presence of malignant neoplasms.
- No vimseltinib-related food consumption or organ weight effects or macroscopic observations were noted.
- Vimseltinib-related clinical observations for animals administered 12.5 mg/kg/day included a swollen dorsal cervical area and scabs on the dorsal cervical area.
- Vimseltinib-related, increased body weight or body weight gain was noted for males administered ≥ 4.0 mg/kg/day and females administered ≥ 1.0 mg/kg/day.
- No vimseltinib-related effects on the occurrence or types of neoplasms were noted. No vimseltinib-related microscopic findings, including mixed cell inflammation in meninges, were noted in the brain of animals at any dose level. Non-neoplastic, vimseltinib-related findings were noted in the spleen, femur, and/or stifle joint. In the spleen, minimally or slightly increased pigmented macrophages were noted in animals administered ≥ 1.0 mg/kg/day. In the femur and/or stifle joint, minimal or slight edema was noted in animals administered ≥ 4.0 mg/kg/day, with a higher incidence and/or severity in males.

The Applicant is conducting a 104-Week rat carcinogenicity study of vimseltinib in Sprague Dawley rats (DCC-3014-04-0025, eCTD 2.6.7 Table 21). (b) (4)

(b) (4)

. The Applicant plans to submit the final study report as a postmarketing requirement (PMR).

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. The 26-week carcinogenicity study in 001178-T (hemizygous) RasH2 transgenic mice (Study DCC-3014-04-0018) was reviewed and presented to the ECAC. ECAC agreed with the Applicant's position.

The Applicant is currently conducting a 104-week carcinogenicity study in Sprague Dawley rats to be submitted as a PMR.

5.5.4. Reproductive and Developmental Toxicology

5.5.4.1. Fertility and Early Embryonic Development

The Applicant's Position:

Table 12 Fertility and Early Embryonic Development in Male and Female Rats

Study Number: DCC-3014-04-0020	
Study Title: Fertility and Early Embryonic Development Study of DCC-3014 by Oral (Gavage) Administration Rats	
Key Study Findings: The NOAEL for vimseltinib for general toxicity was not achieved and the LOAEL was 1 mg/kg in males and 2.5 mg/kg in females. The NOAEL for mating and fertility was 5 and 10 mg/kg in males and females, respectively, the highest doses tested, and 5 mg/kg/day in both males and females for early embryonic development due to increased post-implantation loss and uterine weights at 10 mg/kg/day.	
GLP compliance: Yes	
Dose and frequency of dosing:	Male rats were administered 0, 1.0, 2.5, or 5.0 mg/kg/day vimseltinib once daily for 10 weeks prior to cohabitation, during cohabitation with untreated females, and continuing through the day before euthanasia for a minimum of 99 doses.

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	Female rats were administered 0, 2.5, 5.0, or 10 mg/kg/day vimseltinib once daily for 2 weeks prior to cohabitation with untreated males, during cohabitation, and continuing until GD 7							
Route of administration:	Oral Gavage							
Formulation/Vehicle:	0.4% (w/v) hydroxypropyl methylcellulose (80-120 cps) in reverse osmosis water (2 mL/kg)							
Species/Strain:	Sprague Dawley Rat							
Number/Sex/Group:	22/sex/dose group							
Age:	74 days							
Satellite groups/Unique design:	Satellite toxicokinetic group consisting of 3, 6, 6, and 6 females dosed at 0, 2.5, 5.0, or 10 mg/kg/day. Analysis included DCC-3014 and DP-7005.							
Toxicokinetics – vimseltinib Systemic exposures to vimseltinib in pregnant females on GD 7 increased with increasing dose and were dose proportional. Following administration of vimseltinib, systemic exposures to DP-7005 in pregnant females on GD 7 increased with increasing vimseltinib dose and were slightly greater than dose proportional. The DP-7005 to vimseltinib C _{max} and AUC ₀₋₂₄ ratios ranged from 0.907 to 1.85% and 1.02 to 1.39%, respectively, on GD 7, indicating higher exposure for vimseltinib compared to DP-7005								
Sex	Male				Female			
Daily Dose (mg/kg/day)	0	1.0	2.5	5.0	0	2.5	5.0	10
Number of Toxicity Animals at Study Start	22	22	22	22	22	22	22	22
Findings - Vimseltinib-related mortality (euthanasia due to adverse clinical signs) was observed in males at ≥2.5 mg/kg/day and females at ≥5 mg/kg/day, and adverse clinical signs were noted in both sexes at ≥1 mg/kg/day. Adverse clinical signs included swollen hindlimbs/paws, accompanied in some animals by limited use of extremities, discolored skin, skin scabs, serous exudate, and/or vocalization on manipulation of extremities (considered indicative of pain). Periorbital red staining and discharge of the eye also occurred at ≥1 mg/kg/day, primarily in males. Other vimseltinib-related effects included reduced mean body weight gain and food consumption in females at ≥5 mg/kg/day during the first week of dose administration; increased macroscopic observations in the lymph nodes of males at ≥1 mg/kg/day; reduced reproductive organ weights in males at 5 mg/kg/day; increased post-implantation loss in treated females at 10 mg/kg/day; and increased uterine weights at 10 mg/kg/day. No vimseltinib-related effects were observed on sperm parameters in treated males, estrous cycling in treated females, or mating and fertility in treated males and females at any dose level.								
Died or Sacrificed Moribund	Males – 0, 0, 3, 6. Females – 0, 0, 2, 3							
Body Weight and Food Consumption	Males – N/A, N/A Females - Premating Body Weight Gain (%; control group mean is shown and percent different vs control mean is shown. *=p ≤ 0.05 based on actual data, not on percent difference; **=p ≤ 0.01 based on actual data, not on percent difference) Days 1-8 - 6.7 g, -4%, -40%, -64% Days 8-15 – 8.4 g, +64%** , +77%** , +56%*							

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	Female FC – N/A
Clinical Observations	Clinical Observations Premating Swollen hindlimb(s)/hindpaw(s) Limited usage, hindlimb(s)/hindpaw(s) Discolored skin Skin, lesion with discharge Gestation Skin scabs
Necropsy findings	N/A

Abbreviations: AUC₀₋₂₄=area under the concentration versus time curve from 0 to 24 hours; C_{max}=maximum drug concentration; GD 7=gestational day 7; LOAEL=lowest observed adverse effect level; N/A=not applicable; NOAEL=no observed adverse effect level.

Table 13 Embryo-Fetal Development in Rats

Study Number: DCC-3014-04-0011 Study Title: An Embryo-Fetal Development Study of DCC- 3014 by Oral (Gavage) Administration in Rats Key Study Findings: - Vimseltinib at a dose of 15 mg/kg/day was a selective developmental toxicant (teratogenic) in rats. Under the conditions of this study at a maternal dose of 15 mg/kg/day malformations of the cardiovascular and skeletal systems occurred. Additional indications of developmental toxicity, including structural anatomic variations and indications of developmental delay, also occurred at this dose. - No adverse maternal effects were attributed to DCC-3014 administration, and therefore, the maternal no-observed-adverse-effect level (NOAEL) for DCC-3014 was 15 mg/kg/day DCC-3014: C_{max} 19000 ng/mL and AUC(0-t); 313000 hr*ng/mL, the highest dose tested. - Although a limited number of skeletal variations were induced at 2.5 and 5 mg/kg/day, they were attributed to developmental delay that would be anticipated to resolve with continued development and were therefore considered non-adverse. Based on these data, the developmental NOAEL for DCC-3014 was 5 mg/kg/day [DCC-3014: maternal C_{max} 2350 ng/mL and AUC(0-t); 40900 hr*ng/mL]. Following administration of DCC-3014, maternal systemic exposure to DCC-3014 and DP-7005 was observed on GD 11, increased with increasing dose for the dose levels evaluated, and was approximately dose-proportional. GLP compliance: Yes

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Dose and frequency of dosing:	Female time-mated rats were administered 0, 2.5, 5, or 15 mg/kg/day vimseltinib once daily on Gestation Days 6 through 17 (GD 6 through 17).			
Route of administration:	Oral Gavage			
Formulation/Vehicle:	0.4% (w/v) hydroxypropyl methylcellulose (80-120 cps) in reverse osmosis water (2 mL/kg)			
Species/Strain:	Sprague Dawley Rat			
Number/Sex/Group:	25/sex/dose group			
Age:	59-76 days			
Satellite groups:	Satellite toxicokinetic group consisting of 3, 6, 6, and 6 females dosed at 0, 2.5, 5.0, or 15 mg/kg/day. Analysis included DCC-3014 and DP-7005.			
Toxicokinetics – vimseltinib Systemic exposure to vimseltinib in pregnant females on GD11 increased with increasing dose for the dose levels evaluated. Taking into consideration the variability observed, the increase for AUC ₍₀₋₂₄₎ was slightly greater than dose proportional between 2.5 and 5 mg/kg/day and dose proportional between 5 and 15 mg/kg/day. Systemic exposure to DP-7005 in pregnant females on GD11 increased with increasing dose levels for the dose levels evaluated. Taking into consideration the variability observed, the increase for AUC(0-24) was dose proportional between 2.5 and 5 mg/kg/day and greater than dose proportional between 5 and 15 mg/kg/day. The mean DP-7005 to DCC-3014 AUC(0-24) ratios ranged from 0.747 to 1.23 % on GD 11 which indicated higher exposure for DCC-3014 compared to DP-7005.				
Sex	Female			
Daily Dose (mg/kg/day)	0	2.5	5.0	10
Number of Toxicity Animals at Study Start	25	25	25	25
Findings - All females survived to scheduled euthanasia on GD 21, with the exception of one pregnant female in the 5 mg/kg/day dose group that was found dead on GD 18. This unscheduled death was considered unrelated to DCC-3014 because it was not dose dependent and was likely a result of an injury sustained in the home cage.				
Died or Sacrificed Moribund	Males – 0, 0, 3, 6. Females – 0, 0, 2, 3			
Body Weight and Food Consumption	Mean maternal body weight gains for the entire dosing interval of GD 6 to 18 were 108.1%, 107.7%, and 92.7% of controls in the 2.5, 5, and 15 mg/kg/day dose groups, respectively. Mean maternal food consumption values for the entire dosing interval of GD 6 to 18 were 94.7%, 93.1%, and 89.3% of controls in the 2.5, 5, and 15 mg/kg/day dose groups, respectively.			
Clinical Observations	There were no DCC-3014-related clinical observations during the course of this study.			
Necropsy findings	There were no DCC-3014-related macroscopic observations detected during necropsy examination in females at any dose. In addition, there were no DCC-			

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	3014-related effects on any ovarian and uterine or litter parameters at 2.5 and 5 mg/kg/day dose groups.
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Abbreviations: AUC₀₋₂₄=area under the concentration versus time curve from 0 to 24 hours; C_{max}=maximum drug concentration; GD 11=gestational day 11; N/A=not applicable; NOAEL=no observed adverse effect level.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position. Based on data from animal studies, vimseltinib can cause fetal harm. In Study No. DCC-3014-04-0011, after administration during the period of fetal organogenesis, structural abnormalities occurred at ≥ 2.5 mg/kg/day (approximately 3 times the exposure at the recommended dose based on AUC). Fetuses from females receiving 2.5 and 5 mg/kg/day had increased incidences of small parietals and supernumerary suture bones. Fetuses from females receiving 5 mg/kg/day also had incomplete ossification of supraoccipitals. Fetuses from females receiving 15 mg/kg/day (approximately 23 times the exposure at the recommended dose based on AUC) also had incomplete ossification of multiple sites including the supraoccipital, thoracic centra, and skull. Heart and liver malformations were also observed at 15 mg/kg/day as both organs were observed to be misshapen.

In a fertility and early embryonic development study (Study No. DCC-3014-04-0020), male rats were administered 1, 2.5, or 5 mg/kg/day of vimseltinib starting 10 weeks before cohabitation, during cohabitation with untreated females, and at least 2 weeks post-cohabitation. Lower epididymal and testes weights were observed at 5 mg/kg/day (approximately 12 times the exposure at the recommended dose based on AUC). There were no treatment-related effects on mating, fertility, or sperm parameters at any dose tested. Female rats were administered 2.5, 5, or 10 mg/kg/day of vimseltinib 2 weeks prior to cohabitation with untreated males and during cohabitation until gestational day 7. Although there were no treatment-related effects on mating or estrous cycles, vimseltinib administered daily resulted in post-implantation loss at 10 mg/kg/day in female rats (approximately 20 times the exposure at the recommended dose based on AUC).

The Applicant also performed a pre- and post-natal study (Study No. DCC-3014-04-0029) to observe the effects of oral administration of vimseltinib from the period of implantation to lactation. The reproductive health of the F₁ generation was also assessed.

F₀ female rats were treated with 0.3, 1, or 3 mg/kg/day of vimseltinib starting on gestational day (GD) 6 until lactation day (LD) 20. A total of 6 F₀ rats (1, 1, and 4 in the 0.3, 1, and 3 mg/kg/day groups respectively) were euthanized after total litter losses between LD 0-5. F₁ rats from high dose females had reduced survival.

Sex: Female		0 mg/kg /day	0.3 mg/kg /day	1 mg/kg /day	3 mg/kg /day
Day(s) Relative to Littering (Litter: A)		Group F0-1	Group F0-2	Group F0-3	Group F0-4
Group Size - Females		22	22	22	22
Female with Liveborn [f]	N+ve	20	22	22	19
Viability Index (Birth-4) (%) [k]	Mean	98.99	91.83	92.19	70.27**
	SD	2.50	23.15	21.77	38.92
	N	20	22	22	19
	%Diff	-	-7.24	-6.87	-29.02
Lactation Index (%) 4Postcull-21 [k]	Mean	100.00	100.00	99.40	90.36**
	SD	0.00	0.00	2.73	25.26
	N	20	21	21	16
	%Diff	-	0.00	-0.60	-9.64
No of Pups with Unsched Death	Sum	4	22	13	83

Source: Excerpted from Applicant Submission

The only endpoint affected by vimseltinib administration in surviving F₁ pups was a higher age of balanoprenuputial separation from F₀ rats that received 1 or 3 mg/kg/day.

5.5.5. Other Toxicology Studies

5.5.5.1. Phototoxicity

The Applicant's Position:

In Vitro 3T3 Neutral Red Uptake Phototoxicity Assessment of Vimseltinib

An in vitro 3T3 neutral red uptake assay was conducted to assess potential phototoxicity of vimseltinib. The relative reduction in viability of BALB/c 3T3 mouse fibroblasts exposed to vimseltinib and ultraviolet radiation (+UVR; 5 J/cm² of UVA and 18 or 19 or 20 mJ/cm² of UVB), was compared with the viability of fibroblasts exposed to vimseltinib in the absence of ultraviolet radiation (-UVR). Relative cell viability remained unchanged across all vimseltinib concentrations under both non-irradiation and irradiation conditions: thus, IC₅₀ values could not be calculated due to the lack of cytotoxicity. Vimseltinib was not phototoxic to BALB/c 3T3 cells in the presence or absence of simulated solar light.

The FDA's Assessment:

The FDA generally agrees with the Applicant's position.

5.5.6. Safety Margins

The Applicant's Position:

The calculated safety margins for the definitive repeat dose toxicity studies with vimseltinib were calculated by dividing the total AUC₀₋₂₄ from the respective toxicology study at the NOAEL, STD₁₀, or HNSTD with the human total steady state AUC₀₋₂₄ (13,400 ng*hr/mL) dosed at 30 mg twice weekly (Population Pharmacokinetic Modeling Report, eCTD 5.3.3.5). The margins were based on exposures that were available at the end of the dosing period unless otherwise noted. Margins were determined based on sex combined group mean values unless otherwise noted. Total exposures were used given that vimseltinib is highly protein bound in mouse, rat, dog and human plasma with fraction unbound of 2.8%, 0.65%, 3.3%, and 3.3%, respectively.

Table 14 Calculated Safety Margins from Definitive Repeat Dose Toxicity Studies

Type of Study	Toxicity Category ^a	Dose (mg/kg/day)	AUC ₀₋₂₄ ^b (ng*hr/mL)	C _{max} ^b (ng/mL)	Exposure Margins ^c
Repeat Dose Studies					
1 mo oral rat (DCC-3014-04-0003; eCTD 4.2.3.2)	NOAEL	(b) (4)			
1 mo oral mouse (DCC-3014-04-0017; eCTD 4.2.3.4.2)	NOAEL				
1 mo oral dog (DCC-3014-04-0004; eCTD 4.2.3.2)	HNSTD				
3 mo oral rat (DCC-3014-04-0008; eCTD 4.2.3.2)	NOAEL				
3 mo oral dog (DCC-3014-04-0007; eCTD 4.2.3.2)	NOAEL				
6 mo oral rat (DCC-3014-04-0012; eCTD 4.2.3.2)	STD ₁₀				
9 mo oral dog (DCC-3014-04-0013; eCTD 4.2.3.2)	NOAEL				
Carcinogenicity Study					
6 mo Tg oral mouse (DCC-3014-04-0018; eCTD 4.2.3.4.1)	NOAEL				
Developmental and Reproductive Toxicity Studies					
FEED oral rat (DCC-3014-04-0020; eCTD 4.2.3.5.1)	F0 NOAEL				
	F1 NOAEL				
	NOAEL				
EFD oral rat (DCC-3014-04-0011; eCTD 4.2.3.5.2)	F0 NOAEL				
	F1 NOAEL				
	F0 NOAEL				

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Type of Study	Toxicity Category ^a	Dose (mg/kg/day)	AUC ₀₋₂₄ ^b (ng*hr/mL)	C _{max} ^b (ng/mL)	Exposure Margins ^c
PPND oral rat (DCC-3014-04-0029; eCTD 4.2.3.5.2)	F1 Systemic NOAEL	(b) (4)			
	F1 Developmental NOAEL				
	F2 NOAEL				

Abbreviations: AUC=area under the concentration time curve; C_{max}=maximum concentration; EFD=Embryo-fetal development; F=Female; F0=maternal generation; F1=first filial generation; F2=second filial generation; FEED=Fertility and early embryonic development; HNSTD=Highest nonseverely toxic dose; M=Male; NOAEL=No observed adverse effect level; PPND=Pre and postnatal development; STD₁₀=Severely toxic dose in 10% of rodents.

^aDose is either the NOAEL, STD₁₀, or HNSTD for the study

^bTotal exposure derived from the end of the study unless otherwise indicated

^cMargins were calculated by dividing the total nonclinical AUC₀₋₂₄ by the total human steady state AUC₀₋₂₄ (13,400 ng*hr/mL) after administration of vimseltinib 30 mg twice weekly

(b) (4)

The FDA's Assessment:

The FDA disagrees with the listing of NOAELs.

X

X

Sheryse Taylor
Primary Reviewer

Matthew Thompson
Team Lead

6 Clinical Pharmacology

6.1.Executive Summary

The FDA’s Assessment:

The Clinical Pharmacology review focused on the appropriateness of the proposed dosage, use in participants with hepatic impairment, and potential drug-drug interactions (DDI).

The Applicant’s proposed dosage of vimseltinib 30 mg orally twice weekly, with a minimum of 72 hours between doses, with or without food is generally acceptable based on the integrated analysis of PK along with the dose- and exposure-response relationships for efficacy and safety.

The current submission included data evaluating the effect of vimseltinib on the PK and safety in patients with mild hepatic impairment. As there was an insufficient number of patients with moderate hepatic impairment using the classification from the National Cancer Institute’s Organ Dysfunction Working Group (NCI-ODWG), a post-marketing requirement (PMR) was issued to evaluate the PK and safety of vimseltinib in participants with moderate hepatic impairment (NCI-ODWG).

In addition, vimseltinib’s potential for DDIs was inadequately addressed. Based on in vitro data, vimseltinib was shown to inhibit BCRP, OATP1B1/OATP1B3, and OCT2, but no clinical data is available to determine the clinical consequence of these DDIs. Therefore, three PMRs were issued to evaluate vimseltinib with substrates of BCRP, OATP1B1/OATP1B3, and OCT2.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed the information submitted in NDA 219304 and recommends approval. They key review issues and recommendations are summarized in Table 15.

Table 15: FDA-Key Clinical Pharmacology Issues and Recommendations

Review Issue	Recommendations and Comments
Pivotal and supportive evidence of effectiveness	The primary evidence of effectiveness is the ORR observed in Study MOTION. See Section 8.1.
General dosing instructions	The Applicant’s proposed dosage of 30 mg orally twice weekly, with a minimum of 72 hours between doses, with or without food is supported by the ORR observed in 83 patients in the vimseltinib arm and safety data from 253 patients receiving vimseltinib from Study MOTION and other clinical trials.

Review Issue	Recommendations and Comments
Dosing in patient subgroups (intrinsic and extrinsic factors)	<u>Hepatic Impairment:</u> No dosage adjustment is recommended in patients with mild hepatic impairment (bilirubin $\leq$ULN and AST $>$ULN or bilirubin >1 to $1.5 \times$ ULN and any AST). The recommended dosage in patients with moderate-or-severe hepatic impairment has not been established (bilirubin >1.5 to $3 \times$ ULN and any AST; bilirubin $>3 \times$ ULN and any AST, respectively). <u>Renal Impairment:</u> No dosage adjustment is recommended in patients with mild-or-moderate renal impairment (eGFR ≥ 30 mL/min). The recommended dosage in patients with severe renal impairment has not been established (eGFR <30 mL/min). <u>Age:</u> No clinically significant differences in vimseltinib's PK were observed based on age (20 to 91 years). <u>Sex and Race:</u> No clinically significant differences in vimseltinib's PK were observed based on race (Asian, Black or African American, White).
Drug-drug interactions	Avoid concomitant use of vimseltinib with P-gp substrates. If concomitant use of a P-gp substrate is unavoidable, administer vimseltinib at least 4 hours before taking the P-gp substrate unless otherwise recommended in the substrate Prescribing Information.
QTc Assessment	At the maximum recommended dose of vimseltinib, clinically significant QTc interval prolongation was not observed. However, as vimseltinib causes concentration-dependent increase in the QTcF interval and the impact of hepatic impairment on vimseltinib exposure has not been characterized, the effect on the QTcF interval in patients with moderate or severe hepatic impairment is unknown.
Bioavailability between the to-be-marketed and clinical trial formulations	Study MOTION did not administer the commercial formulation of vimseltinib, and no clinical study compared the commercial formulation to the formulation used in Study MOTION. Instead, the Applicant is seeking a biowaiver.
Outstanding issues	• A PMR was issued to evaluate vimseltinib's effects in patients with moderate hepatic impairment (NCI-ODWG). • Vimseltinib inhibits substrates of BCRP, OATP1B1, OATP1B3, and OCT2 in vitro and has the potential to cause drug interactions with substrates of these transporters. A

Review Issue	Recommendations and Comments
	clinical drug-interaction study with substrates of these transporters will be conducted as PMRs.
Labeling	Overall, the proposed labeling recommendations are acceptable.

Source: FDA generated table.

6.1.2. Post-Marketing Requirements and Commitments

The rationale and descriptions of PMRs and PMC are summarized in Table 16.

Table 16: FDA-Post-Marketing Requirements Pertinent to Clinical Pharmacology

PMR or PMC	Rationale	Description
PMR	The risk of hepatic impairment on increasing vimseltinib plasma exposure, leading to increased adverse reactions, has not been ruled out and additional data is needed to determine the appropriate dosage of vimseltinib in patients with moderate hepatic impairment (NCI-ODWG).	Conduct a clinical pharmacokinetic trial of vimseltinib in patients with moderate hepatic impairment (NCI-ODWG).
PMR	Vimseltinib inhibits BCRP in vitro. The potential inhibition of vimseltinib may increase the systemic concentrations of BCRP substrates, which may increase the potential toxicity of BCRP substrate drugs.	Conduct a clinical pharmacokinetic trial of vimseltinib with substrates of BCRP.
PMR	Vimseltinib inhibits OATP1B1 and OATP1B3 in vitro. The potential inhibition of vimseltinib may increase the systemic concentrations of OATP1B1 and OATP1B3 substrates, which may increase the potential toxicity of OATP1B1 and OATP1B3 substrate drugs.	Conduct a clinical pharmacokinetic trial of vimseltinib with substrates of OATP1B1 and OATP1B3.
PMR	Vimseltinib inhibits OCT2 in vitro. The potential inhibition of vimseltinib may increase the systemic concentrations of OCT2 substrates, which may increase the potential toxicity of OCT2 substrate drugs.	Conduct a clinical pharmacokinetic trial of vimseltinib with substrates of OCT2.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical PK profile of vimseltinib was investigated in 6 clinical studies.

Three Phase 1 clinical pharmacology studies in healthy participants have been completed:

- A PK study including evaluation of food effects (DCC-3014-01-002)
- A human absorption, metabolism, and excretion study (DCC-3014-01-003)
- A study to assess the potential for drug-drug interactions with a P-gp inhibitor and a gastric acid-reducing agent (DCC-3014-01-006)

One Phase 1 clinical pharmacology study is ongoing:

- A hepatic impairment study (DCC-3014-01-004)

Two patient studies are ongoing:

- The supportive Phase 1/2 first-in-human study (DCC-3014-01-001) in participants with TGCT and advanced malignant solid tumor (MST)
- The pivotal Phase 3 study DCC-3014-03-001 (MOTION) in participants with TGCT

Population PK (PopPK) analysis of data from healthy participants and participants with TGCT and advanced MST was conducted to characterize the PK of vimseltinib and the effects of intrinsic and extrinsic factors on the PK of vimseltinib. Physiological-based pharmacokinetic (PBPK) modeling and simulation were performed to assess drug-drug interaction liability of vimseltinib as an inducer of CYP2B6, inhibitor of permeability glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic cation transporter 2 (OCT2). Exposure-response (E-R) analyses were conducted to investigate relationships between vimseltinib exposure and efficacy and safety endpoints and evaluate the suitability of the investigated dosing regimen of 30 mg twice weekly.

Concentration QTc modeling was performed using data from participants with advanced MST from the Phase 1/2 study (DCC-3014-01-001) and data from healthy participants from DCC-3014-01-002.

The FDA's Assessment:

FDA generally agrees with the Applicant's position, except for the following:

- Physiologically based pharmacokinetic (PBPK) modeling and simulation was also used to evaluate vimseltinib as an inhibitor of OATP1B1 and OATP1B3.

- The Applicant intends to perform exploratory PK analyses based on NCI classification for moderate and severe hepatic impairment cohorts after the NDA's PDUFA action date.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

The totality of evidence shows that vimseltinib 30 mg twice weekly is the optimal dosing regimen in patients with TGCT. The efficacy, safety, and PK/PD data from the Phase 1/2 study (DCC-3014-01-001) were evaluated to determine the recommended dose to evaluate in the Expansion Cohorts of the Phase 1/2 Study and the Phase 3 MOTION study. The 30 mg twice weekly dose studied in the dose escalation cohort of the Phase 1/2 study was selected based on the manageable safety profile, PK, pharmacodynamic, and the objective responses observed.

A loading dose was not recommended as the simulated median time to steady state in participants with TGCT receiving the 30 mg twice weekly dose of vimseltinib was similar with or without 5 daily 30 mg vimseltinib loading doses.

The available clinical data from the pivotal MOTION study, along with efficacy and safety data collected to date from the Phase 1/2 study, continue to support vimseltinib administration at the recommended dose of 30 mg twice weekly with no loading dose in participants with TGCT.

In the pivotal MOTION study, vimseltinib 30 mg twice weekly demonstrated statistically significant improvements in ORR for participants with TGCT at Week 25 compared to placebo based on independent radiological review (IRR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (40% versus 0%; $p < 0.0001$) and per tumor volume score (TVS) (67% versus 0%; $p < 0.0001$). In addition, the study met all key secondary endpoints demonstrating statistically significant and clinically meaningful improvements in range of motion (ROM), physical function, worst stiffness, QoL, and worst pain compared to placebo. Adverse events observed with vimseltinib were manageable.

Maximal vimseltinib target engagement in participants with TGCT was demonstrated by dose-dependent reduction in nonclassical monocytes (NCMs) and a steep increase in CSF1 levels at 30 mg twice weekly and 10 mg daily doses of vimseltinib.

The FDA's Assessment:

FDA generally agrees with the Applicant's position. The proposed dosage of vimseltinib 30 mg twice weekly is supported by the available data; however, limited dose ranging and dose optimization was performed. See FDA's assessment on Section 6.3.2.2 for more details.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

Intrinsic Factors

Hepatic Impairment

Hepatic excretion is expected to account for a substantial portion of the elimination of vimseltinib. The potential impact of baseline hepatic function on vimseltinib exposure and safety is currently being investigated in Study DCC-3014-01-004. The interim PK analysis of the results from participants with mild hepatic impairment (as per Child-Pugh classification) and their matched (by weight, sex, race and age) controls with normal hepatic function demonstrated that following a single 10 mg vimseltinib dose:

Mild hepatic impairment resulted in 42% lower geometric mean C_{max} for total vimseltinib compared to matched participants with normal hepatic function (geometric mean AUC_{0-inf} was 24% lower, but the 90% CIs included 100%). There was no evidence of increased total vimseltinib exposure in participants with mild hepatic impairment.

There was no evidence of increased total DP-7005 exposure in participants with mild hepatic impairment.

Mild hepatic impairment did not affect protein binding of vimseltinib nor DP-7005. There was no evidence of concentration-dependent protein binding.

Liver function based on National Cancer Institute classification was not identified as a covariate in the PopPK analysis.

No dose adjustment is recommended in patients with mild hepatic impairment (Child-Pugh A).

The safety and efficacy of vimseltinib in patients with moderate and severe hepatic impairment (Child-Pugh B and C) have not been established; evaluation of the PK of vimseltinib in patients with moderate and severe hepatic impairment (Child-Pugh B and C) is ongoing.

Renal Impairment

Renal excretion is not expected to account for a substantial portion of the elimination of unchanged vimseltinib. Based on the PopPK analysis, where estimated glomerular filtration rate (eGFR) was not identified as a covariate, no relevant differences in steady state exposure are anticipated for mild and moderate renal function ($eGFR \geq 37.7$ mL/min/1.73 m²).

No dose adjustment is recommended for patients with mild or moderate renal impairment. No clinical data is available in patients with severe renal impairment; a recommended dose of vimseltinib has not been established in patients with severe renal impairment.

Race

In the PopPK analysis, an exploratory covariate-parameter relationship was identified for participants of Black or African American race, who had a ~1.3-fold higher apparent peripheral volume of distribution (V_p/F) compared to non-Black or African American participants. However, the effect on steady state exposure parameters was within the 80% to 125% limits.

Participants With TGCT Versus Healthy Participants

In the PopPK analysis, healthy participants had a ~0.7-fold lower apparent central volume of distribution (V_c/F) and a ~2.1-fold increased V_p/F compared to participants with TGCT. Healthy participants were estimated to have a 1.13-fold higher maximum concentration during a dosing interval at steady state ($C_{max,ss}$) than that of the reference participant. The effect did not exceed the 80% to 125% reference area.

Other Intrinsic Factors

In the PopPK analysis, the effect of body weight was included using allometric scaling with fixed exponents such that participants with higher body weight had higher apparent clearance (CL/F), V_c/F , V_p/F , and apparent inter-compartmental clearance (Q/F). Participants with lower body weight had a higher vimseltinib exposure in terms of average concentration during a dosing interval at steady state ($C_{avg,ss}$), $C_{max,ss}$, and minimum concentration during a dosing interval at steady state ($C_{min,ss}$) compared to heavier participants. The effects of the other identified covariates were limited and did not exceed the 80% to 125% reference area. Therefore, no dose adjustments based on body weight is recommended.

Extrinsic Factors

Effects of Other Drugs on Vimseltinib

P-gp Inhibitors

Concomitant administration of single-dose vimseltinib with 200 mg of itraconazole (a P-gp inhibitor) once daily showed that whilst peak exposure (C_{max}) to vimseltinib was comparable when administered alone and in the presence of itraconazole, total exposure to vimseltinib (area under the plasma concentration curve for a specified time [AUC_{0-t}] and area under the plasma concentration curve from zero to infinity [AUC_{0-inf}]) was approximately 17% to 22% higher in the presence of itraconazole, suggesting that P-gp inhibitors have a weak effect on vimseltinib.

The coadministration of a P-gp inhibitor reduces vimseltinib CL/F by 18%. Since the change in steady-state exposure is driven by the change in CL/F for drugs with a long half-life such as vimseltinib, this reduction in CL/F was used in the E-R analyses to predict the proportions of safety events following administration of vimseltinib administered with and without a P-gp inhibitor. Following 30 mg twice weekly dosing, the proportions of safety events at Week 25 were predicted to be similar when vimseltinib was administered with and without a P-gp inhibitor.

Proton Pump Inhibitors

Concomitant administration of vimseltinib with rabeprazole (a proton pump inhibitor) 20 mg once daily reduced peak (C_{max}) and total exposures to vimseltinib (AUC_{0-t} and AUC_{0-inf}) by approximately 21% to 26% suggesting that proton pump inhibitors have a weak effect on vimseltinib absorption.

Effects of Vimseltinib on Other Drugs

CYP Isoform-selective Substrates

Vimseltinib caused [REDACTED] (b) (4)
[REDACTED]. Based on PBPK modeling, no interaction was predicted following coadministration of bupropion, a CYP2B6 substrate, with vimseltinib 30 mg twice weekly.

Drug Transporter Systems

Vimseltinib inhibited P-gp, BCRP and OCT2 in vitro in clinically relevant concentrations.

P-glycoprotein Substrates

Based on PBPK modeling, [REDACTED] (b) (4)
[REDACTED] However, weak to moderate interaction was predicted following coadministration of dabigatran with vimseltinib 30 mg twice weekly. Simulations showed that the risk of dabigatran interaction with vimseltinib can be eliminated when dabigatran etexilate is administered (b) (4) hours after vimseltinib.

BCRP Substrates

Based on PBPK modeling, [REDACTED] (b) (4)
[REDACTED]

OCT2 substrates

Based on PBPK modeling, [REDACTED] (b) (4)
[REDACTED].

For food effect, refer to Section.

The FDA's Assessment:

FDA generally agrees, except for the following:

Hepatic Impairment

- FDA considers hepatic impairment using the NCI-ODWG criteria more clinically relevant than the Child-Pugh classification.
- Study DCC-3014-01-004 has evaluated participants with mild hepatic impairment (Child-Pugh). This study had an insufficient number of patients with mild hepatic impairment

(NCI-ODWG), and no patients with moderate or severe hepatic impairment (either Child-Pugh or NCI-ODWG).

- Based on the PopPK analysis of hepatic impairment using NCI-ODWG, mild hepatic impairment did not significantly affect the PK of vimseltinib. However, this analysis was limited to participants with mild hepatic impairment. There were no participants with moderate or severe hepatic impairment (NCI-ODWG) in the popPK analyses.

Renal Impairment

- FDA agrees that the PopPK analysis suggests no impact of renal impairment on vimseltinib clearance for patient with $\text{eGFR} \geq 37.7 \text{ mL/min/1.73 m}^2$. Additionally, the human mass balance study provides supportive evidence that renal impairment is unlikely to affect clearance because renal excretion played a limited role in vimseltinib's elimination. See Section 6.3.1 for more details.

DDI - Effects of Vimseltinib on Other Drugs

- FDA does not classify interactions with transporters using weak or moderate categories.
- Vimseltinib (b) (4)
Vimseltinib inhibited OAT1B1, OATP1B3, MATE1, and MATE2-K in vitro at clinically relevant concentrations, in addition to P-gp, BCRP, and OCT2.
- FDA disagrees with the Applicant's position on the DDI risk with P-gp substrates. Vimseltinib was predicted to increase dabigatran's AUC and C_{max} up to 3-fold when considering the uncertainty on the in vitro generated IC_{50} value of P-gp. The inhibitory effects of vimseltinib may be mitigated by administering dabigatran 4 hours after vimseltinib dosing. (b) (4)
For details, see Section 19.4.3. See Section 6.3.2.4 for FDA's recommendation on P-gp substrates.
- FDA disagrees with the Applicant's position on the DDI risk with BCRP substrates. Vimseltinib was predicted to increase rosuvastatin's AUC and C_{max} up to 2.6- and 6.3-fold, respectively, when considering the uncertainty on the in vitro generated IC_{50} value of BCRP. (b) (4)
For details, see Section 19.4.3.
- The Applicant's model with rosuvastatin evaluated vimseltinib's effects on a substrate of BCRP, OATP1B1, and OATP1B3. For details, see Section 19.4.3.
- FDA disagrees with the Applicant's position on the DDI risk with OCT2 substrates. (b) (4)
For details, see Section 19.4.3.

Food Effect

- See Section 6.3.1 for details on FDA's assessment.

6.2.2.3. Outstanding Issues

The Applicant's Position:

As discussed during the Pre-NDA meeting, the Phase 1 study DCC-3014-01-004 evaluating the effects of hepatic impairment on the PK of vimseltinib is ongoing. An interim PK analysis of the data from participants with mild hepatic impairment was submitted in the NDA.

The PK results from the moderate and severe hepatic impairment cohorts will be submitted to the NDA upon completion.

The FDA's Assessment:

FDA generally agrees, except for the following:

- Study DCC-3014-01-004 has evaluated participants with mild hepatic impairment (Child-Pugh). This study had an insufficient number of participants with mild hepatic impairment (NCI-ODWG), and no participants with moderate or severe hepatic impairment (either Child-Pugh or NCI-ODWG).
- PopPK analysis of hepatic impairment using NCI-ODWG was limited to participants with mild hepatic impairment. There were no participants with moderate or severe hepatic impairment (NCI-ODWG) in the popPK analyses.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

The nonclinical pharmacology and PK profile of vimseltinib was investigated by in vitro studies with human biomaterials, including assessments of plasma protein binding, metabolism, the potential for induction or inhibition of CYP enzymes, interactions with transporters, and hERG channel current inhibition.

In human plasma, protein binding of vimseltinib at 10 μ M was demonstrated to be 96.5%; thus, the free fraction of vimseltinib was determined to be 3.5%. Among the animal species tested, the percent bound values at the same concentration ranged from 95.4% in monkey to 99.3% in rat. The bound percentage of DP-7005 (the *N*-des-*iso*-propyl active metabolite of vimseltinib) in human plasma was 92.4%. The percent bound in animals ranged from 84.7% in monkey to 98.3% in rat.

The half-life of vimseltinib in human hepatocyte preparations was ≥ 4 hours, as no substrate loss was observed after 240 minutes of incubation. In metabolite identification studies in human hepatocytes, DP-7005 was the only ultraviolet-detectable metabolite. ^{14} C-vimseltinib was metabolized in human hepatocytes and microsomes via oxidation, *N*-dealkylation, and dehydrogenation. No Phase 2 conjugated metabolites were detected. Metabolites detected in

human hepatocytes and microsomes were also found in other species. In addition to unchanged vimseltinib, up to 7 metabolites were tentatively identified/characterized in hepatocytes and microsomes. In human hepatocytes, >96% of the radioactivity was associated with unchanged ¹⁴C-vimseltinib. In human microsomes, >90% of the radioactivity was associated with unchanged ¹⁴C-vimseltinib. DP-7005 accounted for <3% radioactivity in human microsomes. Reaction phenotyping studies in microsomal preparations and recombinant human CYP enzyme incubations to characterize human CYP enzyme activity indicated a minor role of CYP enzymes in the human phase 1 metabolism of vimseltinib and minimal risk for drug-drug interactions involving vimseltinib CYP phase 1 metabolism.

In vitro, both vimseltinib and DP-7005 exhibited IC₅₀ values >40 µM for all CYP isoforms studied, and IC₅₀ values >100 µM were exhibited by vimseltinib for 5 out of 7 CYP isoforms. Additionally, neither vimseltinib nor DP-7005 exhibited time-dependent or metabolism-dependent inhibition of any CYP isoform, demonstrating little to no risk for time- or metabolism-dependent inhibition of CYP isoforms. Vimseltinib and DP-7005 exhibit a low/minimal liability for a drug-drug interaction mediated by CYP inhibition.

Treatment of cultured human hepatocytes with up to 100 µM vimseltinib demonstrated low to minimal risk for CYP3A4 or CYP1A2 enzyme induction and a slight risk for CYP2B6 induction at anticipated clinical exposures, suggesting a potential risk for perpetrator drug-drug interactions involving CYP metabolism. CYP2B6 induction was further investigated in the PBPK modeling, which did not predict any interaction following coadministration of bupropion (a CYP2B6 substrate) with vimseltinib 30 mg twice weekly.

Nonclinical studies indicated that vimseltinib may alter the PK of concurrent medications that are substrates for BCRP, P-gp, and OCT2.

Potential effects of vimseltinib on cardiac electrophysiology were tested using a GLP hERG patch clamp electrophysiology assay. At concentrations of 10 µM and 30 µM, vimseltinib did not significantly inhibit hERG channel current. In addition, vimseltinib (0.1 µM to 25 µM) exhibited negligible binding to the hERG channel in a non-GLP in vitro binding assay.

Clinical Pharmacology and Pharmacokinetics

Pharmacokinetics

The clinical pharmacology of vimseltinib was studied in the ongoing Phase 1/2 study in participants with TGCT and advanced MST, in the ongoing MOTION study in participants with TGCT, and in 4 Phase 1 clinical pharmacology studies (one of which is ongoing).

The Phase 1/2 study, MOTION, and Study DCC-3014-01-002 contributed data for the PopPK analysis and the E-R analysis. Physiologically based pharmacokinetic modeling and simulations were performed using data from Study DCC-3014-01-002, Study DCC-3014-01-003, Study DCC-3014-01-004 (Part 1 only), and Study DCC-3014-01-006.

Absorption, Distribution, Metabolism, and Excretion

Absorption

Vimseltinib was rapidly absorbed across the dose range studied in the clinical pharmacology studies, with single doses that ranged from 6 mg to 30 mg and repeat doses that ranged from 40 mg to 50 mg once daily.

After oral administration of a single 30 mg dose of vimseltinib (given as 3 capsules each containing 10 mg) under fasted conditions in Study DCC-3014-01-002, median time to maximum drug concentration (T_{max}) ranged from 1 to 2 hours. C_{max} ranged from 305 to 433 ng/mL, and AUC_{0-inf} ranged from 42,900 to 59,100 h•ng/mL.

In the Phase 1/2 study, after oral administration of a 30 mg dose of vimseltinib on Cycle 1 Day 1 to participants with TGCT in dose escalation, median T_{max} and mean C_{max} were consistent with the results from Study DCC-3014-01-002: median T_{max} ranged from 1.60 to 1.70 hours, and C_{max} ranged from 273 to 320 ng/mL.

Due to its pH dependent solubility, vimseltinib has the potential to be subject to a drug interaction with acid-reducing agents. Study DCC-3014-01-006 evaluated the drug interaction potential of a single dose of vimseltinib as a victim drug when co-administered with the proton pump inhibitor rabeprazole in healthy participants. The results suggested concomitant administration of proton pump inhibitors has a weak effect on vimseltinib absorption.

Administering vimseltinib with a high-fat meal decreased the rate of vimseltinib absorption, possibly due to delayed gastric emptying, but there was no food effect on the extent of absorption.

Distribution

Mild hepatic impairment did not appear to affect vimseltinib plasma protein binding as geometric mean unbound vimseltinib fraction remained between approximately 6% and 7% in participants regardless of hepatic function classification or concentration.

The PopPK model suggests an apparent volume of the central compartment of 88.0 L and an apparent volume of the peripheral compartment of 28.9 L. Covariate analysis suggested that healthy participants had a lower V_c/F , and higher V_p/F , compared to participants with TGCT. However, the effect on steady-state exposure parameters was within the 80% to 125% limits.

Individual whole blood/plasma ratios of total radioactivity in Study DCC-3014-01-003 ranged from 0.559 (at 10.0 hours) to 0.898 (at 0.5 hours). Based on AUC_{0-inf} , the geometric mean whole blood-to-plasma total radioactivity ratio was 0.751, indicating no appreciable red blood cell partitioning.

Metabolism

Metabolic profiling as part of Study DCC-3014-01-003 determined that primary metabolism occurred by oxidation, *N*-demethylation, and *N*-dealkylation; secondary biotransformation pathways included *N*-demethylation, dehydrogenation, and oxidation. In male healthy participants, 15 detectible metabolites were produced, 8 of which were identified. No major

circulating metabolites were detected. The most abundant, albeit minor metabolite was M3 (DP-7005), accounting for 9.67% of the dose in urine and 5.63% of the dose in feces. DP-7005, like vimseltinib, is a CSF1R inhibitor (IC₅₀ value of 65 nM compared to 2.8 nM for vimseltinib).

In Study DCC-3014-01-003, peak and overall exposure to the minor active DP-7005 metabolite in plasma was appreciably lower than that observed for vimseltinib. Geometric mean molecular weight–corrected metabolite-to-parent ratios (MPRs) for C_{max}, AUC_{0-t}, and AUC_{0-inf} were 2.58%, 4.48%, and 5.01%, respectively. The MPRs in Study DCC-3014-01-002, Study DCC-3014-01-004, and Study DCC-3014-01-006 were in a similar range.

Elimination

Elimination of vimseltinib occurred by metabolism and urinary and fecal excretions. In Study DCC-3014-01-003, when extrapolated to infinity, 37.5% of the administered ¹⁴C-vimseltinib dose was excreted in urine and 42.9% in feces.

Following single-dose administration of 30 mg vimseltinib to healthy participants in a fasted condition in Study DCC-3014-01-002, geometric mean (geometric coefficient of variation) CL/F ranged from 0.507 L/h to 0.699 L/h. Terminal elimination phase half-life (t_{1/2}) ranged from 134 to 137 hours (39.6%). Following single-dose administration of 30 mg vimseltinib to healthy participants in Study DCC-3014-01-006, CL/F and t_{1/2} were in a similar range.

In the PopPK analysis, the median effective half-life of vimseltinib based on all participants in the analysis population was 136 hours, consistent with the t_{1/2} observed in Study DCC-3014-01-002.

Dose Proportionality

In Study DCC-3014-01-002, dose proportionality was confirmed in healthy participants for vimseltinib C_{max} and AUC_{0-24h} following single oral doses of vimseltinib 6 mg to 50 mg since the slopes (β₁) in the linear regression for these parameters were approximately 1 and the 90% confidence intervals (CIs) of the slope estimates included the value of 1 (C_{max}: 0.9572 [0.8464, 1.0680]; AUC_{0-24h}: 0.9343 [0.8376, 1.0309]). Additionally, vimseltinib AUC_{0-inf} was dose proportional between 6 mg and 30 mg; the linear regression slope (90% CIs) was 0.8804 (0.6802, 1.0805).

In the Dose Escalation Phase of the Phase 1/2 study, plasma exposure of vimseltinib following single-dose administration of vimseltinib 20 mg to 30 mg, as measured by geometric mean plasma AUC_{0-4h}, AUC_{0-8h}, and C_{max}, increased with dose in participants with TGCT. Following multiple doses, the trend for higher exposure associated with higher dose was maintained in participants with TGCT receiving daily maintenance doses. Increased exposure for DP-7005 was associated with higher doses.

Steady State

In the PopPK analysis, simulations based on empirical Bayes estimates of the full analysis population showed that the 30 mg twice weekly dosing regimen of vimseltinib results in a

median accumulation ratio of 2.59. The simulated median time to steady state in participants with TGCT receiving the 30 mg twice weekly dose was similar (28 days) with or without 5 once daily 30 mg loading doses.

Effect of Food

Vimseltinib can be taken with or without food.

Administering vimseltinib with a high-fat meal decreased the rate of vimseltinib absorption, possibly due to delayed gastric emptying, but there was no food effect on the extent of absorption.

Following administration of 30 mg vimseltinib with a high-fat meal, C_{max} of vimseltinib was approximately 30% lower compared to fasted conditions (geometric LS means ratio [90% CIs] of 69.86% [62.92%, 77.58%]), and median T_{max} was delayed by 5 hours (6.0 hours compared to 1 hour under fasted conditions).

AUC_{0-120h} , AUC_{0-t} , and AUC_{0-inf} for vimseltinib were comparable under fed and fasted conditions with the ratios of geometric LS means and the corresponding 90% CIs within the accepted 80.00% to 125.00% limits.

The PopPK analysis suggested that fed participants had an approximately 6-fold longer mean absorption time (MAT) than fasted participants; however, this had a limited effect on steady state exposure metrics.

Effect on QT Interval

A concentration QTc modeling analysis was performed based on the data from participants with MST in the Phase 1/2 study and healthy participants from Study DCC-3014-01-002 (who are physiologically similar to participants with TGCT). The results from the cardiodynamic evaluation of the 40 mg and 50 mg doses demonstrated that vimseltinib has no clinically relevant effect on heart rate or on cardiac conduction (the PR and QRS intervals). There was no clinically meaningful effect on the QTc interval, and an effect on $\Delta\Delta QTcF$ exceeding 10 ms can be excluded within the observed ranges of plasma concentrations of vimseltinib, up to 1774 ng/mL.

Exposure-Response Analyses

Data from the Phase 1/2 study and MOTION were used to inform the E-R model development and analysis.

The exposure-response relationships between vimseltinib $C_{avg,ss}$ and ORR per RECIST v1.1 and per TVS at Week 25 in participants with TGCT from MOTION was well characterized by a logistic regression model. An exposure-efficacy analysis based on data from participants with TGCT did not show association between vimseltinib exposure and ORR per RECIST v1.1 or TVS. A flat exposure-efficacy relationship was identified across the exposure range for the evaluated dosing regimen.

The exposure-safety relationships between vimseltinib $C_{\max,ss}$ and the time to first event of periorbital edema, rash, AST elevation, and alanine aminotransferase (ALT) elevation in patients with TGCT or MST from the Phase 1/2 study and MOTION were well characterized by Cox proportional hazards models. For all safety endpoints, the event incidence was estimated to increase with increasing $C_{\max,ss}$, with an initial increase for low $C_{\max,ss}$, followed by a plateau. The impact of vimseltinib exposure was more pronounced for AST elevation events, while the relationship was relatively flat for the other endpoints. For periorbital edema, rash, and ALT elevation, the difference in the median predicted proportions of these safety events at Week 25 was marginal at <5% following 20 mg twice weekly, compared to 30 mg twice weekly. For AST elevation, the difference was -7.3%.

Pharmacodynamics

The pharmacodynamic effect of vimseltinib on NCMs (circulating monocytes in peripheral blood, which express CSF1R and are sensitive to anti-CSF1/CSF1R targeted therapies), and plasma CSF1 levels were investigated as biomarkers to study vimseltinib target engagement.

Changes in pharmacodynamics biomarkers were assessed among the participants with TGCT and MST from the safety population in the Phase 1/2 study. Specifically, the percentage change from baseline in NCM and fold changes in the levels of CSF1 in plasma were summarized by visits across Dose Escalation cohorts up to Week 25.

Vimseltinib demonstrated a dose-dependent decrease in the levels of circulating NCM in Dose Escalation cohorts who received 10 mg to 40 mg twice weekly doses and 6 mg to 20 mg daily doses. The mean reduction in NCM levels from baseline at Cycle 2 Day 1 in participants with TGCT was in the range of 65% to 80%. The maximum NCM reduction was reached by Cycle 2 Day 1 (Week 5) for most cohorts and was maintained throughout the dosing period.

Increased levels of CSF1 in plasma were observed across all cohorts. A steep increase in mean fold changes over baseline CSF1 levels at Cycle 2 Day 1 was observed from 20 mg twice weekly dose to 30 mg twice weekly, or from 6 mg daily dose to 10 mg daily dose. The fold changes in CSF1 levels in participants with TGCT were in a similar range, except for the lower dose cohort (6 mg daily dose). Similar to the NCM changes, the maximum fold changes in CSF1 levels across the cohorts were reached by Cycle 2 Day 1.

The Applicant's Position:

The PK and PD characteristics of vimseltinib, together with the E-R analyses, support the proposed administration of vimseltinib at 30 mg twice weekly in patients with TGCT.

The FDA's Assessment:

FDA generally agrees, except for the following:

Food Effect

Although there was no significant impact of food on AUC_{0-inf} and AUC_{0-t}, C_{max} was decreased in the presence of food (Table 17). This decreased C_{max} is not considered clinically meaningful, since only a small decrease in exposure was seen, and changes in C_{max} are not expected to significantly impact antitumor activity.

Table 17: FDA-Bioavailability Results from Study DCC-3014-01-002

Reference	Test	Parameter	Reference Geometric LS Mean	Test Geometric LS Mean	Ratio of Geometric LS Mean	Lower 90% CI	Upper 90% CI
Fasting	Fed	AUC _{0-inf}	63181	65336	103	98	109
Fasting	Fed	AUC _{0-t}	58215	59176	102	98	106
Fasting	Fed	C _{max}	490	344	70	62	79

N=12 in each group for each PK parameter.

Source: FDA's analysis.

Absorption

- FDA agrees with the Applicant's assessment of absorption. A biowaiver was requested to bridge the formulation between the commercial formulation and the formulation used in study MOTION. The biowaiver was found to be acceptable. For details, see the review of ROMVIMZA by the Office of Product Quality.

Metabolism

- DP-7005 is not considered an active metabolite, as DP-7005 is unlikely to play a role in efficacy or safety. DP-7005's activity is 23-fold lower than the parent drug, and systemic levels of DP-7005 in the body appear too low to achieve clinical activity (i.e., DP-7005's IC₅₀ is lower than its C_{max}). Furthermore, DP-7005's impact on safety was not evaluated, as DP-7005 was a minor metabolite in humans.
- Vimseltinib (b) (4)
- Vimseltinib is a P-gp substrate but is not a substrate of BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K.
- Vimseltinib inhibited OAT1B1, OATP1B3, MATE1, and MATE2-K in vitro at clinically relevant concentrations, in addition to P-gp, BCRP, and OCT2.

Excretion

- Following a single oral dose of radiolabeled vimseltinib, approximately 43% of the dose was recovered in feces (9.1% unchanged) and 38% in urine (5.1% unchanged) after a single radiolabeled dose. Plasma metabolites were minor (<10% of total plasma radioactivity exposure).

Clinical P-gp and Acid-Reducing Agent Study (Study DCC-3014-01-006)

- Although vimseltinib's AUC and C_{max} were decreased in the presence of a PPI (Table 18), the decreased exposure is not anticipated to be clinically meaningful, since (1) only a small decrease in exposure was seen and (2) the exposure-efficacy analyses saw that exposure (C_{avgss}) wasn't related to efficacy, and C_{avgss} is highly correlated with AUC.

Table 18: FDA-PK Results from Study DCC-3014-01-006

Reference	Test	Parameter	Reference Geometric LS Mean	Test Geometric LS Mean	Ratio of Geometric LS Mean	Lower 90% CI	Upper 90% CI
Arm 1	Arm 2	AUC _{0-t}	51776	60705	117	100	137
Arm 1	Arm 2	AUC _{0-inf}	57771	70519	122	103	144
Arm 1	Arm 2	C _{max}	425	408	96	80	116
Arm 1	Arm 3	AUC _{0-t}	51776	38960	75	64	88
Arm 1	Arm 3	AUC _{0-inf}	57771	45492	79	67	92
Arm 1	Arm 3	C _{max}	425	313	74	61	89

Arm 1: 30 mg dose of vimseltinib given one time. Arm 2 = itraconazole 200 mg solution given orally once daily from D1 to D24. Vimseltinib 30 mg orally given on D5. Arm 3 = rabeprazole 20 mg given orally once daily on D1 to D5. Vimseltinib 30 mg orally given on D5.

Units for AUC and C_{max} are h*ng/mL and ng/mL, respectively. Sample size ranged between 23 and 30, depending on the PK parameter and treatment group.

Source: FDA's analysis.

Pharmacodynamics

- Vimseltinib's dose-dependent effects on decreased circulating NCM and increased CSF1 levels in the plasma were unclear in patients with TGCT.

PopPK

- For details on the popPK analyses, see Section 19.4.1 for the pharmacometrics team's assessment.

E-R

- Study DCC-3014-01-002 did not contribute to E-R analyses.
- For details on the E-R analyses, see Section 19.4.2 for the pharmacometrics team's assessment.

PBPK

- Study DCC-30140-01-004 did not contribute to PBPK analyses.
- For details on the PBPK analyses and FDA's assessment, see Section 19.4.3.
- QTc: In general, although vimseltinib did not cause clinically significant QTc prolongation at the maximum recommended dose, it can increase QTcF interval in a concentration-dependent manner. Since the impact of hepatic impairment on vimseltinib

exposure is not yet known, it is uncertain what the impact on QTc interval might be in patients with moderate or severe liver impairment.

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes. Clinical studies evaluating vimseltinib 30 mg twice weekly in participants with TGCT have demonstrated strong clinical benefit and manageable safety profile, with PK/PD and E-R data supporting the recommended dose (see Section 6.2.1 and 6.2.2 of this Assessment Aid).

The FDA's Assessment:

FDA agrees that the completed clinical studies provide supportive evidence of effectiveness of vimseltinib in the proposed patient population. See Section 6.2.

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The Applicant's Position:

Yes. The recommended dosing regimen of vimseltinib in patients aged 18 years and older is 30 mg twice weekly at least 3 days apart with or without food. If a vimseltinib dose is missed by more than 2 days, the patient should skip the missed dose and return to the regular dosing schedule. This regimen is supported by its pharmacological properties and by clinical efficacy and safety data generated to date.

Vimseltinib dose may be temporarily withheld if the recommended dose is not tolerated. Vimseltinib may be resumed on a reduced dose as shown in the table below when the clinical condition improves. Vimseltinib should be discontinued in patients unable to tolerate a 14 mg dose.

Recommended Dose Reduction for Adverse Reactions

Dose Reduction	Twice Weekly Dose
First	20 mg
Second	14 mg

The FDA's Assessment:

FDA generally agrees that the proposed dosage is appropriate for the general patient population based on the dose- and exposure-response relationships for efficacy and safety. Doses should be separated by a minimum of 72 hours, as directed on the blister package. The blisterpack is anticipated to reduce patient nonadherence to the dosing regimen.

Dose-Response and Exposure-Response Relationships

In Study DCC-3014-01-001, three dose levels were evaluated in patients with TGCT with the following efficacy results (Table 19Table 19).

Table 19: FDA-Dose-Efficacy Results from Study DCC-3014-01-001

Cohort	Dosage	ORR (DCO 10/5/2020)	ORR (Final results)
9	6 mg daily (42 mg per week)	0% N=5	58% N=12
5	30 mg twice weekly (60 mg per week)	50% N=6	83% N=12
8	10 mg once daily (70 mg per week)	55% N=11	75% N=8

Source: Applicant's analysis.

At the data cutoff (DCO) of September 5, 2020, which was when the Applicant proposed the Recommended Phase 2 Dose (RP2D) to FDA, the Applicant chose Cohort 5 based on (1) Cohort 5 having 1 CR, whereas Cohort 8 had none, and (2) Cohort 5 having a lower or similar incidence of the most common TEAEs, compared to Cohort 8, in the Applicant's opinion.

In MOTION, 39% of patients experienced a dose reduction and 48% of patients remained on 30 mg by Week 25. The following data support the dosage of 30 mg twice weekly:

- There appeared to be a positive relationship for dose and efficacy in the Phase 1/2 study for ORR. However, the exposure-efficacy analysis was inconclusive and was performed with limited doses (20 mg twice weekly (BIW) and 30 mg BIW), and for the single dose, the trend appeared to be flat.
- The DOR was similar between responders who had dose reductions to those who did not.
- In the exposure-safety analysis, which was conducted in 285 participants, including 12 participants with 6 mg QD exhibited the following trends:
 - Shallow, positive trends for periorbital edema, rash, and ALT increase.
 - No apparent trend for CPK increase.
 - A steep, positive trend for AST increase. However, AST increases led to dose reductions/interruptions in only 2.5% of patients treated with vimseltinib in MOTION in the double-blind and open-label period.

- There was a significant overlap in $C_{max,ss}$ between patients who experienced asthenia, blood CPK elevation, periorbital edema, pruritus, and pooled rash and rash maculopapular events, compared to patients who didn't experience those events.
- A more convenient dosing (i.e., a once daily dosing of 10 mg) would not improve the safety profile or dosage modifications, since it would only have a minor decrease in $C_{max,ss}$, based on limited data from the Phase 1/2, dose-finding study which had approximately 12 patients per cohort.

For details on the E-R analyses, see Section 19.4.2 for the pharmacometrics team's assessment.

Based on the PK profile, FDA recommends the following instructions when the patients misses the correct dose timing or if vomiting occurs.

Missed Dose

As vimseltinib has a relatively long half-life ($t_{1/2} = 134$ to 137 hours), missing a dose by 48 hours wasn't anticipated to significantly impact the steady state concentrations. This was evaluated further in the following popPK simulations (Table 20).

Table 20: FDA-Summary Statistics of Simulated Vimseltinib PK Parameters for Medication Error Scenarios on Week 6 (W6)

PK Parameters (Week 6)	30 mg BIW for 6 weeks (Reference)	30 mg BIW for 5 weeks followed by 30 mg on D1 and D2 on Week 6	30 mg BIW for 5 weeks followed by 30 mg on D1 and D3 on Week 6
AUC _{0-168h,W6} (h*mg/L)			
Geomean (gCV)	95.5 (48.7)	102 (48.2)	98.7 (48.4)
Median (min, max)	95.9 (21.9, 381)	102 (23.5, 396)	99.1 (22.8, 389)
$C_{max, W6}$ (ng/mL)			
Geomean (gCV)	828 (44.8)	950 (42.6)	885 (43.7)
Median (min, max)	838 (217, 2960)	957 (270, 3120)	893 (241, 3040)

Abbreviations: Geomean=Geometric mean. gCV=geometric coefficient of variation. N=1810 for each simulation.
Source: Applicant's analysis.

Based on Table 20, if doses were administered 24 hours apart, such increase in C_{max} does not appear to be clinically meaningful (i.e., 14%). Therefore, missing the dose by 48 hours is also not anticipated to significantly impact C_{max} . A missed dose of >48 hours was not considered, since the minimum dosing interval was 72 hours apart. Taking two doses within 24 hours would increase the C_{max} by 2-fold, based on PK linearity, and would be expected to worsen the safety. Therefore, FDA recommends the following for missed doses: If a dose is missed by 48 hours or less, take the missed dose as soon as possible and take the next dose on its regularly scheduled day. If a dose is missed by more than 48 hours, skip the missed dose, and take the next dose on its regularly scheduled day.

Vomiting

FDA recommends the following for vomiting: If vomiting occurs within 30 minutes of taking a dose, repeat that dose. Otherwise, take the next dose on its regularly scheduled day.

$T_{\max}$ was evaluated to determine recommendations for vomiting. As the $T_{\max}$ ranged between 0.5 to 4 hours, 30 minutes was selected, as this was on the lower range of $T_{\max}$, which would avoid potentially duplicating dose administration and increasing toxicity.

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors (e.g. race, ethnicity, age, performance status, genetic subpopulations, etc.)?

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations. A summary of the effects of intrinsic factors on PK is presented in Section .

The FDA's Assessment:

FDA generally agrees, with the clarifications and exceptions noted in Section 6.2.2.2.

6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

The Applicant's Position:

Food Effect

Administering vimseltinib with a high-fat meal decreased the rate of vimseltinib absorption, possibly due to delayed gastric emptying, but there was no food effect on the extent of absorption.

Following administration of 30 mg vimseltinib with a high-fat meal, $C_{\max}$ of vimseltinib was approximately 30% lower compared with fasted conditions (geometric LS Means ratio [90% CIs] of 69.86% [62.92%, 77.58%]) and median $T_{\max}$ was delayed by 5 hours (6.0 hours compared with 1.0 hour under fasted conditions).

AUC_{0-120h} , AUC_{0-t} , and AUC_{0-inf} for vimseltinib were comparable under fed and fasted conditions with the ratios of geometric LS means and the corresponding 90% CIs within the accepted 80% to 125% limits.

The PopPK analysis suggested that fed participants had an approximately 6-fold longer MAT than fasted participants; however, this had a limited effect on steady-state exposure metrics.

In conclusion, vimseltinib can be taken with or without food.

Effect of Other Drugs on Vimseltinib

CYP Inhibitors and Inducers

Vimseltinib is metabolically stable in human microsomes and recombinant CYP enzymes, indicating a minor role of CYP enzymes in the human phase 1 metabolism of vimseltinib and minimal risk for victim drug-drug-interactions involving CYP phase 1 metabolism.

Inhibitors of Transporters

Nonclinical data indicated that vimseltinib is a weak substrate of P-gp and exhibits low potential to be a victim of a drug-drug interaction mediated by P-gp inhibitors. Study DCC-3014-01-006 evaluated the drug interaction potential of a single dose of vimseltinib as a victim drug when co-administered with a strong P-gp inhibitor, itraconazole, in healthy participants.

Concomitant administration of itraconazole 200 mg once daily showed that while peak exposure (C_{max}) to vimseltinib was comparable, total exposure (AUC_{0-t} and AUC_{0-inf}) was approximately 17% to 22% higher, suggesting that P-gp inhibitors have a weak effect on vimseltinib.

The co-administration of a P-gp inhibitor reduces vimseltinib CL/F by 18%. Since the change in steady-state exposure is driven by the change in CL/F for drugs with a long half-life, such as vimseltinib, this reduction in CL/F was used in the E-R analyses to predict the proportions of safety events following administration of vimseltinib administered with and without a P-gp inhibitor. Following 30 mg twice-weekly dosing, the proportions of safety events at Week 25 were predicted to be similar when vimseltinib was administered with and without a P-gp inhibitor.

Gastric Acid-reducing Agents

Due to its pH-dependent solubility, vimseltinib has the potential to be subject to a drug interaction with acid-reducing agents. Study DCC-3014-01-006 evaluated the drug interaction potential of a single dose of vimseltinib as a victim drug when co-administered with the proton pump inhibitor rabeprazole in healthy participants.

Concomitant administration of rabeprazole 20 mg once daily reduced peak (C_{max}) and total exposures (AUC_{0-t} and AUC_{0-inf}) to vimseltinib by approximately 21% to 26%, suggesting that proton pump inhibitors have a weak effect on vimseltinib absorption.

Effect of Vimseltinib on Other Drugs

CYP Induction

Vimseltinib demonstrated low to minimal risk for CYP3A4 or CYP1A2 enzyme induction during in vitro studies with human hepatocytes. A slight risk was demonstrated for CYP2B6

induction at anticipated clinical exposures, suggesting a potential risk for perpetrator drug-drug interactions involving CYP metabolism.

PBPK modeling to simulate the extent of drug-drug interaction between vimseltinib and bupropion (a CYP2B6 substrate) did not predict any interaction following co-administration of bupropion with vimseltinib 30 mg twice weekly.

Inhibition of Transporters

Nonclinical studies indicated that vimseltinib may alter the PK of concurrent medications that are substrates for BCRP, P-gp, and OCT2.

PBPK modeling was performed to simulate the extent of drug-drug interaction between vimseltinib and (b) (4) and dabigatran (P-gp substrates), rosuvastatin (a BCRP and OATP1B1/3 substrate), and (b) (4) (an OCT2 substrate).

Weak to moderate interaction was predicted following co-administration of dabigatran or (b) (4) with vimseltinib 30 mg twice weekly.

Simulations showed that the risk of dabigatran interaction with vimseltinib can be eliminated when dabigatran etexilate is administered (b) (4) hours after vimseltinib. (b) (4)

(b) (4)

(b) (4)

P-gp and (b) (4) substrates should be taken at least (b) (4) and (b) (4) hours after vimseltinib administration, respectively, to reduce the risk of potential drug interactions.

The FDA's Assessment:

Food Effect: FDA agrees that food does not have a clinically significant impact on vimseltinib PK and can be taken without regards to meals. See Section 6.3.1 for more details.

DDI and PBPK: FDA is recommending a 4-hour separation between vimseltinib and P-gp substrates, based on PBPK risk assessment. FDA also disagrees with the Applicant's assessment of DDIs on CYP3A induction in vitro, inhibition of transporters, and the PBPK modeling on transporters. See Section 6.2.2.2 and Section 19.4.3 for more details.

X

X

Sarah Kim-McOlash
Primary Reviewer

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

Table 21 Listing of Clinical Studies Relevant to this NDA

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
Studies to Support Efficacy and Safety						
DCC-3014-03-001 (MOTION) NCT05059262 Ongoing	<u>Primary:</u> - To evaluate anti-tumor activity of vimseltinib using RECIST v1.1 by blinded IRR <u>Secondary:</u> - To assess anti-tumor activity of vimseltinib using TVS and mRECIST by blinded IRR - To assess the effects of vimseltinib on ROM - To assess the effects of vimseltinib on physical function, worst stiffness, worst pain, and QoL using	Phase 3, randomized, placebo-controlled, double-blind study Part 1: Double- blind, placebo- controlled Part 2: Open- label, placebo crossover to vimseltinib	Oral vimseltinib 30 mg or matching placebo twice weekly until independent radiological confirmation of progression or other discontinuation criterion or commercial availability	Participants with TGCT (age ≥18 years) Total: 123 randomized 2:1 (N=83 vimseltinib; N=40 placebo)	Double-blind Treatment Period: 24 weeks Open-label crossover Treatment Period: Week 25 to EOT	30 centers in 13 countries

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
	PRO measures - To assess safety and tolerability of vimseltinib					
DCC-3014-01-001 NCT03069469 Ongoing	<u>Primary:</u> - To assess the safety and tolerability of vimseltinib - To characterize the PK profile of vimseltinib - To determine the MTD of vimseltinib - To determine the RP2D of vimseltinib - To evaluate anti-tumor activity of vimseltinib using RECIST v1.1 in TGCT (Expansion Cohort A only) <u>Secondary:</u> - To evaluate anti-tumor activity of vimseltinib using TVS and mRECIST - To assess the effects of vimseltinib on ROM - To assess the effects of	Phase 1/2 multicenter, open- label, single-arm study Phase 1 3+3 dose escalation to determine RP2D in participants with advanced MST or TGCT. Phase 2 dose expansion to evaluate safety, tolerability, preliminary tumor activity in participants with TGCT, incl.Cohort A (no prior anti-CSF1 or anti-CSF1R)a and Cohort B (prior anti-CSF1 or anti-CSF1R)	<u>All cohorts:</u> Oral administration; treatment until progression or other discontinuation criterion or commercial availability <u>Cohort 1:</u> LD=none; MD=10 mg QD in 28-day cycles <u>Cohort 2:</u> LD=10 mg QD×5 days; MD=10 mg twice weekly in 28- day cycles <u>Cohort 3:</u> LD=20 mg QD×5 days; MD=20 mg once a week in 28- day cycles <u>Cohort 4:</u> LD=20 mg QD×5 days; MD=20 mg twice weekly in 28- day cycles	Participants with advanced MST or histologically confirmed TGCT (age ≥18 years) Total: 135 (37 MST patients; 98 TGCT patients) Dose Escalation: 69 Dose Expansion: 65	First dose to EOT	25 centers in 9 countries

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
	vimseltinib on physical function, worst pain, and worst stiffness using PRO measures		<u>Cohort 5:</u> LD=30 mg QD×5 days; MD=30 mg twice weekly in 28- day cycles <u>Cohort 6:</u> LD=40 mg QD×5 days; MD=40 mg twice weekly in 28- day cycles <u>Cohort 7:</u> LD=50 mg QD×3 days; MD=20 mg QD in 28-day cycles <u>Cohort 8:</u> LD=30 mg QD×3 days; MD=10 mg QD in 28-day cycles <u>Cohort 9:</u> LD=20 mg QD×3 days; MD=6 mg QD in 28-day cycles <u>Expansion Cohort A and B:</u> 30 mg twice weekly in 28-day cycles	(Cohort A: 46; Cohort B: 20)		
Studies to support Safety						
DCC-3014- 01-004 Ongoing	<u>Primary:</u> - To evaluate the PK of vimseltinib in participants with HI	Phase 1, open- label study of the PK, safety, and tolerability of single- dose vimseltinib in	Single oral dose of 10 mg vimseltinib capsule	Participants with HI and participants	Single dose	3 centers in 2 counties

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
	<u>Secondary:</u> - To evaluate the PK of vimseltinib's active metabolite, DP-7005, in participants with HI - To determine the Fu of vimseltinib and DP- 7005 - To evaluate safety and tolerability	participants with HI compared to healthy control participants		with normal hepatic function (age: 18 to 75 years, inclusive) Total: ~48 <u>Part 1:</u> 8 with mild HI and 8 (matched) with NHF ^b <u>Part 2:</u> 8 with moderate HI and 8 (matched) with NHF ^b <u>Part 3:</u> 8 with severe HI and 8 (matched) with NHF ^b		
DCC-3014-01-002 Complete	<u>Primary:</u> - To characterize the plasma PK of vimseltinib and its metabolite DP-7005 after oral dosing <u>Secondary:</u> - To assess the effect of a high-fat meal on the PK of	Phase 1 study to evaluate PK in healthy participants <u>Arms 1a-1c:</u> single-dose PK <u>Arms 1d-1e:</u> single-blind, placebo-controlled <u>Arm 2:</u> food	<u>Arm 1a:</u> single-dose 6 mg on Day 1 <u>Arm 1b:</u> single-dose 10 mg on Day 1 of Period 1 and Period 2 <u>Arm 1c:</u> single-dose 30 mg on Day 1 <u>Arm 1d:</u> 50 mg QD×2 days	Healthy adult participants (age 18-60 years) Total: 114 Arm 1a: 15 Arm 1b: 15 Arm 1c: 15	Arms 1a, 1c, 2, and 3= single -dose Arm 1b=single -dose on 2 days Arm 1d=2 days	4 centers in the United States

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
	vimseltinib and its metabolite DP-7005 after a single oral dose - To evaluate the intrasubject variability of vimseltinib and its metabolite DP-7005 after single oral doses - To evaluate the rBA of a proposed commercial formulation of vimseltinib (test formulation, capsule) compared with the existing clinical formulation (reference formulation, capsule) ^d - To evaluate the safety and tolerability of vimseltinib and its metabolite DP-7005 after oral dosing	effect, randomized crossover <u>Arm 3: rBA, randomized crossover^c</u>	<u>Arm 1e: 40 mg QD×5 days</u> <u>Arm 2: single-dose 30 mg with or without high-fat meal</u> <u>Arm 3: single-dose 30 mg clinical or commercial formulation^c</u> <u>Oral administration</u>	Arm 1d: 25 Arm 1e: 26 Arm 2: 18	Arm 1e=5 days	
DCC-3014-01-003 Complete	<u>Primary:</u> - To characterize the AME of a single oral dose of 30 mg (approximately 72 µCi) ¹⁴ C-DCC-3014 - To characterize the PK of vimseltinib, metabolite DP-7005, and TRA following	Phase 1, open-label study of the AME and PK in healthy male participants	Single oral 30 mg (approximately 72 µCi) dose of radiolabeled DCC- 3014 in a capsule	Healthy male participants (age 18-55 years) Total: 8	Single dose	1 center in the United States

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
	administration of ¹⁴ C-DCC-3014 <u>Secondary:</u> - To evaluate the safety and tolerability of a single oral dose of 30 mg (approximately 72 µCi) ¹⁴ C-DCC-3014					
DCC-3014-01-004 Ongoing	<u>Primary:</u> - To evaluate the PK of vimseltinib in participants with HI <u>Secondary:</u> - To evaluate the PK of vimseltinib's active metabolite, DP-7005, in participants with HI - To determine the Fu of vimseltinib and DP- 7005 - To evaluate safety and tolerability	Phase 1, open- label study of the PK, safety, and tolerability of single-dose vimseltinib in participants with HI compared to healthy control participants	Single oral dose of 10 mg vimseltinib capsule	Participants with HI and participants with normal hepatic function (age: 18 to 75 years, inclusive) Total: ~48 <u>Part 1:</u> 8 with mild HI and 8 (matched) with NHF ^b <u>Part 2:</u> 8 with moderate HI and 8 (matched) with NHF ^b	Single dose	3 centers in 2 counties

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
				Part 3: 8 with severe HI and 8 (matched) with NHF ^b		
DCC-3014-01-006 Complete	<u>Primary:</u> - To evaluate the effect of itraconazole on the single-dose PK of vimseltinib following one oral dose of vimseltinib - To evaluate the effect of rabeprazole on the single-dose PK of vimseltinib following one oral dose of vimseltinib <u>Secondary:</u> - To evaluate the effect of itraconazole on the single-dose PK of vimseltinib metabolite DP-7005 following one oral dose of vimseltinib - To evaluate the effect of rabeprazole on the single-dose PK of vimseltinib	A Phase 1, open-label, randomized, parallel design study to evaluate the effects of P-gp inhibition and gastric acid suppression on single-dose PK of vimseltinib in healthy adult participants <u>Arm 1:</u> single-dose vimseltinib <u>Arm 2:</u> itraconazole (a P-gp inhibitor) + single-dose vimseltinib <u>Arm 3:</u> rabeprazole (a PPI) + single-dose vimseltinib	<u>Arm 1:</u> Single-dose vimseltinib 30 mg on Day 1 <u>Arm 2:</u> Itraconazole 200 mg QD from Day 1 through Day 24, single-dose vimseltinib 30 mg on Day 5 <u>Arm 3:</u> Rabeprazole 20 mg QD from Day 1 through Day 5, single-dose vimseltinib 30 mg on Day 5 <u>Oral administration</u>	Healthy participants (age 18-60 years) Total: 89 Arm 1: 29 Arm 2: 30 Arm 3: 30	Arm 1, 2, 3 vimseltinib= single dose, 1 day Arm 2 itraconazole =24 days Arm 3 rabeprazole =5 days	1 center in the United States

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Study identifier/ status	Objective(s) of the Study	Study Design and Type of Control	Test Product(s), Dosage Regimen, Route of Administration	Study Population/ number of participants	Duration of Treatment	No. of Centers and Countries
	metabolite DP-7005 following one oral dose of vimseltinib - To evaluate the safety and tolerability of vimseltinib alone and when co-administered with itraconazole or rabeprazole					

Abbreviations: AME=absorption, metabolism, and excretion; CSF1=colony-stimulating factor 1; CSF1R=colony- stimulating factor 1 receptor; CSR=clinical study report; EOT=end-of-trial; HI=hepatic impairment; IRR=independent radiological review; LD=loading dose; MD=maintenance dose; mRECIST=modified Response Evaluation Criteria in Solid Tumors; MST=malignant solid tumor; MTD=maximum tolerated dose; NHF=normal hepatic function; ORR=objective response rate; P-gp=P-glycoprotein; PK=pharmacokinetic(s); PPI=proton pump inhibitor; PRO=patient-reported outcome; QD=once daily; QoL=quality of life; rBA=relative bioavailability; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1; ROM=range of motion; RP2D=recommended Phase 2 dose; TGCT=tenosynovial giant cell tumor; TRA=total radioactivity; TVS=tumor volume score.

^a With the exception of imatinib or nilotinib.

^b Part 1 of Study DCC-3014-01-004 has been completed; Parts 2 and 3 are still ongoing.

^c Arm 3 was not conducted, and no participants were enrolled or dosed for this arm.

^d This secondary objective was not conducted.

The Applicant's Position:

Table 21 provides a listing of clinical studies relevant to this application.

The FDA's Assessment:

The MOTION study was the basis for efficacy and safety (Section 6 of the USPI for vimseltinib) approval of vimseltinib for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity was based on the results from Week 25 of Part 1 (double-blind portion). The review was based on the 123 patients who were randomized to receive vimseltinib (n=83) or placebo (n=40). One patient in the placebo arm was not eligible for efficacy evaluation as the patient discontinued treatment within one month after providing consent. All patients received at least one dose of vimseltinib 30 mg.

The pooled safety population (n=253) to support Sections 6 of product labeling reflects exposure to vimseltinib in 83 patients with TGCT enrolled in the double-blind portion and in 35 patients in the open-label portion who crossed over to vimseltinib in MOTION, and in 135 patients with TGCT or solid tumors in other clinical trials. This safety pool contributed to the evaluation of the incidence of any adverse event and any serious adverse events that may have occurred at a low incidence.

As part of the review strategy, FDA conducted an independent review of efficacy data for MOTION. The results from the supportive trial, DCC-3014-01-001, were reviewed for safety; however, the data for efficacy were not independently verified by the review team. For the purposes of safety evaluation regarding hepatotoxicity, FDA evaluated n=253 patients who were treated with at least one dose of vimseltinib. Patients enrolled in the pharmacologic studies DCC-3014-01-002, 01-003, 01-004, and 01-006 which enrolled healthy volunteers who received a single-dose of vimseltinib were not included in the pooled safety population (n=253).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. DCC-3014-03-001 (MOTION)

Trial Design

The Applicant's Description:

This is a pivotal Phase 3, placebo-controlled study of vimseltinib in patients with TGCT, consisting of 2 parts: Part 1 was double blind and Part 2 was open label.

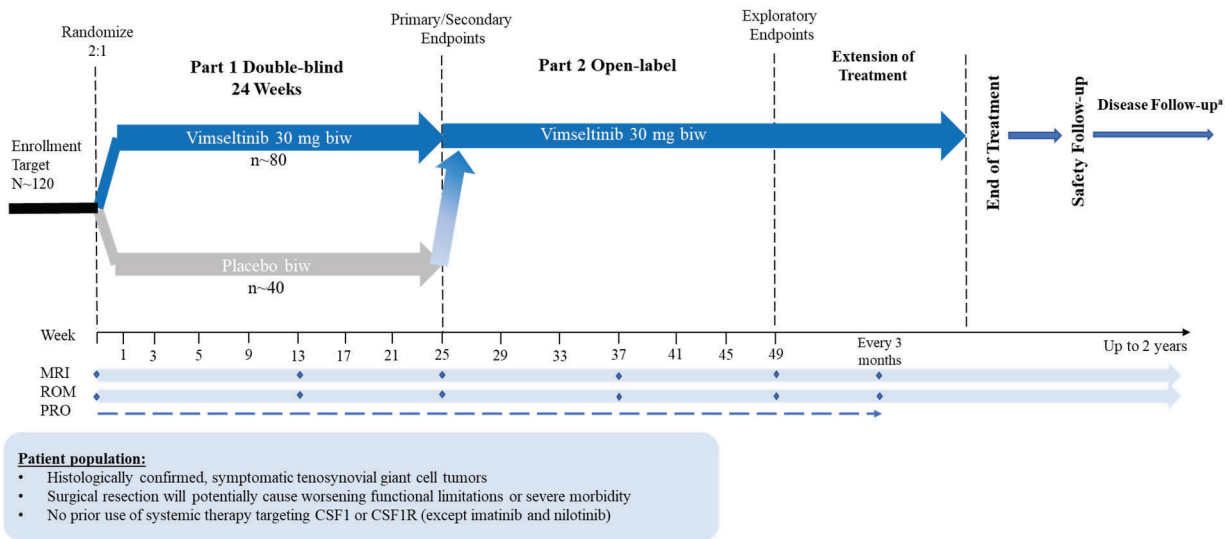
The double-blind and randomized design of this study allowed for adequate assessment of vimseltinib compared to a control group. The selection of placebo as the control group was justified because in most participating countries there were no approved systemic, nonsurgical therapies for the treatment of TGCT in patients not amenable to surgery. While pexidartinib is approved in the United States, it is associated with a risk of potentially fatal liver injury and available under restricted access (REMS program) ([TURALIO, USPI 2023](#)).

The study design is outlined in Figure 8. The study consisted of a 42-day screening period prior to the first dose of study drug, a Part 1 double-blind treatment period of 24 weeks (referred to in 28-day cycles) and a Part 2 open label period until Week 49.

Participants were randomized in a 2:1 ratio to receive either vimseltinib at the dose of 30 mg twice weekly or placebo for 24 weeks. Interactive response technology was used to randomize and assign study drug. Randomization was stratified for tumor location (lower limb/all other) and region (U.S./non-U.S.).

After completion of the End of Part 1 assessments, participants who wished to continue to the open-label part of this study (Part 2) were unblinded. Participants randomized to placebo crossed over to receive vimseltinib and participants initially randomized to vimseltinib continued to receive vimseltinib in Part 2.

Figure 8 Motion Study Schema



Abbreviations: biw=twice weekly; CSF1=colony-stimulating factor 1; CSF1R=colony-stimulating factor 1 receptor; MRI=magnetic resonance imaging; n=number of participants in a category; N=sample size; PRO=patient-reported outcome; ROM=range of motion.

^a Disease follow-up was performed for up to 2 years.

Note: Participants were eligible to receive study drug until radiological confirmation of disease progression as defined in the protocol, unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib and for as long as vimseltinib was being developed to support the indication, and continuation of treatment did not conflict with the Sponsor's right to terminate the study.

The FDA's Assessment:

FDA agrees with the Applicant's description of the study design. The dose studied in MOTION was 30 mg orally taken twice weekly. Patients were allowed to undergo surgical resection only after completion of Part 1.

Eligibility Criteria

The Applicant's Description:

Symptomatic patients ≥ 18 years of age with histologically confirmed TGCT for whom surgical resection could potentially cause worsening functional limitation or severe morbidity were eligible. Patients who previously received anti-CSF1/CSF1R therapy (except for imatinib or nilotinib) were excluded.

The FDA's Assessment:

The Applicant highlighted a few eligibility criteria which the review team agrees with; however, the review team included the following additional key eligibility criteria:

- Patients must have symptomatic disease in a joint where ROM can be assessed.
- Patients must have symptomatic disease with at least mild or moderate pain or stiffness.
- Patients must have bilirubin, AST and ALT levels $\leq$ upper limit of normal (ULN).
- Patients must have disease that is likely to worsen, or result in significant morbidity, if surgery is performed. A surgical team review prior to enrollment was required for all patients to provide specific rationale for why surgery was likely to worsen morbidity.
- If a patient requires analgesic, analgesic use must be stable. Patients must complete 14 consecutive days of questionnaires during the screening period and be able to complete PRO via an electronic device.
- Patients may have been pretreated with systemic therapy such as imatinib or nilotinib and may not have been previously treated with systemic therapy that targets CSF1 or CSF1R.
- Patients with active liver or biliary disease including nonalcoholic steatohepatitis (NASH) or cirrhosis were excluded.

Study Endpoints

The Applicant's Description:

Primary Endpoint

- ORR (including complete response [CR] and partial response [PR]) per RECIST v1.1 at Week 25

Key Secondary Endpoints

- ORR per TVS at Week 25
- Change from baseline in active ROM of the affected joint, relative to a reference standard, at Week 25
- Change from baseline in the Patient-reported Outcomes Measurement Information System -Physical Function (PROMIS-PF) score at Week 25
- Change from baseline in the Worst Stiffness numeric rating scale (NRS) score at Week 25
- Change from baseline in euroQol visual analogue scale (EQ-VAS) (also known as 5-level EuroQual-5D [EQ-5D-5L] VAS) at Week 25
- Response of at least a 30% improvement in the mean Brief Pain Inventory (BPI) Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25

Other Secondary Endpoints:

- ORR per RECIST v1.1
- ORR assessed by mRECIST at Week 25

- Duration of response (DOR) (time from first PR or CR to disease progression or death) assessed using RECIST v1.1, TVS, and mRECIST
- Incidence of treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), related TEAEs, dose reductions, dose interruptions, and discontinuation of study drug due to AE
- Changes from baseline in laboratory parameters, ECGs, and vital signs

The FDA's Assessment:

TGCT is a slow-growing progressive and debilitating but non-lethal disease. ORR may be used to measure the reduction in tumor burden over time. Due to the slow growing nature of the tumor and the symptomatic and functional impacts of the tumor location, supportive evidence of clinical benefit based on clinical outcome assessments (COAs) that can evaluate improvement in pain, range of motion, and physical function is useful to understand the drug effect.

FDA agrees with Applicant's provided list of study endpoints. A detailed description of the primary and key secondary endpoints are provided below.

ORR by RECIST and Tumor Volume Score (TVS):

Best overall response of complete or partial response at Week-25 per RECIST 1.1 (as primary) and TVS (as key secondary) as assessed by blinded independent central review were included in this study. TVS is a semi-quantitative MRI scoring system that describes tumor mass and is based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved.

Active ROM:

ROM is designed to measure movement of joints in unit of degrees. Active and passive ROM was assessed using a goniometer. Active is defined as measuring a motion produced by the participant's voluntary, unassisted muscle contraction, whereas passive is defined as measuring a motion produced by the participant of external force by an examiner during assessments.

There were two forms used to collect ROM data: 1) screening through the end of Part 1 visit (Week 25), which collected both affected and non-affected joint data, and 2) from the end of Part 1 visit through the rest of the trial, which only collected data on the affected joint. The data collected included the joint, side of body, motions assessed, and degrees measured (the start and end position of motion) for active and passive motion. For each specific joint, the relevant planes of measurement were delineated on the case report form. ROM assessments were conducted at screening, Cycle 4, end of Part 1 visit (Week-25), and end of treatment (EOT).

The measurement (in degrees) of the affected joint was used to derive a relative ROM obtained through normalization to the measurement from a reference standard value provided by the American Medical Association (AMA) per motion and type (active or passive) (Gerhardt, 2002). At Screening, the motion with the smallest relative ROM value (worst) was identified, and this motion was used for evaluating the change in relative ROM. Only the motion with the most impaired ROM at screening was selected for subsequent analyses. If there were ties, the multiple motions with the same relative ROM value at screening were identified, and the average of the relative ROM values were calculated at each post-Screening visit and used in the analysis as the single relative ROM value for that specific visit. The main analysis of relative ROM was based on the active measurement relative to a reference standard.

Change from baseline to Week-25 in active ROM was included as a key secondary endpoint.

PROMIS-PF:

PROMIS Physical Function (PROMIS-PF) is an item bank that consists of patient reported outcome (PRO) instrument designed to assess patients’ perspectives on their physical functioning, including functioning based on use of one’s upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living (IADLs). For MOTION, the Applicant selected 15 items to measure tumor location-specific physical function (referred to as upper and lower extremity scales). The lower extremity scale includes 13 items and is intended for use by participants with lower extremity tumors (e.g., knee, ankle, hip, etc.). The upper extremity scale includes 11 items and is intended for use by participants with upper extremity tumors (e.g., digits, hand, elbow, etc.). Nine items overlap between the two scales. Each item uses a 5-point verbal rating scale ranging from 1 (“Unable to do”) to 5 (“Without any difficulty”). The recall period is unspecified. The PROMIS Physical items were administered electronically (via Clinical Ink Engage mobile application) at Week 1 Day 7 during screening period, Week 3 Day 1 during Cycle 1, Week 1 Day 1 and Week 2 Day 6 during Cycle 2 through Cycle 6, and end of Part 1.

The table below shows the subset of 15 questions from PROMIS-PF item bank that were selected for inclusion in the assessment of functioning of upper and lower extremities as it related to tumor location.

Table 22: FDA-PROMIS Scoring Based on Tumor Location

Lower	Upper	Question
x	x	Are you able to push open a heavy door?
x	x	Are you able to exercise for an hour?
x	x	Are you able to carry a heavy object (over 10 pounds/5kgs)?

Lower	Upper	Question
x	x	Are you able to dress yourself, including tying shoelaces and buttoning your clothes?
x	x	Are you able to carry a laundry basket up a flight of stairs?
x		Are you able to stand for one hour?
x		Are you able to go up and down stairs at a normal pace?
x		Are you able to go for a walk for at least 15 minutes?
	x	Are you able to lift 10 pounds (5kg) above your shoulder?
	x	Are you able to change a light bulb overhead?
x	x	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?
x	x	Does your health now limit you in lifting or carrying groceries?
x	x	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?
x	x	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?
x		Does your health now limit you in bending, kneeling, or stooping?

Source: Table-3 from Statistical analysis plan document for MOTION study

The 15-item PROMIS® Physical Function measure generates a total score that ranges from 0 to 100, where higher scores indicate better physical function. This score uses a T-score metric with a mean of 50 and standard deviation (SD) of 10 for a relevant reference population (i.e., U.S. general population).

According to the Applicant, the scoring of the PROMIS Physical Function score used item-level calibrations via the Assessment Center Application Programming Interface (API), and no item level imputation was to be made for the PROMIS Physical Function scores based on the response pattern scoring.

If a participant answered at least half of the questions for their tumor location, then the T-score generated based on the API scoring manual was used for analysis and those questions with missing responses were ignored for scoring. If a participant answered fewer than half of the questions for their tumor location, then the T-score was calculated and presented in listings but was not used for analysis.

Brief Pain Inventory Short Form (BPI-SF):

Item 3 of the BPI-SF (Worst Pain NRS) is a single item in the 9-item BPI-SF, a PRO instrument. BPI-SF Item 3 is designed to assess pain intensity at its worst. This item is rated using an 11-point numeric rating scale ranging from 0 (“No pain”) to 10 (“Pain as bad as you can imagine”). The recall period is the previous 24 hours. The BPI-SF was administered on Day1 through Day 7 at Week 1 and Week 2 during screening; Day 2 through Day 7 at Week 1; Day 1 through Day 6 at Week 2; Day 1, Day 3 through Day 7

at Week 3 during Cycle 1; Day 1 through Day 7 at Week 1 through Week 3 during Cycle 2-6; and End of Part 1.

BPI-SF Item 3 generates a single item score ranging from 0 to 10, where higher scores indicate greater pain intensity.

A responder analysis based on the BPI Worst Pain NRS item and analgesic use was performed as primary analysis (referred to as BPI-30 response). The change in mean BPI Worst Pain NRS for responder assessment was assessed by comparing data collected during a 14-day period prior to the current visit with baseline values collected prior to the first dose of study drug. A minimum of 4 measurements out of the 14 days was required to compute the mean; otherwise, it was set to missing. A responder (BPI-30 response) was defined as a patient who:

- (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and
- (ii) did not experience a 30% or greater increase in narcotic analgesic use.

Worst-Stiffness and EQ-5D-5L VAS:

FDA focused its review of COA data on the ROM, PROMIS-PF, and BPI-SF information. The PRO data supporting EQ-5D-5L VAS and Worst Stiffness NRS endpoints of were not reviewed by FDA due to the following reasons:

1. FDA did not agree with the scoring algorithm used for the Worst Stiffness NRS endpoint. FDA recommended the Applicant to use the PRO data collected during the 14-consecutive-day period that is closest to C1D1. However, this approach was not used for MOTION and the Worst Stiffness was measured every alternate day starting from Cycle-1.
2. The EQ-5D-5L VAS is a generic preference-based measure intended to provide health utility index values for use in economic analyses and lacks evidence of content validity for use in estimating clinical benefit.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The original version of the statistical analysis plan (SAP) (v1.0) was approved on 21 Nov 2022. The SAP was amended, and SAP v2.0 was approved on 09 Aug 2023. No major changes from protocol planned analyses were introduced in the amended version of the SAP.

Efficacy analyses were performed on the intent-to-treat (ITT) Set. The ITT Set consisted of participants who were randomized to a study treatment regimen.

The preponderance of missing data for the key secondary efficacy endpoints of active ROM, PROMIS-PF, Worst Stiffness NRS, and EQ-VAS were evaluated. If there was more than 10% of missing data at Week 25 in any of the endpoints, then the impact of the missing data was explored for that endpoint and included, but not limited to, the following analyses:

- Multiple imputation based on randomized treatment to mimic missing at random
- A Pattern Mixture Model approach where participants who discontinued treatment due to an AE on vimseltinib were imputed based on the missing not at random assumption and imputed as if they received placebo

To control overall type I error, a hierarchical testing procedure was used. Statistical testing was performed for the analysis of primary and key secondary endpoints in the following order at a two-sided 0.05 alpha level for each:

- ORR per RECIST v1.1 at Week 25
- ORR per TVS at Week 25
- Mean change from baseline in active ROM at Week 25
- Mean change from baseline in the PROMIS-PF score at Week 25
- Mean change from baseline in the Worst Stiffness NRS score at Week 25
- Mean change from baseline in EQ-VAS at Week 25
- Proportion of responders based on BPI-30 Worst Pain NRS score and narcotic analgesic use at Week 25

The primary efficacy endpoint and key secondary efficacy endpoints were analyzed in participant subgroups defined as follows:

- Tumor location (lower limb versus all other)
- Region (U.S. versus non-U.S.)
- Participants with disease located in large joints (shoulder, elbow, hip, or knee) versus small joints (joints other than the shoulder, elbow, hip, or knee)
- Participants with disease located in the knee
- Disease subtype (localized versus diffuse)
- Participants at sites in the EU region only
- Age ($18 \leq \text{age} < 50$, $50 \leq \text{age} < 65$, $\text{age} \geq 65$)
-  (female versus male)
- Prior surgery (yes versus no)

- Prior imatinib/nilotinib (yes versus no)

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan for MOTION. Additional details regarding the statistical analysis plan in MOTION are provided below.

Sample size assumptions:

In this study, a total of 120 patients were planned to be randomized in a 2:1 ratio to vimseltinib and placebo arms. This sample size would provide 98% power to detect a statistically significant difference between treatment groups, assuming true ORRs of 35% and 5% in the vimseltinib arm and the placebo arm, respectively, using a two-sided Fisher's exact test at 5% type I error rate level.

Analysis Methods:

The assessments schedules and analysis methods for the primary and key secondary endpoints are listed below. Key secondary endpoints were tested hierarchically in the order listed in the table below to adjust for multiplicity in the hypothesis tests. For the key secondary endpoints that are based on change from baseline assessments, mixed model for repeated measurements (MMRM) with the sandwich estimator to estimate the variance-covariance matrix was used. Each of these models included fixed effects for treatment group, timepoint, treatment group by timepoint interaction, stratification factors (region and tumor location), and the baseline value of the corresponding endpoint. The different timepoints that were included in the model specific to each endpoint are included in the below table.

Table 23: FDA-Primary Analyses Methods for Key Endpoints

Efficacy Endpoint	Analysis method
ORR (RECIST 1.1 and TVS)	Stratified Cochran-Mantel-Haenszel (CMH) test
ROM (only affected joint)	MMRM Timepoints: Weeks-13 and 25 (Day 1 of Cycles 4 and 7 resp)
PROMIS-PF	MMRM Timepoints: Weeks 5, 9, 13, 17, 21, 25
Worst Stiffness NRS	MMRM

	Timepoints: Weeks 5, 9, 13, 17, 21, 25
EQ-5D-5L VAS	MMRM
BPI-30 Worst Pain NRS	Fisher's Exact test

MMRM: mixed model for repeated measurements
Source: FDA produced table

Protocol Amendments

The Applicant's Description:

The original protocol was approved on 15 Dec 2020. The protocol underwent 3 global amendments and 4 regional amendments. Modifications did not impact the integrity of the study or interpretation of the results.

The FDA's Assessment:

FDA outlines the key protocol amendments below. All amendments were activated.

1. Protocol Amendment 1, dated February 11, 2021:

Applicant responded to FDA comments from the EOP meeting January 12, 2021.

- Protocol updated to ensure case report forms specify the reason why surgical resection would lead to functional morbidity or impairment.
- Schedule of assessments clarified to note frequency of liver function assessment.
- Minor modifications were made regarding the PRO analyses.

2. Amendment 2, March 7, 2022:

Applicant updated protocol to address regulatory concerns.

- Applicant removed requirement for serum creatinine ≤ 1.5 ULN.
- Applicant added dose interruption guidance regarding cardiotoxicity risk.
- Protocol updated to prohibit medications that are OCT2 substrates.
- Protocol updated to add prophylactic measures for photosensitivity.
- Safety monitoring procedures for Part 1 and Part 2 crossover were aligned.

3. Amendment 3, May 31, 2023:

No patients were enrolled under Protocol Amendment 3 because enrollment was completed. Applicant updated protocol to move ORR per RECIST to secondary endpoint and categorize secondary endpoints into hierarchical (Key-Secondary) and non-hierarchical (Other secondary endpoints). Additionally, the Applicant updated the protocol in response to requests from regulatory authorities and the study's safety data

monitoring committee to add:

- a. Guidance for management of Grade 2 prolonged QTc.
- b. Creatinine phosphokinase (CPK) assessments to be conducted at a central laboratory.
- c. Guidance for dose interruptions for Grade ≥ 3 CPK elevation.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of ICH/Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

The FDA's Assessment:

The MOTION study states that the trial was conducted in accordance with the International Council for Harmonization Good Clinical Practice guidelines, the ethical principles stated in the Declaration of Helsinki and applicable laws and regulations.

Financial Disclosure

The Applicant's Position:

All investigators have been researched for conflicts of interest. None were identified as having financial interests/arrangements with the Applicant.

The FDA's Assessment:

The Applicant submitted a Financial Interests and Arrangements of Clinical Investigators Certification for MOTION and the supportive study DCC-3014-01-001 (See Section 8.1.4 for details). For MOTION the Applicant did not enter into any financial arrangements with the clinical investigators.

For MOTION there were a total of 261 investigators at clinical sites that enrolled study patients. Signed financial disclosures could not be located for 5 sub-investigators for MOTION.

Financial forms for the 256 investigators from MOTION showed no disclosable financial interests or arrangements.

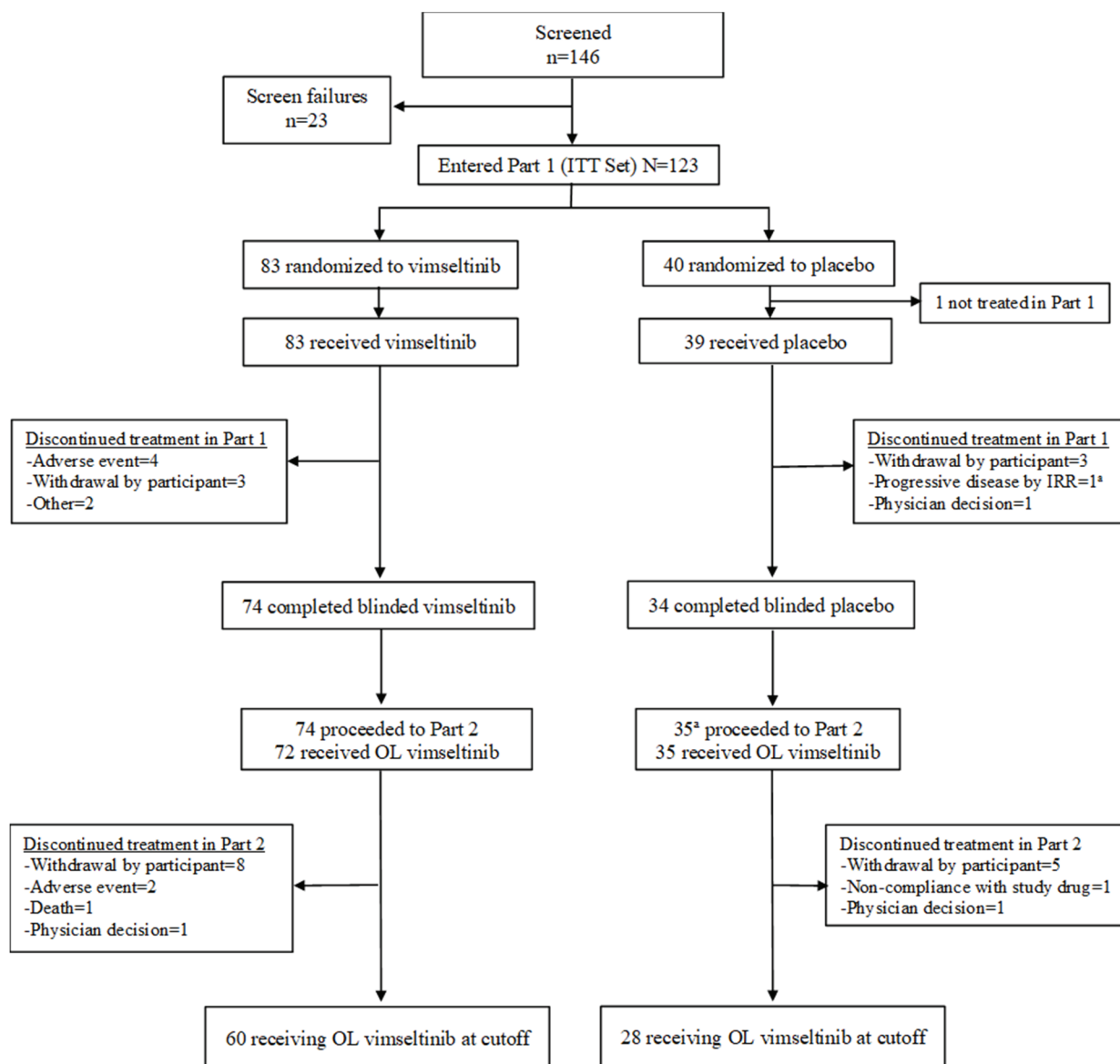
For the 5 investigators in the MOTION study without signed financial disclosures, the Applicant made repeated attempts to contact these investigators; however, they were unable to locate them due to the investigators no longer being associated with the institution where the study was performed. The Applicant independently reviewed internal financial records and confirmed that there were no direct payments to any of these 5 investigators. See Section 19.2 for additional details.

Patient Disposition

Data:

The data cutoff date for analysis of the MOTION trial was 22 August 2023 (all participants completed Week 25). Participant disposition is presented in Figure 9Figure 9.

Figure 9 Participant Disposition, MOTION ITT Set



Abbreviations: IRR=independent radiological review; ITT=intent-to-treat; n=number of participants in a category; N=sample size; OL=open label.

^a One participant experienced progressive disease by IRR and crossed over early to Part 2.

Note: Data cutoff date was 22 Aug 2023.

Sources: Module 5.3.5.1 DCC-3014-03-001 Table 14.1.1.2, Table 14.1.1.4, ADSL

The Applicant's Position:

Disposition was similar between the 2 treatment groups; however, in the double-blind period, more participants discontinued treatment due to an AE in the vimseltinib treatment arm than in the placebo arm (4 [4.8%] participants versus 0, respectively).

The FDA's Assessment:

FDA agrees with Applicant's description of patient disposition in MOTION. The most common reason for treatment discontinuation was patient withdrawal. Reasons for patient withdrawal from the study appeared well balanced, except for withdrawal due to an adverse reaction in the vimseltinib arm. No patient in the placebo arm withdrew due to an AE.

Protocol Violations/Deviations

Data:

All protocol deviations, including important protocol deviations (IPDs) and major protocol deviations, are summarized in Table 24. There were 6 participants (4.9%) with IPDs who were excluded from the Per Protocol Set for efficacy analyses.

Table 24 Major and Important Protocol Deviations, MOTION ITT Set

Category, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Any protocol deviation	63 (75.9)	34 (85.0)	97 (78.9)
Any IPD ^a	1 (1.2)	5 (12.5)	6 (4.9)
Investigational product (other)	1 (1.2)	1 (2.5)	2 (1.6)
Exclusion criteria-did not satisfy entry criteria	0	2 (5.0)	2 (1.6)
Investigational product-wrong treatment or dose	0	1 (2.5)	1 (0.8)
Prohibited medications	0	3 (7.5)	3 (2.4)
Any major protocol deviation ^a	63 (75.9)	34 (85.0)	97 (78.9)
Study procedures	39 (47.0)	20 (50.0)	59 (48.0)
Informed consent	18 (21.7)	12 (30.0)	30 (24.4)
Prohibited medications	15 (18.1)	11 (27.5)	26 (21.1)
Study procedures-lab issues	9 (10.8)	4 (10.0)	13 (10.6)
Exclusion criteria-did not satisfy entry criteria	8 (9.6)	6 (15.0)	14 (11.4)
Study procedures-randomization	5 (6.0)	3 (7.5)	8 (6.5)

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ROMVIMZA (vimseltinib)

Category, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Investigational product (other)	4 (4.8)	6 (15.0)	10 (8.1)
Safety	4 (4.8)	0	4 (3.3)
Study procedures-dosing	2 (2.4)	0	2 (1.6)
Study procedures-out of window	2 (2.4)	1 (2.5)	3 (2.4)
Investigational product-wrong treatment or dose	1 (1.2)	2 (5.0)	3 (2.4)
Other reason	1 (1.2)	0	1 (0.8)
Study documentation	1 (1.2)	1 (2.5)	2 (1.6)
Inclusion criteria-did not satisfy entry criteria	0	1 (2.5)	1 (0.8)

Abbreviation: IPD=important protocol deviation; ITT=intent-to-treat; n=number of participants in a category; N=sample size; PP=Per Protocol.

^a Major protocol deviations were identified as those deviations from the study protocol that may significantly impact the completeness, accuracy, and/or reliability of the study data; that may significantly affect participant's rights, safety, or well-being. Important protocol deviations consisted of major protocol deviations resulting in the exclusion from the PP Set because they may affect efficacy.

Note 1: Percentage was based on the number of participants in ITT Set.

Note 2: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.1.2, ADDV.

The Applicant's Position:

There were more IPDs for the placebo treatment arm than the vimseltinib arm. The incidences of major protocol deviations were similar between the treatment groups.

FDA's Assessment:

The incidence of important protocol deviations (1.2%, 13%) was lower in the vimseltinib arm than in the placebo arm, respectively and the incidences of major protocol deviations were similar (76%, 85%) respectively, in both arms. In the vimseltinib treatment arm, there was one important protocol deviation, where a single patient did not log their doses of vimseltinib during Cycle 2 and did not receive 7 doses of vimseltinib during Cycle 4. In the placebo arm, there were no instances of patients in the treatment arm receiving wrong doses or taking inappropriate other medications. In the placebo arm, 3 patients received inappropriate other medications while enrolled, and one patient took improper doses of placebo during Cycle 1. It is unlikely that protocol deviations had a significant impact on efficacy analyses.

Table of Demographic Characteristics

Data:

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Demographic and baseline characteristics of participants are presented in Table 25.

Table 25 Demographic Characteristics and Baseline Characteristics, MOTION ITT Set

Category, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Age at informed consent (years) ^a			
Mean (STD)	43.8 (13.92)	42.5 (13.67)	43.4 (13.80)
Median	45.0	43.0	44.0
Min, max	20, 78	21, 72	20, 78
Age group (years), n (%) ^b			
18 to <50	54 (65.1)	27 (67.5)	81 (65.9)
50 to <65	24 (28.9)	9 (22.5)	33 (26.8)
65 to <75	3 (3.6)	4 (10.0)	7 (5.7)
75 to <85	2 (2.4)	0	2 (1.6)
Sex, n (%) ^b			
Male	37 (44.6)	13 (32.5)	50 (40.7)
Female	46 (55.4)	27 (67.5)	73 (59.3)
Race, n (%) ^b			
Asian	1 (1.2)	4 (10.0)	5 (4.1)
Black or African American	4 (4.8)	0	4 (3.3)
White	59 (71.1)	21 (52.5)	80 (65.0)
Not reported	18 (21.7)	13 (32.5)	31 (25.2)
Unknown	1 (1.2)	2 (5.0)	3 (2.4)
Ethnicity, n (%) ^b			
Hispanic or Latino	3 (3.6)	1 (2.5)	4 (3.3)
Not Hispanic or Latino	62 (74.7)	23 (57.5)	85 (69.1)
Not reported	17 (20.5)	15 (37.5)	32 (26.0)
Unknown	1 (1.2)	1 (2.5)	2 (1.6)
Baseline BMI (kg/m ²)			
n	81	40	121
Mean (STD)	27.52 (5.919)	27.08 (6.148)	27.37 (5.974)

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Category, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Median	26.20	25.90	26.20
Min, max	18.8, 46.0	17.2, 44.6	17.2, 46.0
Region, n (%) ^b			
U.S.	9 (10.8)	4 (10.0)	13 (10.6)
Non-U.S.	74 (89.2)	36 (90.0)	110 (89.4)
Tumor location based on IRT, n (%) ^b			
Lower limb	73 (88.0)	36 (90.0)	109 (88.6)
All other	10 (12.0)	4 (10.0)	14 (11.4)

Abbreviations: BMI=body mass index; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in a category; max=maximum; min=minimum; n=number of participants in a category; N=sample size; STD=standard deviation.

^a Age at informed consent (years) was calculated as (year of informed consent – year of birth) if not collected on the case report form.

^b Percentage was based on number of participants in ITT Set.

Note: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.1.3.1.1, ADSL.

The Applicant's Position:

In general, demographic and baseline characteristics were similar between treatment arms. There were more White participants in the vimseltinib arm (59 participants [71.1%]) than the placebo arm (21 participants [52.5%], respectively)

The characteristics of participants with TGCT in MOTION were representative of the target patient population.

The FDA's Assessment:

FDA has independently verified the demographics information provided here and agrees with Applicant's position except for tumor location based on IRT where FDA noted a discrepancy on how the tumor location was coded based on the joint type reported. As per FDA analysis, some inconsistencies were found on how some of the joints, such as hip, knee, and ankle, were mistakenly coded into "All other" category instead of "Lower Limb" category. A cross tabulation of the joint type and the tumor location (per IRT) variable are provided in the table below, highlighting the inconsistencies.

Table 26 FDA: Cross Tabulation of Tumor Location based on IRT and Affected Joint, MOTION

Tumor Location based on IRT	JOINT (Primary Affected Joint)									
	Ankle	Elbow	Foot	Hand	Hip	Knee	Other	Shoulder	Wrist	Total

All Other	1	1	0	2	3	1	1	2	3	14
Lower Limb	14	0	4	0	9	82	0	0	0	109
Total	15	1	4	2	12	83	1	2	3	123

Source: FDA Analysis; ADSL dataset.

Given that this is one of the stratification factors included in the primary analysis, all the analyses were performed using the rederived tumor location to assess the impact of misclassification. The analysis results remained unchanged with the use of the rederived tumor location variable.

Some countries do not collect data on race and ethnicity; therefore, the results for these categories report high percentages of patients for whom these have not been captured. Data on racial distribution of TGCT is scarce in the literature. One study conducted in 83 patients with TGCT who received pexidartinib, showed that 65% of patients were White, 18% per Other. 8% were Black, and 1.2% were missing. There were no Native Americans or Native Hawaiian or other Pacific Islander reported (Lin 2024).

There were a total of 11% of patients enrolled in the vimseltinib arm and 10% of patients enrolled in the placebo arm in the US. In Asia, there was only one (2.5%) patient enrolled in the placebo arm. In Europe, which included sites in France, Italy, Netherlands, Germany, Great Britain, Spain, Norway, Poland, and Switzerland, 69% of patients were enrolled in the vimsletinib placebo arm and 80% enrolled in the placebo arm. Lastly, Australia enrolled 15% and 5%, in the vimseltinib arm and placebo arm, respectively. The ORR per subgroup analysis (US vs. other) is displayed in Figure 11 below.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

The most frequently reported medical history PTs in the ITT Set included hypertension (18.7%), arthralgia (17.9%), tumor biopsy (11.4%), and depression (10.6%).

Disease history for TGCT participants is provided in Table 27. Table 27 28

Table 27 28 TGCT Disease History, MOTION ITT Set

Categories, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Disease subtype, n (%)			
Diffuse TGCT	57 (68.7)	28 (70.0)	85 (69.1)
Localized TGCT	26 (31.3)	10 (25.0)	36 (29.3)
Missing	0	2 (5.0)	2 (1.6)

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Categories, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Primary affected joint, n (%)			
Knee	56 (67.5)	27 (67.5)	83 (67.5)
Ankle	9 (10.8)	6 (15.0)	15 (12.2)
Hip	11 (13.3)	1 (2.5)	12 (9.8)
Foot	1 (1.2)	3 (7.5)	4 (3.3)
Wrist	2 (2.4)	1 (2.5)	3 (2.4)
Hand	2 (2.4)	0	2 (1.6)
Shoulder	1 (1.2)	1 (2.5)	2 (1.6)
Elbow	1 (1.2)	0	1 (0.8)
Other	0	1 (2.5)	1 (0.8)

Abbreviations: ITT=intent-to-treat; n=number of participants in a category; N=sample size; TGCT=tenosynovial giant cell tumor.

Note 1: TGCT disease history was reported by the Investigator. Percentage is based on number of participants in ITT Set.

Note 2: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.1.4.2.1, ADSL.

The Applicant's Position:

TGCT history was similar between treatment arms and is anticipated to be representative of the intended population.

The FDA's Assessment:

FDA has independently analyzed these data and agrees with the Applicant's assessment. Localized TGCT is more common than diffuse TGCT and the knee is the most common joint affected in patients with TGCT. While localized TGCT is more common, patients with diffuse TGCT are more likely to experience recurrence (Stacchiotti 2023). Thus, patients with localized TGCT are less likely to be eligible to receive vimseltinib.

In MOTION, diffuse TGCT was more common in both the treatment arm (69%) and the placebo arm (70%), and joints affected were evenly distributed between treatment and placebo arms.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

Mean (standard deviation [STD]) relative dose intensity (RDI) in the double-blind period was 81.25% (18.207%) for vimseltinib and 91.62% (11.226%) for placebo. Median (min, max) RDI in the double-blind period was 87.5% (14.6%, 102.1%) for vimseltinib and 95.8% (50.0%, 100.0%) for placebo.

The median RDI for the on-study vimseltinib treatment period, including both double-blind and open-label, was 81.3%.

Prior and Concomitant Procedures, Medications, and Therapies

The majority of participants (74.0%) reported at least 1 prior TGCT surgery or procedure. In addition, 22.8% reported receiving a prior TGCT systemic therapy, which included imatinib (18.7%) and nilotinib (4.9%), and 8.9% reported prior TGCT radiation therapy.

The majority of participants received at least 1 prior or concomitant medication. Common prior medications included paracetamol (25.4%) and ibuprofen (18.9%). Common concomitant medications in the double-blind period included paracetamol (43.4%) and ibuprofen (28.7%).

Rescue Medication Use

Not applicable.

The Applicant's Position:

Treatment compliance and RDI were similar between the vimseltinib and placebo arms. Prior TGCT surgeries and procedures were as expected for the study population.

The FDA's Assessment:

Prior TGCT surgeries or procedures were completed in 64 patients (77%) in the vimseltinib arm and 27 patients (68%) in the placebo arm. This is consistent with expected disease history in the study population. Prior systemic treatments (with no patients receiving prior treatment with CSF1R directed therapy) was similar in both groups.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

The analysis of the primary efficacy endpoint in Study MOTION at Week 25 demonstrated a statistically significant difference in ORR between vimseltinib and placebo arms (Table 28 and Figure 10Figure 10).

The ORR was 40% (95% CI: 29%, 51%) in the vimseltinib arm compared with no responses (95% CI: 0%, 9%) in the placebo arm (p<0.0001). The median DOR was not reached; DOR ranged from 2.5+ to 19.4+ months.

Table 28 Analysis of Overall Response Rate at Week 25 per IRR Using RECIST V1.1, ITT Population, MOTION

Efficacy Parameter	Vimseltinib N = 83	Placebo N = 40
Primary Endpoint		
Overall response rate per RECIST v1.1 (95% CI)	40% (29%, 51%)	0% (0%, 9%)
Complete response	5%	0%
Partial response	35%	0%
p-value	<0.0001	
Duration of response median (range in months) ^{a,b}	NR (2.5+, 19.4+)	N/A

Abbreviations: CI=confidence interval; IRR=blinded independent radiological review; NR=not reached

Data cutoff date for ORR analysis: Aug 22, 2023.

^a “+” indicates that the patient’s response was ongoing at last assessment as of the data cutoff date.

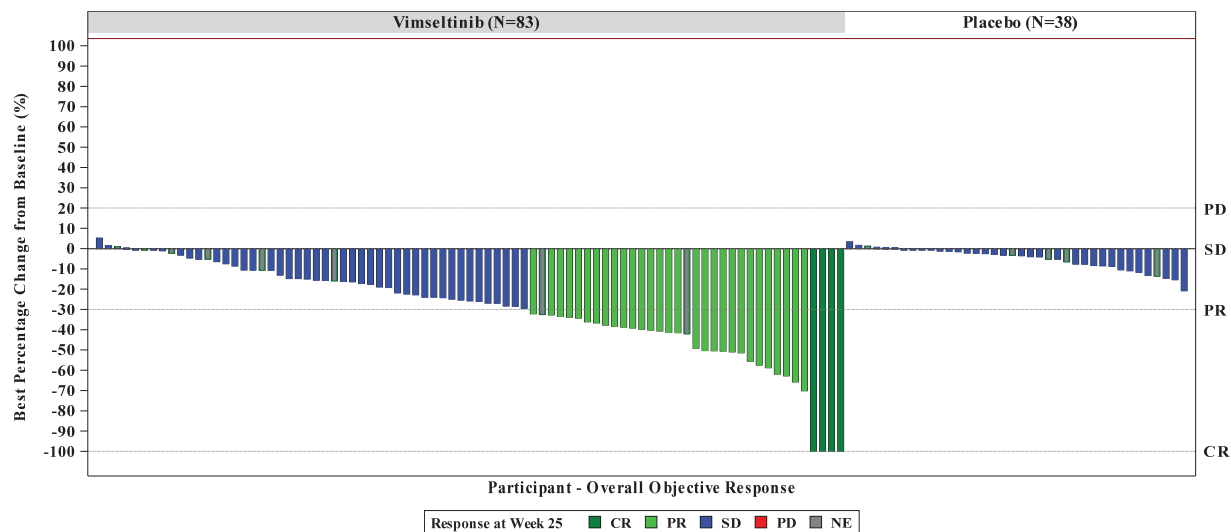
^b Data cutoff date Feb 22, 2024.

Source: ADRS1.

Results from the sensitivity analysis in the ITT Set also demonstrated a statistically significant difference in ORR per RECIST v1.1 up to Week 25 by blinded IRR between vimseltinib and placebo. The ORR was 42.2% (95% CI: 31.4%, 53.5%) for the vimseltinib arm and 0% (95% CI: 0%, 8.8%) for the placebo arm.

Vimseltinib was associated with higher response rates per RECIST v1.1 across all subgroups in an analysis of treatment difference in ORR per RECIST v1.1 at Week 25 based on IRR by subgroup.

Figure 10 Waterfall Plot of Overall Objective Response in Target Lesions per RECIST v1.1 at Week 25 (Double-Blind Period) Based on IRR, MOTION ITT Set



Abbreviations: CR=complete response; IRR=independent radiological review; ITT=intent-to-treat; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Note: Participants with target lesion(s) at baseline and at least 1 post-baseline assessment were shown. Baseline was defined as the most recent non-missing measurement prior to the first administration of study drug.

Source: DCC-3014-03-001 Figure 14.2.1.1.1.2, ADRS1.

The Applicant's Position:

The study met its primary endpoint of ORR at Week 25 per RECIST v1.1 based on IRR. This was confirmed by a sensitivity analysis. Results from analyses of subgroups with adequate sample size were consistent with those from primary endpoint analyses.

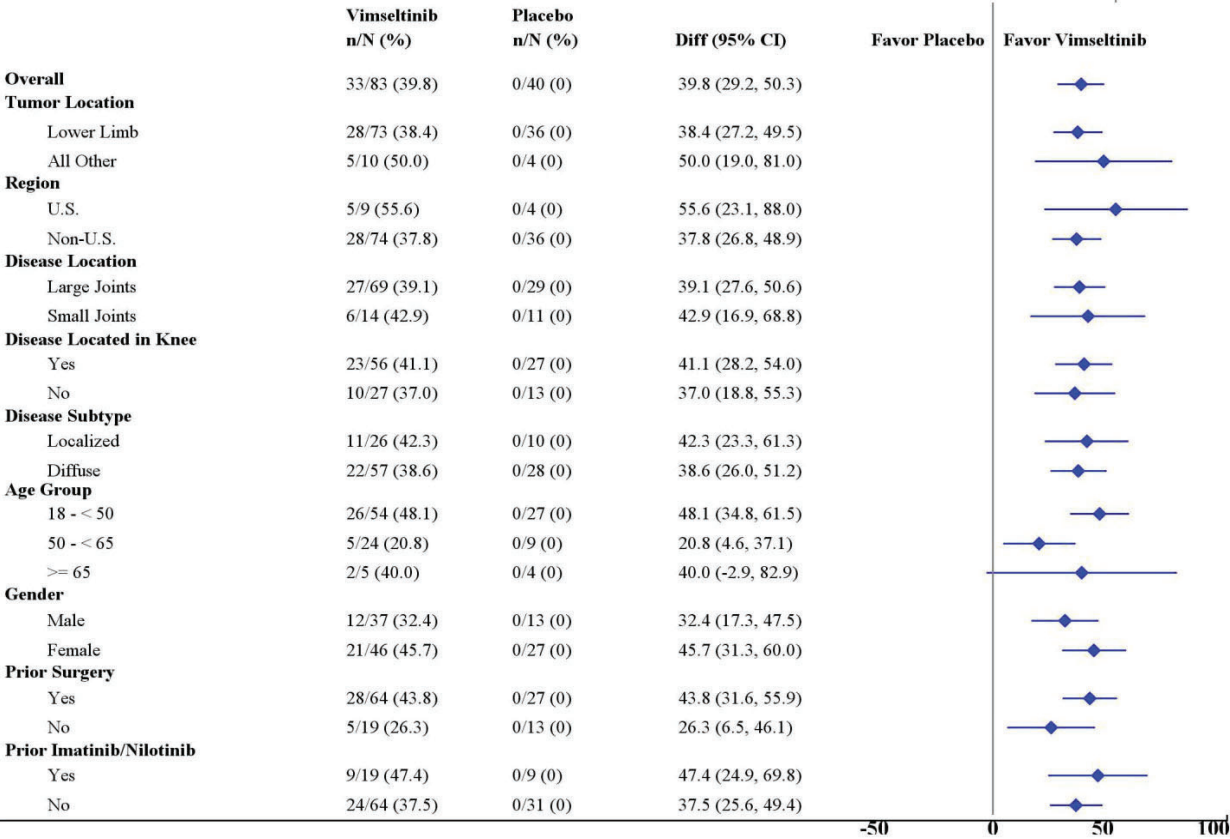
The FDA's Assessment:

FDA agrees with the Applicant's summary of the primary endpoint results for ORR and the Applicant's position regarding the demonstration of statistically significant ORR difference between the arms. FDA also considers the difference in ORR to be clinically meaningful and to represent an acceptable primary endpoint in this context.

Subgroup analyses results of ORR at Week 25 per IRR in the ITT analysis set are presented in the forest plot below. These subgroups results are considered exploratory. The efficacy results in subpopulations with small sample size should be interpreted with caution. In the subgroups with adequate sample size, such as sex, age, ECOG

performance, and disease status at baseline, the observed response rates were similar to the response rate in the overall population.

Figure 11: FDA-Subgroup analysis of ORR at Week-25 in MOTION



Source: CSR Figure-5

The DoR results presented are based on an additional 6 months of follow-up from the time of ORR analysis. The data cutoff date for DOR analysis was February 22, 2024. In addition to the median DOR, durability of responses in each arm are presented in the table below. Although the durability at 9 months is presented below for reference, the Applicant noted that not all participants had reached the timepoint to have a follow-up scan at 9 months after the first documentation of response. However, the submitted DOR results generally demonstrate durability in response in patients who have received up to 9 months of follow-up after the initial confirmed response.

Table 29: FDA-Durability of Responses

	Vimseltinib N = 83	Placebo N = 40
Duration of Response ¹		

Median (Range in months) ²	NR (2.5+, 19.4+)	N/A
DOR ≥ 6 months ³	28 (85%)	-
DOR ≥ 9 months ³	19 (58%)	-

NR=Not reached; N/A=Not applicable; “+”: Ongoing response as of the data cutoff date.

¹ DOR results are based on an additional 6 months of follow-up from the time of ORR analysis.

² The median DOR was estimated using the Kaplan-Meier method.

³ The durability of responses are based on observed durations.

Source: FDA generated table.

Data Quality and Integrity

The Applicant’s Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, or change the conclusions drawn.

The FDA’s Assessment:

FDA agrees with the Applicant’s position regarding data quality and integrity.

Efficacy Results – Secondary and other relevant endpoints

Data:

Key Secondary Endpoints

A summary of response data as determined by IRR and clinical outcome assessments in the double-blind treatment period for the ITT Set is provided in Table 30.

Table 30 Key Secondary Efficacy Results at Week 25 – MOTION (ITT Set)

Efficacy Parameter	Vimseltinib (N=83)	Placebo (N=40)
Objective Response Rate per TVS ^a	56 (67%)	0
(95% CI)	(56%, 77%)	(0%, 9%)
p-value	<0.0001	
Mean change from baseline in active ROM (baseline mean)	18.4 (6.46)	3.8 (7.19)
(95% CI)	(5.6, 31.2)	(-10.5, 18.0)
Difference in LS means (95% CI)	14.6% (4.0, 25.3)	
p-value	0.0077	
Number of participants with data at baseline and Week 25	73	33
Mean change from baseline in PROMIS-PF (baseline mean)	4.6 (0.96)	1.3 (0.88)

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Efficacy Parameter	Vimseltinib (N=83)	Placebo (N=40)
(95% CI)	(2.7, 6.5)	(-0.5, 3.0)
Difference in LS means (95% CI)	3.3 (1.4, 5.2)	
p-value	0.0007	
Number of participants with data at baseline and Week 25	63	30
Mean change from baseline in Worst Stiffness NRS (baseline mean)	-2.1 (0.24)	-0.3 (0.28)
(95% CI)	(-2.5, -1.6)	(-0.8, 0.3)
Difference in LS means (95% CI)	-1.8 (-2.5, -1.1)	
p-value	<0.0001	
Number of participants with data at baseline and Week 25	63	27
Mean change from baseline in EQ-5D-5L VAS (baseline mean)	13.5 (2.35)	6.1 (2.85)
(95% CI)	(8.9, 18.2)	(0.5, 11.8)
Difference in LS means (95% CI)	7.4 (1.4, 13.4)	
p-value	0.0155	
Number of participants with data at baseline and Week 25	64	30
BPI-30 Responders (response rate) ^b	40 (48.2%)	9 (22.5%)
(95% CI)	(37.1%, 59.4%)	(10.8%, 38.5%)
Difference in Responder Rate (95% CI)	26.2% (9.5, 42.8)	
p-value	0.0056	
Number of participants with data at baseline and Week 25	68	31

Abbreviations: AMA=American Medical Association; BPI=Brief Pain Inventory; CI=confidence interval; EQ-5D-5L=5-level EQ-5D; ITT=intent-to-treat; LS=least squares; MMRM=mixed model repeated measurement; n=number of participants in the category; N=sample size; NRS=numeric rating scale; PROMIS-PF=Patient-reported Outcomes Measurement Information System-Physical Function; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1; ROM=range of motion; TVS=Tumor volume score; VAS=Visual Analog Scale.

^a Tumor volume score was defined as the estimated volume of maximally distended synovial cavity or tendon sheath involved, measured in 10% increments.

^b Response of at least a 30% improvement in the mean BPI Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25.

Note 1: Mean change from baseline was estimated from the MMRM for each corresponding endpoint. Baseline means presented include all participants and not only the ones with data at baseline and Week 25. Active ROM was normalized to the AMA reference standard.

Note 2: 95% CI for the difference in response rates based on the exact method.

Data cutoff date: 22 Aug 2023

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.2.1.1.1.1, Table 14.2.1.2.1.1, Table 14.2.2.1.1.1, Table 14.2.3.1.1.1, Table 14.2.3.2.1.1, Table 14.2.3.5.1.1, Table 14.2.3.6.1.1, ADRS1 (ORR per TVS), ADMK (ROM), ADQS1 (Worst Stiffness and BPI), ADQS2 (PROMIS-PF and EQ-VAS).

A summary of clinically important responder analyses at Week 25 is provided in Table 31. Improvement in PROMIS-PF, Worst Stiffness NRS, EQ-VAS, and Worst Pain NRS over time for 25 weeks of treatment is shown in Figure 12.

Table 31 Summary of Clinically Important Responder Analyses at Week 25 in Double-blind Treatment Period – MOTION (ITT Set)

Efficacy Parameter	Vimseltinib (N=83)	Placebo (N=40)
Active ROM Responder Rate^a, n (%)	40 (48.2)	8 (20.0)
95% Exact CI ^b	(37.1, 59.4)	(9.1, 35.6)
Difference in Responder Rate (vimseltinib vs placebo), % (95% Stratified CMH CI based on IRT)	28.7 (12.2, 45.2)	
Stratified CMH p-value based on IRT	0.0025	
PROMIS-PF Responder Rate^c, n (%)	36 (43.4)	10 (25.0)
95% Exact CI ^b	(32.5, 54.7)	(12.7, 41.2)
Difference in Responder Rate (vimseltinib vs placebo), % (95% Stratified CMH CI based on IRT)	18.8 (1.7, 35.9)	
Stratified CMH p-value based on IRT	0.0459	
Worst Stiffness NRS Responder Rate^d, n (%)	32 (38.6)	6 (15.0)
95% Exact CI ^b	(28.1, 49.9)	(5.7, 29.8)
Difference in Responder Rate (vimseltinib vs placebo), % (95% Stratified CMH CI based on IRT)	23.9 (8.1, 39.8)	
Stratified CMH p-value based on IRT	0.0080	
EQ-5D-5L VAS Responder Rate^e, n (%)	31 (37.3)	10 (25.0)
95% Exact CI ^b	(27.0, 48.7)	(12.7, 41.2)
Difference in Responder Rate (vimseltinib vs placebo), % (95% Stratified CMH CI based on IRT)	12.6 (-4.1, 29.4)	
Stratified CMH p-value based on IRT	0.1621	

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; EQ-5D-5L=5-level EQ-5D; IRT=Interactive Response Technology; ITT=intent-to-treat; n=number of participants in the category; N=sample size; NRS=numeric rating scale; PROMIS-PF=Patient-reported Outcomes Measurement Information System-Physical Function; ROM=range of motion; VAS=Visual Analog Scale.

^a A participant was deemed a responder if their change from baseline in active ROM at Week 25 was at least 10%.

^b Two-sided 95% exact CI for the proportion in each arm is computed using the Clopper-Pearson method.

^c A participant was deemed a responder if their change from baseline in PROMIS-PF at Week 25 was at least 3.

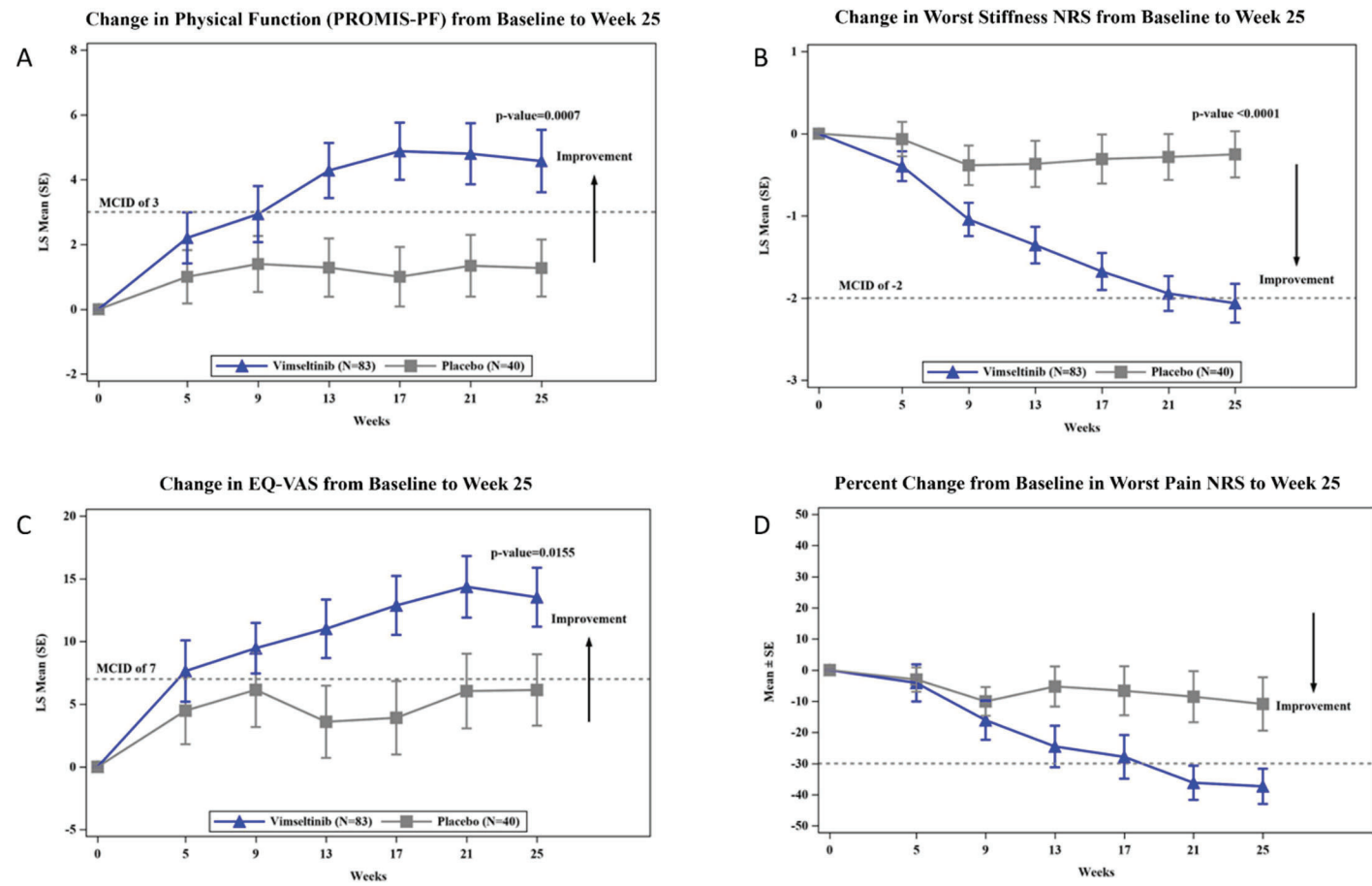
^d A participant was deemed a responder if their change from baseline in Worst Stiffness at Week 25 was equal to or less than -2.

^e A participant was deemed a responder if their change from baseline in EQ-5D-5L VAS at Week 25 was at least 7.

Data cutoff date: 22 Aug 2023

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.2.3.11, ADMK (ROM), ADQS1 (Worst Stiffness), ADQS2 (PROMIS-PF and EQ-VAS).

Figure 12 Improvement in PROMIS-PF (A), Worst Stiffness NRS (B), EQ-VAS (C), and Worst Pain NRS (D) Over Time for 25 Weeks of Treatment



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Abbreviations: MCID= minimal clinically important difference; EQ-VAS= euroQol visual analogue scale; NRS=numeric rating scale; PROMIS-PF=Patient-reported Outcomes Measurement Information System -Physical Function; ROM=range of motion; SE=standard error.

Source: Module 5.3.5.1 DCC-3014-03-001 Figure 14.2.8.1.1.1, Figure 14.2.8.1.2.1, Figure 14.2.8.1.5.1, Figure 14.2.3.6.2.1. ADQS1 (Worst Stiffness NRS and Worst Pain NRS), ADQS2 (PROMIS-PF and EQ-VAS)

Missing data sensitivity analysis of change from baseline in active ROM per American Medical Association standard, PROMIS-PF, Worst Stiffness NRS, and EQ-5D-5L VAS (with mixed model repeated measures [MMRM] model) using multiple imputation based on data from placebo was performed. The results demonstrate robustness to the conclusion that participants receiving vimseltinib had statistically significant greater improvement in active ROM, PROMIS-PF, Worst Stiffness NRS, and EQ-5D-5L VAS compared to those receiving placebo, regardless of the true underlying missing data mechanism (Table 32).

Table 32 Missing Data Sensitivity Analysis of Change From Baseline (Imputation Based on Placebo) in Double-blind Treatment Period – MOTION (ITT Set)

Efficacy Parameter	Vimseltinib (N=83)	Placebo (N=40)
Active ROM per AMA Standard ^a		
LS mean (SE)	13.2 (6.78)	0.2 (6.82)
95% CI of LS mean	(-0.1, 26.5)	(-13.2, 13.5)
Difference (95% CI) in LS mean	13.0 (2.7, 23.3)	
p-value	0.0131	
PROMIS-PF ^b		
LS mean (SE)	4.5 (0.97)	1.4 (0.95)
95% CI of LS mean	(2.6, 6.4)	(-0.5, 3.3)
Difference (95% CI) in LS mean	3.1 (1.2, 5.0)	
p-value	0.0017	
Worst Stiffness NRS ^c		
LS mean (SE)	-1.9 (0.25)	-0.3 (0.30)
95% CI of LS mean	(-2.4, -1.4)	(-0.9, 0.3)
Difference (95% CI) in LS mean	-1.6 (-2.3, -0.9)	
p-value	<0.0001	
EQ-5D-5L VAS ^d		
LS mean (SE)	13.7 (2.59)	6.9 (3.25)
95% CI of LS mean	(8.6, 18.8)	(0.5, 13.3)
Difference (95% CI) in LS mean	6.8 (0.5, 13.0)	
p-value	0.0339	

Abbreviations: AMA=American Medical Association; CI=confidence interval; EQ-5D-5L=5-level EQ-5D; IRT=Interactive Response Technology; ITT=intent-to-treat; LS=least squares; N=sample size; NRS=numeric rating scale;

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PROMIS-PF=Patient-reported Outcomes Measurement Information System-Physical Function; ROM=range of motion; SE=standard error; U.S.=United States; VAS=Visual Analog Scale.

^a Models included treatment + visit + treatment by visit interaction + stratification factor for region (U.S. vs non-U.S.) + joint type (knee, ankle, or other) + the most impaired ROM baseline value.

^b Model included treatment + visit + treatment by visit interaction + stratification factor for region (U.S. vs non-U.S.) and tumor location (lower limb/all other) based on IRT + PROMIS-PF baseline value.

^c Model included treatment + visit + treatment by visit interaction + stratification factor for region (U.S. vs non-U.S.) and tumor location (lower limb/all other) based on IRT + Worst Stiffness NRS baseline value.

^d Model included treatment + visit + treatment by visit interaction + stratification factor for region (U.S. vs non-U.S.) and tumor location (lower limb/all other) based on IRT + VAS baseline value.

Data cutoff date: 22 Aug 2023

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.2.2.1.1.4, Table 14.2.3.1.1.5, Table 14.2.3.2.1.4, Table 14.2.3.5.1.5, ADMK (ROM), ADQS1 (Worst Stiffness NRS), ADQS2 (PROMIS-PF and EQ-VAS).

Vimseltinib was associated with a higher improvement from baseline in active ORR per TVS, ROM per AMA standard, PROMIS-PF, Worst Stiffness, and EQ-5D-5L VAS at Week 25 across nearly all subgroups. Vimseltinib was associated with higher response rates in BPI Worst Pain at Week 25 across all subgroups except for participants aged ≥ 65 years where the sample sizes were small.

The Applicant's Position:

All key secondary endpoints assessed at Week 25 were met and were statistically significant. All key secondary endpoints demonstrated clinically meaningful improvement from baseline at Week 25. Results from subgroup analyses with adequate sample size were consistent with those from key secondary endpoint analyses.

The FDA's Assessment:

FDA's assessment of each of the primary and key secondary endpoints are provided below.

ORR at Week-25 by RECIST 1.1:

FDA agrees with the Applicant's interpretation of the clinically and statistically significant difference between the treatment arms with respect to the ORR by RECIST 1.1 at Week 25.

ORR at Week-25 by TVS:

The analysis of ORR per TVS demonstrated a statistically significant difference in ORR per TVS between vimseltinib and placebo arms. This endpoint has not been validated as a surrogate for any of the established endpoints for clinical benefit claims in oncology, and therefore, FDA considered the results of the analysis of ORR by TVS as supportive of the anti-tumor activity with vimseltinib. The FDA review team thus included a sentence describing these results in Section 14 of product labeling, albeit after the table presenting the key efficacy results of MOTION.

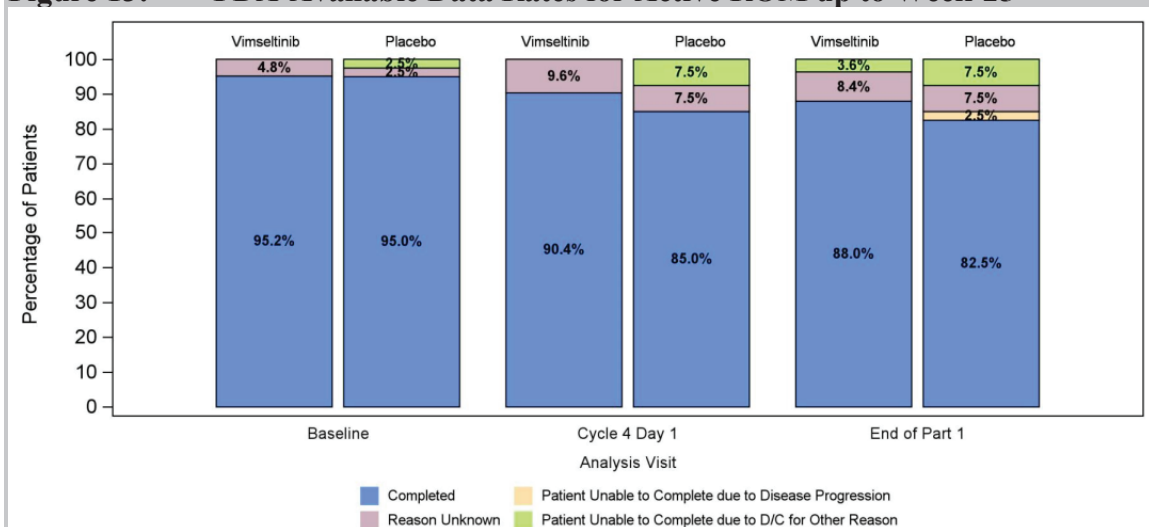
FDA's evaluation of the selected COA/PRO endpoints as presented in Table 32. The results for EQ-5D-5L VAS and Worst Stiffness NRS are not included in this assessment as described

previously. The results of the active ROM, PROMIS-PF, and BPI-30 response at Week 25 analyses are included in Section 14 of product labelling as a table to present the key secondary efficacy results of MOTION.

Active ROM:

The data available rates for active ROM are provided in Figure 13. Overall, only 13% of assessments were missing at Week 25 compared to baseline. FDA considers this missingness as not substantial, and therefore, considers the observed magnitude of effect appears to be reliable.

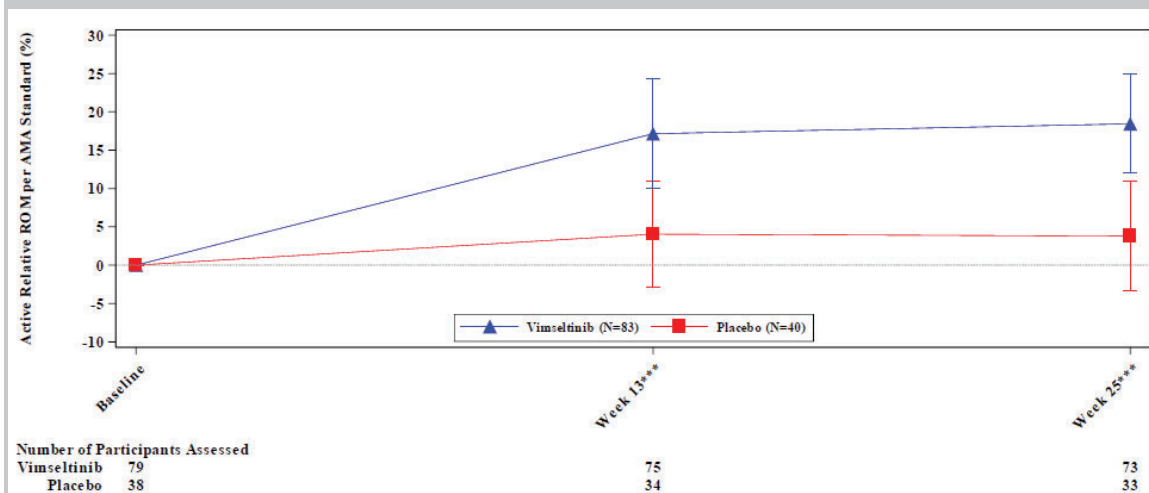
Figure 13: FDA-Available Data Rates for Active ROM up to Week-25



Source: Applicant's response to FDA Information request, dated 9/18/2024.

The analysis of the active ROM demonstrated a statistically significant improvement in mean change from baseline ROM at Week 25 for vimseltinib compared to placebo, with an observed difference in least square (LS) means from placebo of 14.6% (95% CI: 4.0, 25.3; $p=0.0077$). The figure below presents the LS mean change from baseline plot of active ROM at Week-25.

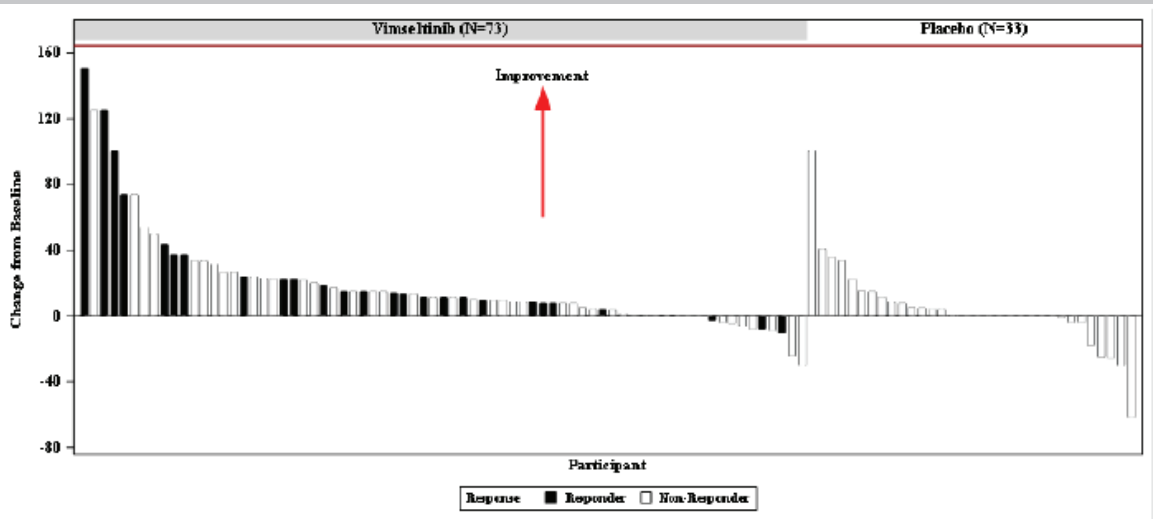
Figure 14: FDA-Least Squares Mean Change From Baseline Plot of active ROM in MOTION Part 1



Source: CSR Figure 14.2.7.1.1.1

Figure 15 below presents the waterfall plot of change from baseline in active ROM at Week 25 by treatment arm with tumor response. The patients treated with vimseltinib demonstrated a greater improvement in change from baseline to Week 25 in active ROM. Some patients on the vimseltinib and on the placebo arms who did not have a tumor response had an improvement in ROM. This figure was included in Section 14 of product labeling.

Figure 15 FDA-Waterfall Plot of Change from Baseline at Week 25 in Active ROM



Source: CSR Figure-8

The Applicant conducted additional sensitivity analysis (Table 32) to assess the impact of missing data in active ROM. In this sensitivity analysis, the missing data were imputed based on the mean value from patients who received placebo using multiple imputation. Based on this sensitivity analysis, the differences in LS mean change from baseline at Week 25 remained similar in magnitude for active ROM (difference in LS mean [95% CI] was 13.0% (2.7%, 23.3%). In addition to this, the Applicant performed additional sensitivity analyses using tipping point analyses to address the concern of informative missingness for the COA endpoints. The results of these sensitivity analysis along with the primary analysis are provided in the table below.

Table 33 FDA-Sensitivity Analyses for Missing Data of Change from Baseline in Active Relative ROM

	Vimseltinib (N=83) LS Mean (95% CI)	Placebo (N=40) LS Mean (95% CI)	LS Mean Difference from Placebo (95% CI)
Primary Results (MMRM)	18.4% (5.6, 31.2)	3.8% (-10.5, 18.0)	14.6% (4.0, 25.3)
Imputation Based on Placebo	13.2% (-0.1, 26.5)	0.2% (-13.2, 13.5)	13.0% (2.7, 23.3)
Multiple Imputation per randomized treatment	18.9% (7.7, 30.0)	4.3% (-7.9, 16.4)	14.6% (4.0, 25.2)
Multiple imputation with participants on Vimseltinib who discontinue due to AE imputed based on placebo	18.8% (7.6, 30.1)	4.3% (-7.8, 16.4)	14.6% (4.0, 25.1)

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	Vimseltinib (N=83) LS Mean (95% CI)	Placebo (N=40) LS Mean (95% CI)	LS Mean Difference from Placebo (95% CI)
Tipping Point Analysis: Delta-adjusting PMM Vimseltinib Penalty = -24%	12.2% (-0.2, 24.6)	1.5% (-11.1, 14.2)	10.7% (-0.1, 21.4)

Source: IR Response dated 10/28/2024.

These sensitivity analyses support the primary analysis conclusions. The delta-adjusting pattern mixture model (PMM) analysis showed that the required penalty for loss of statistical significance was an average worsening of 24% points for patients with missing data in the vimseltinib arm. FDA concludes that the tipping point of 24% to be an extreme scenario and is unlikely.

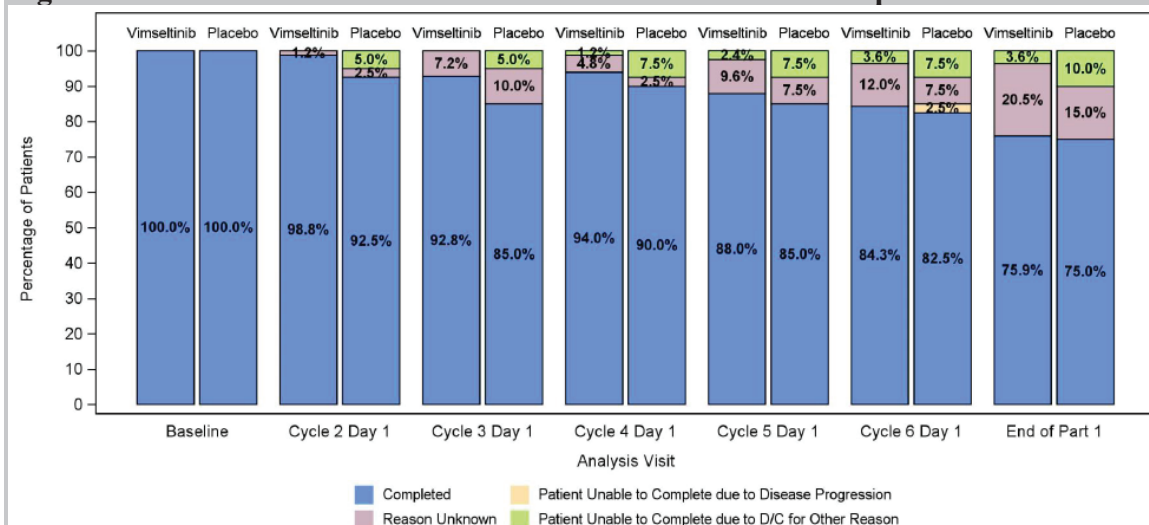
Some patients who were non-responders (as measured by RECIST) to vimseltinib also had improved ROM, and some patients who received placebo also had improved ROM. This points to an incomplete overlap between the ORR measured radiographically and the demonstrated change in ROM. This may be due to several factors, including a placebo effect of being on a perceived effective therapy. However, these incongruous results (i.e., discordance on the vimseltinib arm between RECIST response and ORR, and improved ROM on the placebo arm in the absence of response) were fairly uncommon on both arms overall and do not overall jeopardize reliability/interpretability of ROM results.

Patient-Reported Outcomes:

PROMIS-PF at Week-25:

Available data rate and reasons for missing data of PROMIS-PF assessment are presented in Figure 16 below. The available data rates remained above 75% in both arms, thus FDA considered PROMIS-PF data are sufficient to interpret the analysis results.

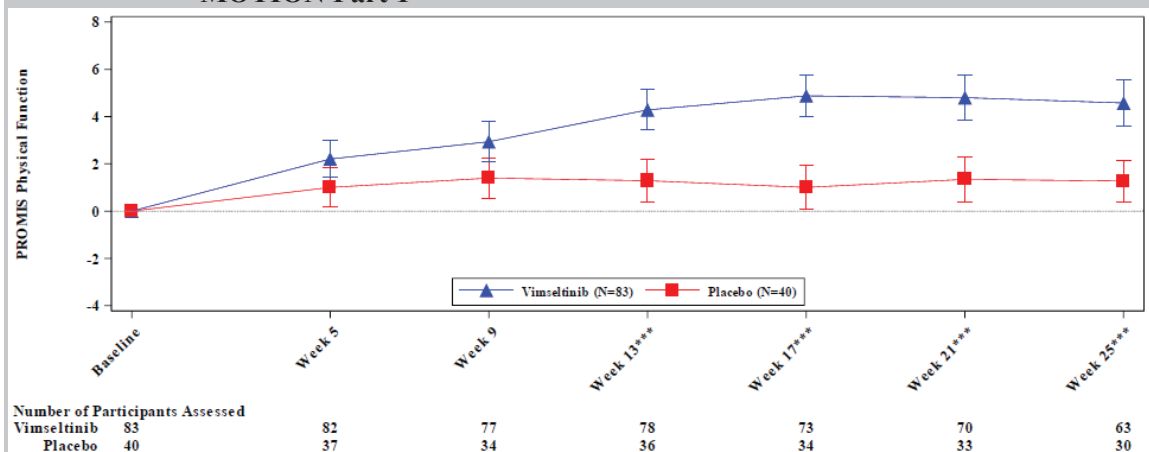
Figure 16 FDA-Available Data Rates for Active PROMIS-PF up to Week-25



Source: Applicant's response to FDA Information request, dated 9/18/2024.

A statistically significant improvement was demonstrated in mean change from baseline in physical function at Week 25 for the vimseltinib arm compared to the placebo arm, with a LS means difference from placebo of 3.3 points (95% CI: 1.4, 5.2); $p < 0.0007$). Figure 17 below presents the LS mean change from baseline plot of PROMIS-PF up to Week 25.

Figure 17: FDA-Least Squares Mean Change From Baseline Plot of PROMIS-PF in MOTION Part 1



Source: CSR Figure 14.2.8.1.1.1

The Applicant conducted additional sensitivity analysis to assess the impact of missing data in PROMIS-PF. All of these sensitivity analyses conducted for PROMIS-PF using imputation methods showed consistent results as the primary analysis conclusions. The

tipping point analysis based on delta-adjusting PMM showed that the required penalty for loss of statistical significance was an average worsening of 3.2 points for patients with missing data in the vimseltinib arm. FDA concludes that the tipping point of -3.2 points to be an extreme scenario and is thus unlikely.

Table 34 FDA-Sensitivity Analyses for Missing Data of Change from Baseline in PROMIS-PF

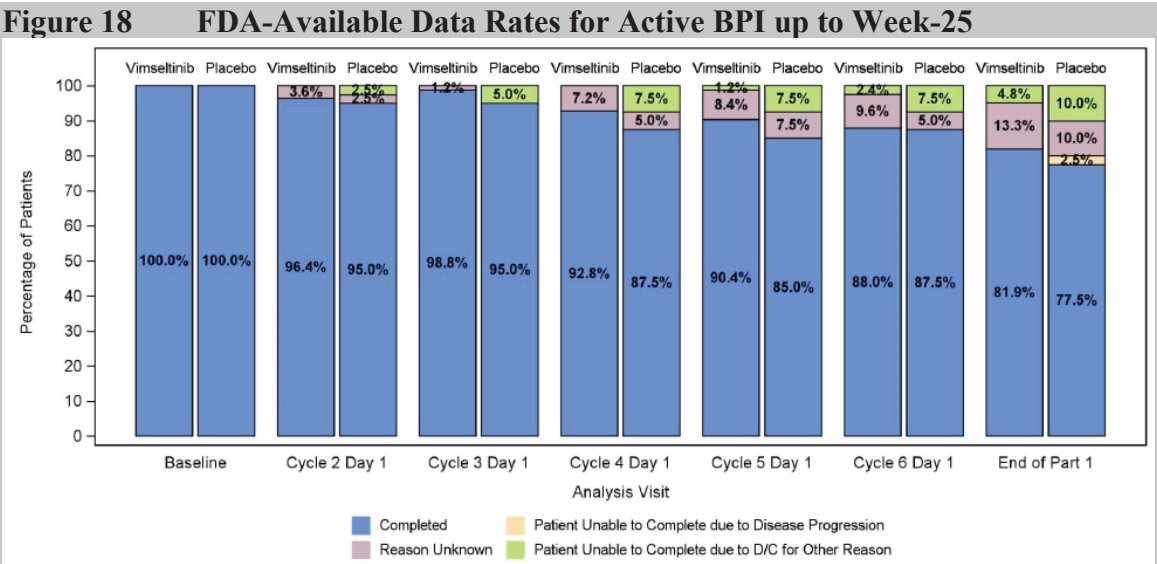
	Vimseltinib (N=83) LS Mean (95% CI)	Placebo (N=40) LS Mean (95% CI)	LS Mean Difference from Placebo (95% CI)
Primary Results (MMRM)	4.6 (2.7, 6.5)	1.3 (-0.5, 3.0)	3.3 (1.4, 5.2)
Imputation Based on Placebo	4.5 (2.6, 6.4)	1.4 (-0.5, 3.3)	3.1 (1.2, 5.0)
Multiple Imputation per randomized treatment	4.6 (2.7, 6.5)	1.3 (-0.5, 3.2)	3.2 (1.3, 5.2)
Multiple imputation with participants on vimseltinib who discontinue due to AE imputed based on placebo	4.5 (2.6, 6.4)	1.3 (-0.5, 3.2)	3.2 (1.2, 5.1)
Tipping Point Analysis: Delta- adjusting PMM vimseltinib Penalty = -3.2	3.3 (1.3, 5.3)	1.3 (-0.5, 3.2)	2.0 (0.0, 4.1)

Source: IR Response dated 10/28/2024.

Following treatment with vimseltinib, the results of the PROMIS-PF (through self-administered questionnaires) demonstrated a clinically meaningful improvement on the impact of the disease on patients' ability to perform daily activity. The results for the PROMIS-PF are included in product labeling.

BPI-30 Response:

Available data rates and reasons for missing data of BPI-30 are presented in Figure 18 below. The available data rates remained above 77% in both arms which was considered to be sufficient to interpret the observed results.



Source: Applicant's response to FDA Information request, dated 9/18/2024.

The stratified CMH test was used to compare BPI-30 response at Week 25 between the 2 treatment arms. A statistically significant improvement in BPI-30 response rates was observed with a difference of 26.2% (95% CI: 9.5, 42.8; p=0.0056).

As part of the sensitivity analysis for BPI-30, the following aspects were assessed:

(i) Impact of analgesic use

Overall, only <5% patients (of n=123 patients enrolled on both arms) had an increase in narcotic analgesic use. The BPI-30 response rates remained the same irrespective of the amount of analgesic use.

(ii) Assessment period of 14 days

The average worst pain on day-1 of each cycle was calculated using the pain assessments obtained during the Weeks-2 and 3 of the prior cycle. At least 4 out of this 14-day assessment period were required to compute the average worst pain value. This 14-day assessment period and the minimum number of assessments (4 out of 14) has been further evaluated to assess the impact of these criteria on BPI-30 response rate results. Two sensitivity analyses were performed by considering.

- at least 4 assessments during only Week-3 (SA-1)
- at least 4 assessments in Week-2 and at least 4 assessments during Week-3 (SA-2).

Both the sensitivity analyses results did show a difference between the arms in terms of BPI-Response rates.

(iii) Impact of 30% change defined as part of responder definition:

As per the literature (Farrar, 2010) a 30% decrease in worst pain is generally considered equivalent to a raw reduction of two points on average in original scale and therefore, the Applicant considered this 30% reduction in pain as part of the responder definition. The results were significant based on this definition. To assess this assumption, FDA requested the Applicant to perform a sensitivity analysis of BPI-worst pain using the original values as recorded. The section below discusses the results based on these analyses.

Responder analyses using BPI-SF worst pain score with 2-point as the cut-off:

The table below presents the number of patients who were considered as responders based on the 2-point change in the average BPI Worst Pain at Week 25. Responder analysis using the 2-point cutoff shows that the response per BPI Worst Pain in the vimseltinib arm is higher than the responses observed in the placebo arm. Based on these results, the magnitude of difference between the arms was similar to that of the primary analysis results.

Table 35: FDA-Responder Analyses of BPI-Worst Pain NRS by Different Cutoffs

	Using a 2-point cutoff	
	Vimseltinib (N=83)	Placebo (N=40)
Week 25 (Cycle 7 Day 1)		
# Expected to report PRO	83	40
Responders at the cycle, n (%) ^a	34 (41.0)	7 (17.5)
Responders with tumor response (CR/PR), n (%) ^b	15 (44.1)	0

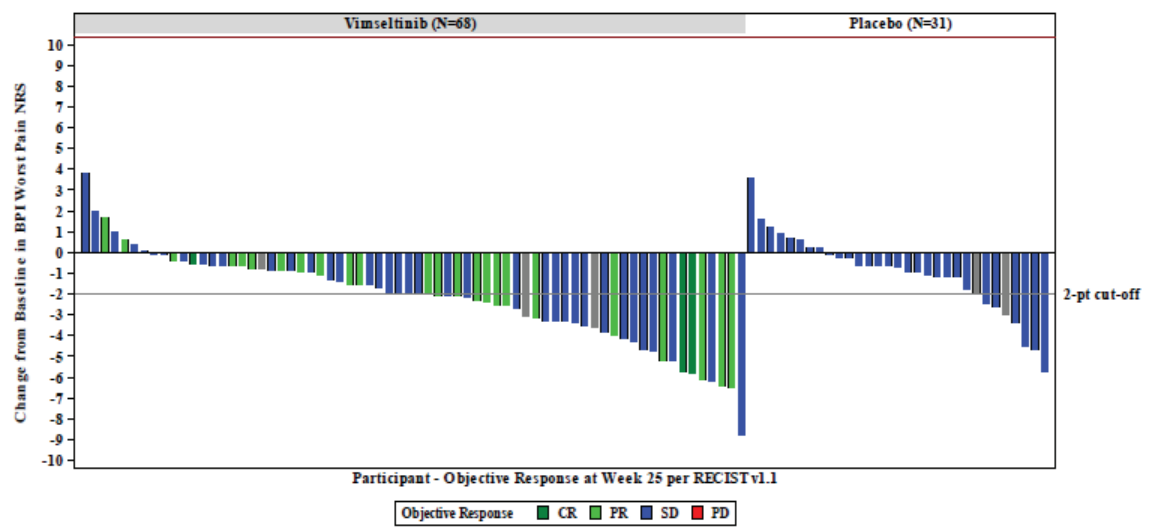
^a Denominator is the number of patients expected to report PRO at each cycle

^b Denominator is the number of responders at each cycle

Source: Applicant’s response to FDA Information Request dated 10/28/2024.

Waterfall plots of change from baseline Week 25 by treatment arm using a 2-point cut-off is presented below.

Figure 19 FDA-Waterfall Plots of Change from Baseline at Week 25 by Treatment Arm Using a 2-Point Cutoff for BPI-Worst Pain



Source: Applicant's response to FDA Information Request dated 10/28/2024.

BPI Worst Pain (change from baseline to Week 25 based on the original reported values) was further assessed using the MMRM model. LS mean difference of -1.6 (95% CI: -2.3, -0.8) for BPI worst pain NRS was observed at Week 25.

From a clinical perspective, BPI assesses the severity of pain and its impact on daily functioning. It measures the impact of pain on daily function, location of pain, pain medications, and amount of pain relief. Pain relief is an important component of improvement in quality of life for patients with TGCT. The results of the BPI-30 demonstrate a clinically meaningful impact in improvement in pain in patients who received vimseltinib over placebo. This is included in product labeling.

Overall, the 15-item PROMIS measure and BPI Worst Pain results are supportive of the ORR and ROM data. Specifically, the data quality was sufficient at Week 25, and there was an early, sustained, and statistically significant (at Week 25) difference observed between vimseltinib and placebo. Interpretation of these results is limited by the clinically meaningful change thresholds as described in detail below regarding PROMIS-PF.

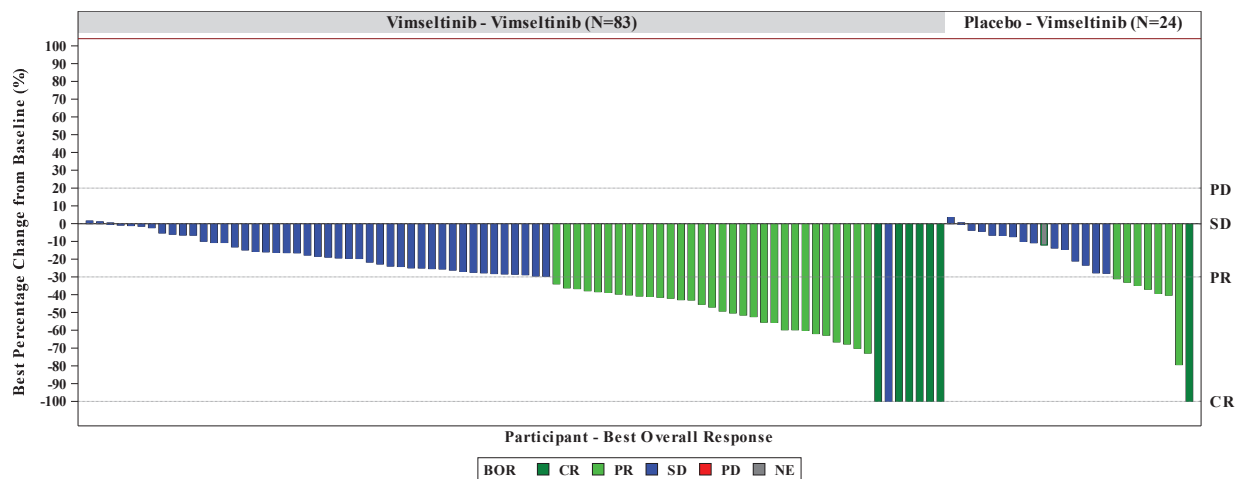
Other Secondary Endpoints

Data:

Objective Response Rate per RECIST v1.1

The response rate was 45% (95% CI: 34%, 56%) for participants randomized to vimseltinib. Waterfall plot of best overall response (BOR) based on IRR per RECIST v1.1 during the on-study vimseltinib period is presented in Figure 20.

Figure 20 Waterfall Plot of Best Overall Response in Target Lesions Based on IRR per RECIST v1.1 in Vimseltinib Treatment Period, MOTION ITT Set



Abbreviations: BOR=best overall response; CR=complete response; IRR=independent radiological review; ITT=intent-to-treat; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

Note 1: Participants with target lesion(s) at baseline and at least 1 post-baseline assessment were shown.

Note 2: Participants randomized to placebo in Part 1 had their reference day as the first dose date of vimseltinib, which occurred in Part 2, and their data from Part 1 while receiving placebo were excluded. Baseline was defined as the most recent non-missing measurement prior to the first administration of vimseltinib.

Note 3: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Figure 14.2.1.1.2, ADRS1.

Duration of Response

Median DOR for participants with an objective response by RECIST and TVS at Week 25 was not reached as of 22 Aug 2023 data cutoff (DOR by RECIST range in months [0.03+, 11.7+]; DOR by TVS range in months [0.03+, 13.9+]) as responses remain ongoing.

An updated analysis of DOR (data cutoff 22 Feb 2024) was performed and is presented in Table . The median DOR for patients with TGCT with an objective response at Week 25 by RECIST v1.1 and TVS was not reached (DOR by RECIST and TVS range in months 2.5+, 19.4+), as responses are ongoing.

The Applicant's Position:

The response for all vimseltinib-treated participants in the double-blind and open-label periods was consistent with that seen in the vimseltinib treatment arm in the double-blind period.

Data indicate that patients with TGCT have demonstrated durable responses to vimseltinib.

The FDA's Assessment:

FDA agrees with Applicant's position. See details of DOR in Section 8.1.2 subsection Efficacy Results – Primary Endpoint (Including Sensitivity Analyses).

Dose/Dose Response

The Applicant's Position:

All participants were dosed at 30 mg twice weekly; therefore, this section is not applicable for this submission.

The FDA's Assessment:

All patients on MOTION were treated at 30 mg twice weekly. See Section 6 of this review for additional details on dosing.

Durability of Response

Data:

See DOR in “Other Secondary Endpoints” above.

Updated analysis of MOTION DOR is provided with this submission, with approximately 49 weeks of follow-up, which showed responses to vimseltinib per RECIST v1.1 at Week 25 were ongoing (Table).

The Applicant's Position:

Responses were long lasting.

The FDA's Assessment:

FDA agrees with the Applicant's assessment, based on the data provided, that the response is durable in patients that received vimseltinib; however, in the vimseltinib arm, the median DOR was not yet reached; DOR ranged from 2.5+ to 19.4+ months. There were no responders in the placebo arm. See details of DOR in Section 8.1.2 subsection Efficacy Results – Primary Endpoint (Including Sensitivity Analyses).

Persistence of Effect

The Applicant's Position:

No long-term efficacy data, with the exception of those presented in the preceding sections, are available at the time of this application.

The FDA's Assessment:

FDA agrees with the Applicant's position. Refer to FDA's assessment of Efficacy Results – Primary Endpoint (Section 8.1.2) for additional details. During the Type B pre-NDA meeting on January 16, 2024, FDA requested an additional 6 months of follow-up duration data from the Applicant which was submitted with the original NDA submission. The additional 6 months of follow-up data had a higher percentage of patients with a ≥ 6 months (85%) and ≥ 9 months (58%) duration of response.

Data:

The 'Efficacy Results – Secondary and Other Relevant Endpoints' sections above provide details of the COA endpoints of ROM, physical function, worst stiffness, and BPI-30.

The minimal clinically important difference (MCID) threshold for active ROM, PROMIS-PF, and Worst Stiffness NRS were determined based on a subset of the participants reaching end of Part 1 using blinded data. The MCID value for EQ-VAS was based on a change of 7 points based on published literature ([Pickard et al, 2007](#)). Distribution- and anchor-based methods were used to calculate potential thresholds based on feedback from the FDA. Distribution-based methods included examining one-half and one-quarter of the baseline standard deviation in the corresponding measure. Anchor-based methods examined the corresponding measure based on how participants/Investigators responded to the "anchor" questionnaire. Anchor questionnaires included patient global impression of severity (PGIS-PF), patient global impression of change (PGIC-PF), PGIC overall, clinical global impression of severity-ROM, clinical global impression of change-ROM, PGIS-ROM, and PGIC-ROM. The final proposed threshold was triangulated using the potential distribution and anchor-based thresholds and informed by the results of the qualitative interviews of the participants conducted within 28 days before the End of Part 1 study visit. These qualitative interviews were part of a cross-sectional substudy embedded into the MOTION study. The responder definitions that were determined using this method is robust and contributes to interpretation of clinically meaningful difference in patient-reported outcome (PRO) scores between the treatment arms.

Missing data for any of the COAs was minimal, and there were no meaningful differences in the rates of missing data between treatment arms. In a separate sensitivity analysis, if the missing data for all participants were imputed based on the mean value

using multiple imputation for participants that received placebo, then the differences in LS mean change from baseline at Week 25 remained significant for all PRO measures (Table 32). The results demonstrate robustness to the conclusion that participants receiving vimseltinib had statistically significant greater improvement in active ROM, PROMIS-PF, Worst Stiffness NRS, and EQ-5D-5L VAS compared to those receiving placebo, regardless of the true underlying missing data mechanism.

The Applicant's Position:

ROM, physical function, stiffness, and pain are concepts that are important and meaningful to patients with TGCT and the clinician-reported outcome and PRO measures in MOTION are considered fit-for-purpose assessments of these concepts. Vimseltinib treatment resulted in significant and meaningful improvements based on predetermined MCIDs in function as measured by active ROM and PROMIS-PF; in symptomatic improvements as measured by Worst Stiffness NRS and Worst Pain NRS; and in QoL as measured by EQ-VAS.

The FDA's Assessment:

The meaningful change thresholds for active ROM assessment, 15-item PROMIS-PF, and Worst Stiffness NRS were determined based on a subset of the participants reaching the end of Part 1 (Week 25) using blinded data. Distribution- and anchor-based methods triangulated with patient exit interviews were used to calculate potential thresholds.

FDA recommends the use of anchor-based methods to establish meaningful within-patient change in COA-based endpoint scores, although other methods (e.g., qualitative evidence) can be used. Distribution-based methods are considered supportive to anchor-based methods.

Based on the submitted qualitative data, FDA agrees that the active ROM assessment (as measured by a goniometer) and the 15-item PROMIS-PF assesses relevant and important aspects of TGCT (i.e., active ROM and physical function, respectively).

FDA was unable to fully evaluate the reliability of the active ROM assessment due to insufficient evidence provided by the Applicant. While the Applicant used multiple anchors to conduct anchor-based analyses, the anchors have several limitations that impact the interpretability of the results of the anchor-based analyses. Despite the limitations of the anchors, the FDA evaluated the distributions of the primary anchor (i.e., PGIS-ROM item score) at baseline and Week 25. However, the sample size is small with some missing data (24.4%) at Week 25 for PGIS-ROM. Therefore, the distributions of the PGIS-ROM score at baseline and Week 25 needs to be interpreted with some caution. Based on this data, as well as the limitations in the PGIS-ROM and PGIC-ROM items, it is difficult to interpret the anchor-based analyses results. As such, it is unknown what

constitutes a meaningful change in the ROM assessment and FDA cannot agree with the Applicant's proposed meaningful change threshold in the active ROM assessment. However, the magnitude of difference between arms, statistical significance, and results from other endpoints including ORR and PROs provide supportive evidence that these ROM results may be clinically relevant and meaningful.

Altered range of motion can significantly impact a person's quality of life. In patients with TGCT, this can often lead to pain, stiffness, swelling, and limited range of motion leading to a diminished quality of life. Many times, previous treatment, including surgery, can worsen ROM over time, especially for those patients with dTGCT. The results for ROM demonstrate a clinically meaningful impact on patients who received vimseltinib versus placebo despite the limitations described above and inclusion of ROM results in product labeling was appropriate. The ROM results translate into an improvement in active ROM and support the ORR results. Overall, patients treated with vimseltinib had improved ROM, with a higher overall degree of improved ROM demonstrated in the patients treated with vimseltinib compared to placebo.

FDA cannot make a definitive conclusion whether the 15-item PROMIS PF measure is well-understood and interpreted appropriately in this context due to the limited approach used by the Applicant to evaluate participant comprehension.

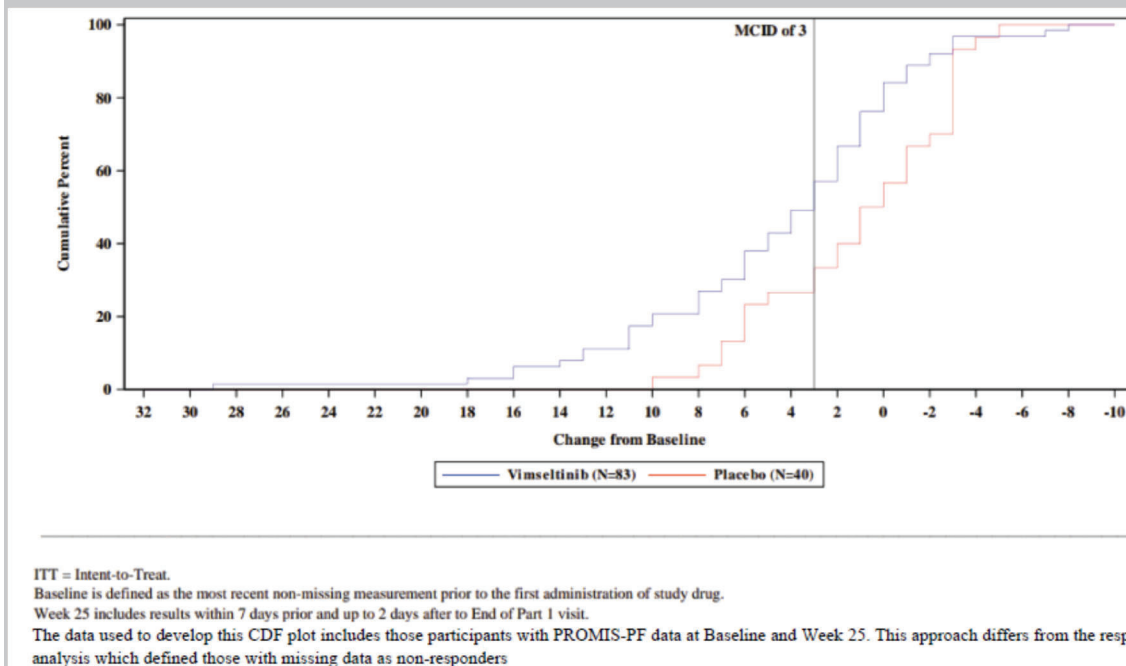
The Applicant did not propose a target anchor change category based on the PGIS-Physical Function item. The Applicant provided insufficient evidence to support the target anchor change category on the PGIC-Physical Function based on the approach used in their exit interview study. Refer to the full COA review. To take a more conservative approach, FDA recommends using a 2-category change on the PGIS-Physical Function item and the "Much improved" response category on the PGIC-Physical Function item as the target anchor change category. Based on this, patients who experienced a 2-category change in the PGIS-Physical Function item had a mean change in the 15-item PROMIS Physical Function score of 7.3 and a median change of 6.5. Patients who reported "Much improved" in the PGIC-Physical Function item had a mean change in the 15-item PROMIS Physical Function score of 4.9 and a median change of 5.0.

The Applicant additionally inspected the eCDF curves for change from baseline to Week 25 in 15-item PROMIS Physical Function score by change in the PGIS-Physical Function and PGIC-Physical Function items. However, the graphs were difficult to interpret due to the small sample size at Week 25 (e.g., poor distribution across response categories).

FDA was unable to determine with confidence a threshold of clinically meaningful change in the 15-item PROMIS Physical Function score based on the submitted anchor-based analyses. However, as seen in [Figure 21](#) change from baseline in the 15-item

Physical Function score showed adequate separation between the vimseltinib and placebo arm across a range that likely includes a clinically meaningful change threshold. A plausible clinical meaningful change threshold range in the 15-item PROMIS PF score could be between 3 and 7-points. FDA determined that despite limitations as described above, inclusion of PROMIS Physical Function results in product labeling was appropriate.

Figure 21 FDA-eCDF Plot of the Change in PROMIS-PF Score from Baseline to Week 25 by Treatment Arm



Source: Figure 14.2.8.4.1 in the Applicant's Clinical study Report DCC-3014-03-001 v1.0/Part 1 Primary Analyses dated March 22, 2024

FDA does not agree with how the Worst Stiffness NRS scores was analyzed as part of the endpoint. In the Type C Meeting Minutes dated May 22, 2023. FDA recommended the Applicant to use the PRO data collected during the 14-consecutive-day period that is closest to C1D1. However, this approach was not used for MOTION. See Section 8.1.2 Subsection Efficacy Results – Secondary and other relevant endpoints for additional FDA review of ROM.

Additional Analyses Conducted on the Individual Trial

The Applicant's Position:

No additional analyses were conducted.

The FDA's Assessment:

FDA agrees no additional analyses were conducted.

8.1.3. DCC-3014-01-001 (Phase 1/2 Supportive Study)

Trial Design

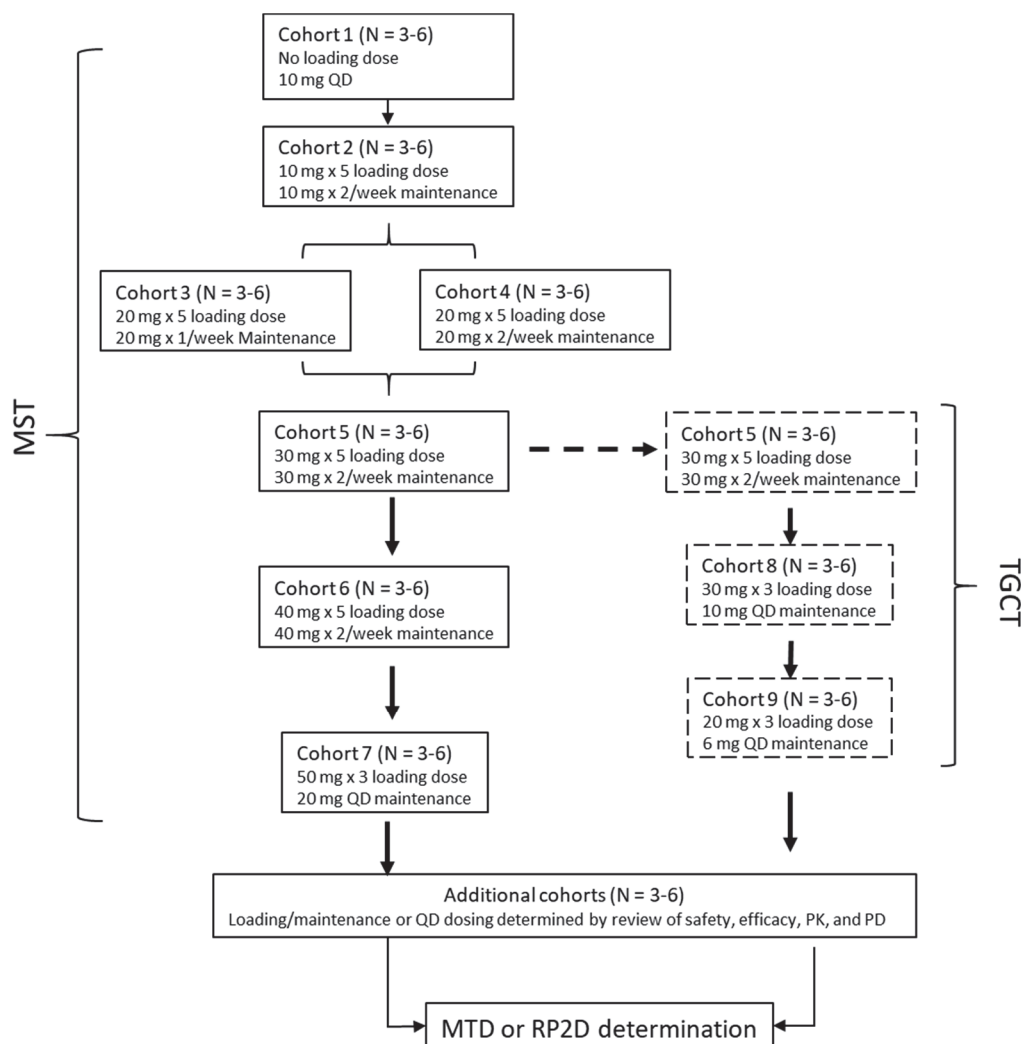
The Applicant's Description:

DCC-3014-01-001 (Phase 1/2 study) is an ongoing open-label Phase 1/2 study of vimseltinib in participants with advanced tumors. The cutoff for the efficacy data presented in this review is 27 Jun 2023.

The study comprised 2 distinct parts: dose escalation (which enrolled both participants with MST and participants with TGCT [Phase 1]) and expansion (which enrolled participants with TGCT only [Phase 2]).

The Dose Escalation Phase design is provided in Figure 22. Dose escalation was based on a pharmacologically guided 3+3 study design in participants with MST and TGCT. The maximum tolerated dose (MTD) was defined as the highest dose level at which no more than 1 of 6 dose limiting toxicity (DLT)-evaluable participants (<33%) experienced a DLT(s) in Cycle 1 during dose escalation. The recommended phase 2 dose (RP2D) may be the MTD or a biologically active or maximally feasible dose that is lower than the MTD.

Figure 22 Schematic Illustration of Dose Escalation, Phase 1/2 Study



Abbreviations: MTD=maximum tolerated dose; N=sample size; PK=pharmacokinetics; QD=once daily; RP2D=recommended Phase 2 dose; TGCT=tenosynovial giant cell tumor.

Note: Cohorts 3 and 4 were run simultaneously. Dose escalation continued by increasing the total dose in the first cycle up to 50% from that set in the previous cohort. An additional lower or intermediate dose level(s) and/or alternate dose schedule(s) could be explored to determine an RP2D in participants with TGCT. More than one cohort at lower dose levels could be run simultaneously. Additional participants could be enrolled to a Dose Escalation Cohort for further evaluation of safety, efficacy, PK, and pharmacodynamics.

Upon determination of the RP2D, 2 expansion cohorts of participants with TGCT were initiated for further evaluation of safety, tolerability, efficacy, PK, pharmacodynamics, and efficacy to support any future study of vimseltinib in this population (Cohort A and Cohort B).

All participants in the Dose Expansion Phase received vimseltinib at the RP2D (30 mg twice weekly on Day 1 and Day 5 with no loading dose at the same time each week). A

data monitoring committee monitored the safety and efficacy data in both phases of the study on a periodic basis to ensure the ongoing safety of study participants.

The study consisted of a screening period conducted within 28 days (Dose Escalation Phase) or 42 days (Expansion Phase) prior to the first dose of study drug, a treatment period of 28-day cycles, an end of treatment visit, and a Follow-up Safety visit 30 days (± 5 days) after the last dose of study drug. Participants were then followed in the Disease Follow-up period for up to 2 years after last dose of study treatment or until radiological progression, start of new subsequent therapy/surgery, or withdrawal of consent.

The FDA's Assessment:

Based on the information presented by the Applicant, the reviewer agrees with Applicant's description of the supportive study. The maximum administered dose of vimseltinib in patients with TGCT was 30 mg twice weekly following a 30 mg x 5 day loading dose. All patients in the Dose Expansion Part received vimseltinib 30 mg twice weekly on Day 1 and Day 5 with no loading dose. A total of 66 patients with TGCT received the RP2D of 30 mg twice weekly. An additional 32 patients with TGCT were treated at other doses.

Eligibility Criteria

The Applicant's Description:

The Dose Escalation Phase enrolled male or female adult participants (≥ 18 years of age)

- with advanced MST that had progressed after treatment with all available therapies known to confer clinical benefit or for which conventional therapy was not considered effective as judged by the Investigator, or
- with histologically confirmed diagnosis of TGCT. A tumor biopsy to confirm TGCT diagnosis was required if no histology/pathology was available at the time of screening.

The Dose Expansion Phase enrolled male and female adult participants (≥ 18 years of age)

- with histologically confirmed diagnosis of TGCT, a tumor biopsy to confirm TGCT diagnosis was required if no histology/pathology was available at the time of screening,
- with disease for which surgical resection would potentially cause worsening of functional limitation or severe morbidity, as determined by surgical consultation or a multidisciplinary tumor board, or

- with symptomatic disease with at least moderate pain per BPI Worst Pain or at least moderate stiffness per Worst Stiffness NRS item (defined as a score of 4 or more, with 10 describing the worst condition) within 30 days of the first dose documented in the medical record.

Participants in Expansion Cohort A had not received prior anti-CSF1 or anti-CSF1R treatment, with the exception of imatinib or nilotinib. Participants in Dose Expansion Cohort B had received prior systemic treatment with anti-CSF1 or anti-CSF1R therapy.

The FDA's Assessment:

The Applicant highlighted the key inclusion criteria. The following are important aspects of the inclusion criteria:

- Dose expansion phase required TGCT patients to have disease for which surgical resection would potentially cause worsening morbidity or functional limitations and symptomatic disease with at least moderate pain or stiffness.
- AST/ALT ≤ 1.5 times upper limit of normal (which was amended over time).

The following patients were not enrolled:

- Expansion Cohort A: previous use of systemic therapy targeting CSF1 or CSF1R; previous therapy with imatinib and nilotinib is allowed.
- Expansion Cohort B: previous discontinuation of anti-CSF1 or anti-CSF1R due to drug-induced liver injury.

The reviewer notes that the a few key eligibility criteria for DCC-3014-01-001 differ from MOTION. In the original DCC-3014-01-001 study, patients were required to have bilirubin ≤ 1.5 times the upper limit of normal (ULN); AST/ALT $\leq 3 \times$ ULN to be eligible to enroll. Throughout the course of the study, amendments to the protocol were made to reflect the possibility of hepatotoxicity. With protocol amendment 5, patients with TGCT were eligible if bilirubin ≤ 1.5 times the ULN; and AST/ALT $\leq 1.5 \times$ ULN. In protocol amendment 6, patients with TGCT had to have bilirubin, AST/ALT $\leq$ ULN and patients with active liver or biliary disease including evidence of fatty liver, nonalcoholic steatohepatitis (NASH), or cirrhosis were excluded. Within the original MOTION protocol, these stricter parameters for eligibility were already in place.

Study Endpoints

The Applicant's Description:

Primary Safety Endpoints

Safety endpoints were evaluated for both phases of the study.

- DLTs (dose escalation phase cohorts only)
- TEAEs and serious adverse events SAEs
- Dose adjustments or discontinuation of study drug due to toxicity
- Change from Baseline in clinical laboratory parameters
 - Hematology
 - Serum chemistry
 - Coagulation factors
 - Urinalysis
- Vital signs
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- ECG findings
- Physical examination findings
- Left ventricular ejection fraction (LVEF) via echocardiogram (ECHO)/multigated acquisition (MUGA) scans findings

Primary Pharmacokinetics Endpoints (Dose Escalation and Dose Expansion Phases)

The following PK endpoints, including but not limited to the following, were evaluated for both vimseltinib and its metabolite, DP-7005, if detected in both phases of the study unless otherwise noted:

- $t_{\max}$
- $C_{\max}$
- Trough observed concentration ($C_{\min}$)
- AUC
- $t_{1/2}$

Primary Efficacy Endpoints (TGCT Dose Expansion Cohort A only)

- ORR (CR+PR) assessed by IRR using RECIST v1.1 at Week 25 (C7D1)
- DOR (time from PR or CR to disease progression or death)

Secondary Endpoints:

Secondary efficacy endpoints for TGCT Dose Expansion Cohort A were:

- ORR assessed by IRR using TVS and mRECIST at Week 25 (C7D1)

- ROM: change from Baseline in relative ROM at Week 25 (C7D1)
- Response based on BPI Worst Pain NRS and narcotic analgesic use by BPI-30 at Week 25 (C7D1)
- PROMIS-PF questionnaire:
 - Change from Baseline at Week 25 (C7D1)
- Worst Stiffness NRS:
 - Change from Baseline at Week 25 (C7D1)

The FDA's Assessment:

FDA agrees with Applicant's descriptions of endpoints. TGCT is a slow-growing progressive and debilitating but non-lethal disease. ORR can be used to measure the reduction in tumor burden over time. Time to event endpoints such as progression-free survival and overall survival and PRO endpoints are not interpretable in a single-arm study.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The planned analyses, definitions, and determination of sample size were described in the final version of the SAP (v3.0; 05 May 2023).

The FDA's Assessment:

FDA agrees with the Applicant's description of the statistical analysis plan for DCC-3014-01-001.

Protocol Amendments

The Applicant's Description:

The original protocol was approved on 27 Sep 2016. No participants were enrolled under the original version of the protocol. The protocol underwent 6 global amendments and 4 regional amendments.

The FDA's Assessment:

FDA outlines the 6 protocol amendments below. All amendments were activated.

1. Amendment 1, December 13, 2016: Protocol updated to incorporate comments made

- by FDA during 30-day review of initial IND application.
- a. Protocol added an abbreviated 3+3 dose escalation phase for patients with hematologic malignancies.
 - b. Protocol clarified that enrollment of patients with hematologic malignancies would be based on the RP2D determined in the escalation phase.
 - c. Dose limiting criteria and dose interruption rules were updated.
2. Amendment 2, August 25, 2017: Protocol updated to amend dose escalation schedule and AE reporting period based on preliminary half-life of DCC-3014.
- a. Dose escalation scheme was amended to include possible loading/maintenance dosing schedules.
 - b. Dose interruptions amended to allow for patients with asymptomatic Grade ≥ 3 elevation in liver transaminases in the absence of bilirubin elevation to continue to receive vimseltinib.
 - c. Protocol amended to note that adverse events should be reported through 75 days of the last dose of vimseltinib (previously 30 days) due to new information regarding drug half-life.
3. Amendment 3, December 20, 2018: Hematologic malignancy cohort was replaced with a solid tumor cohort and a DTGCT cohort.
- a. An objective was added to assess anti-tumor activity in patients with DTGCT.
 - b. Age requirement for patients with DTGCT was set to ≥ 16 years old.
 - c. New schedule of assessment was added for patients with solid tumors and patients with TGCT.
4. Amendment 4, August 21, 2019: Protocol updated to include additional objectives for evaluation of anti-tumor activity in patients with dTGCT.
- a. RECIST v1.1 assessment was added as a primary objective.
 - b. Additional primary, secondary and exploratory endpoints for dTGCT were added.
 - c. Dose limiting toxicities were updated.
5. Amendment 5, March 25, 2020: Protocol modified to broaden inclusion of TGCT population to both localized and diffuse.
- a. Expansion cohort updated to include only patients with TGCT.
 - b. Cohort A redefined for patients with TGCT without prior anti-CSF1/CSF1R treatment.
6. Amendment 6, February 16, 2021: Protocol updated to modify eligibility for TGCT and update dose modification/guidance.
- a. Disease follow-up period for all patients with TGCT was added for up to 2 years after last dose of study treatment, until radiological progression, surgery,

- or other therapy is given.
- b. Dose escalation and expansion phase assessment schedule as modified to reduce patient burden with fewer study visits after 12 months of study treatment.

8.1.4. Cohort B added for patients with TGCT with prior anti-CSF1/CSF1R Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of GCP as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

The FDA's Assessment:

The clinical protocol for the DCC-3014-01-001 study states that the trial was conducted in accordance with the applicable guidelines for Good Clinical Practice and the ethical principles stated in the Declaration of Helsinki.

Financial Disclosure

The Applicant's Position:

All investigators have been researched for conflicts of interest. None were identified as having financial interests/arrangements with the Applicant.

The FDA's Assessment:

The Applicant submitted a Financial Interests and Arrangements of Clinical Investigators certification for DCC-3014-01-001. For DCC-3014-01-001, there was a total of 255 Investigators at clinical sites. A total of 250 investigators associated with DC-3014-01-001 provided financial disclosures and had no disclosable financial interests or arrangements for the covered clinical studies.

Signed financial disclosures could not be found for 5 sub-investigators for DCC-3014-01-001. The respective sites have documented that the sub-investigators are no longer working at the institution where the study was performed, and these sub-investigators have not responded to request for financial disclosure forms. The applicant reviewed internal financial records and confirmed that there were no direct payments to the 5 identified sub-investigators with missing financial disclosure forms.

Patient Disposition

Data:

A total of 134 participants were enrolled in the study prior to the data cutoff of 27 Jun 2023. The Dose Escalation Phase enrolled 69 participants overall (37 participants with MST, 32 with TGCT), and the Dose Expansion Phase enrolled 65 participants with TGCT (46 participants in Cohort A, 19 in Cohort B).

The Applicant's Position:

At the data cutoff, a total of 51 (52.6%) participants with TGCT were ongoing study treatment and 57 (58.8%) remained in the study. The most common reason for discontinuation of treatment was withdrawal by participant (26 [26.8%]). The most common reason for study discontinuation was also withdrawal by participant (16 [16.5%]). At the time of data cutoff, 2 participants with TGCT in each phase were considered to have completed the study.

The FDA's Assessment:

FDA did not independently review the patient disposition data. A total of 97 patients with TGCT enrolled in the study and 65 received the RP2D.

Protocol Violations/Deviations

Data:

Protocol deviations were recorded for 41 (42.3%) participants with TGCT overall.

The Applicant's Position:

Of the 41 participants, 2 reported in participants with TGCT in the Dose Expansion Phase were considered IPDs.

The FDA's Assessment:

FDA did not independently verify this results section and cannot comment on the potential for these protocol deviations to influence the results of the supportive study.

Table of Demographic Characteristics

Data:

A summary of demographics for participants with TGCT is presented in Table 36.

Participants with MST were mainly white (86.5%), non-Hispanic (89.2%), and female (64.9%). Mean overall age was 61.4 years and mean body mass index was 28.77 kg/m².

Table 36 Summary of Demographics, Participants with TGCT, Safety Population

Category	Dose Escalation (N=32)	Dose Expansion (N=65)	Total (N=97)
Age, n (%) ^a			
Mean (SD)	46.8 (13.82)	44.7 (13.46)	45.4 (13.54)
Min, max	23, 73	21, 71	21, 73
Age group, n (%)			
18 - <50	15 (46.9)	37 (56.9)	52 (53.6)
50 - <65	14 (43.8)	25 (38.5)	39 (40.2)
65 - <75	3 (9.4)	3 (4.6)	6 (6.2)
Sex, n (%)			
Male	15 (46.9)	24 (36.9)	39 (40.2)
Female	17 (53.1)	41 (63.1)	58 (59.8)
Race, n (%)			
Asian	1 (3.1)	2 (3.1)	3 (3.1)
Black or African American	0	1 (1.5)	1 (1.0)
Native Hawaiian or Other Pacific Islander	0	1 (1.5)	1 (1.0)
White	31 (96.9)	52 (80.0)	83 (85.6)
Other	0	6 (9.2)	6 (6.2)
Not reported	0	3 (4.6)	3 (3.1)
Ethnicity, n (%)			
Hispanic or Latino	2 (6.3)	5 (7.7)	7 (7.2)
Not Hispanic or Latino	30 (93.8)	54 (83.1)	84 (86.6)
Not reported	0	6 (9.2)	6 (6.2)
BMI (kg/m ²)			
n	31	65	96
Mean (SD)	27.62 (4.310)	26.99 (5.493)	27.20 (5.126)
Min, max	20.9, 38.8	18.5, 39.1	18.5, 39.1

Abbreviations: BMI=body mass index; max=maximum; min=minimum; n=number of participants in the category; N=sample size; SD=standard deviation; TGCT=tenosynovial giant cell tumor.

^a Age (years) is calculated as (date of informed consent – date of birth + 1)/365.25 if age is not collected on the case report form.

Source: Module 5.3.5.2 DCC-3014-01-001 Table 14.1.3.2.

The Applicant's Position:

The characteristics of participants with TGCT in the Phase 1/2 study were representative of the target patient population.

The FDA's Assessment:

The demographic characteristics appear consistent with the proposed patient population. There were more females than males, the majority of patients were White, and mean age was 45 years.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Data:

Frequently reported medical history preferred terms (PTs) for participants with TGCT included arthralgia (54.6%), hypertension (23.7%), menopause (13.4%), joint stiffness (12.4%), and joint swelling (12.4%).

The majority of participants with TGCT had diffuse-type TGCT, with the most common location in the knee or ankle. The mean (STD) overall time from the original TGCT diagnosis to the first dose of vimseltinib was 5.88 (6.817) years. No participant had known metastatic disease (99.0% no metastatic disease, 1.0% unknown).

The Applicant's Position:

The medical and TGCT history is representative of the intended patient population.

The FDA's Assessment:

FDA agrees that the medical and TGCT history of patients in DCC-3014-01-001 is generally consistent with the proposed patient population.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data:

Treatment Compliance

The median total treatment duration in participants with TGCT was 537.0 (range: 6 to 1427) days; median number of cycles was 20.0 (range: 1 to 51). Median RDI was 75.00% (range: 25.0% to 106.3%) for participants with TGCT.

Concomitant Medications

The majority of participants with TGCT reported at least one prior or concomitant medication and/or non-drug therapy. Frequently reported prior medications included paracetamol (18.6% of participants) and ibuprofen (14.4%). Common concomitant

medications included paracetamol (45.4% of participants), ibuprofen (28.9%), furosemide (17.5%), tozinameran (14.4%), and naproxen (11.3%).

Rescue Medication

Not applicable.

The Applicant's Position:

Treatment duration provides adequate representation of long-term exposure with an RDI that demonstrates high treatment compliance.

The FDA's Assessment:

FDA did not independently verify the concomitant medication used in DCC-3014-01-001. However, the Applicant's assessment appears consistent with the data from MOTION.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data:

Objective Response at Week 25 (C7D1) by IRR Using RECIST v1.1 (Expansion Cohort A)

In Cohort A (Expansion Phase, 30 mg twice weekly), ORR at Week 25 (C7D1) as assessed by IRR using RECIST v1.1 was 38% (95% CI: 24%, 53%); 0 participants had achieved CR, and 17 had achieved PR. Results of a sensitivity assessment of investigator review using RECIST v1.1 were consistent with the primary analysis.

Duration of Response by IRR Using RECIST v1.1 (Expansion Cohort A)

During the entire treatment period to data cutoff, ORR in participants with TGCT in Cohort A was 64% (95% CI: 49%, 78%) by IRR using RECIST v1.1. Median DOR was not reached because all responses were ongoing at the time of analysis.

The Applicant's Position:

Vimseltinib demonstrated efficacy in participants with TGCT with no prior specific anti CSF1/CSF1R therapy (except imatinib or nilotinib) at the RP2D.

The FDA's Assessment:

FDA did not independently verify the efficacy results of this study, as the evaluation of efficacy in the proposed indication for vimseltinib is based on MOTION. In DCC-3014-01-001, 97 patients with TGCT were treated with vimseltinib, including 65 patients treated at a dose of 30 mg twice weekly. The results presented by the Applicant

demonstrate that patients with TGCT who have not been previously treated with a targeted CSF1/CSF1R therapy (Cohort A) at a dose of 30 mg twice weekly, had an ORR of 38% at Week 25 and duration of response was not reached. The efficacy results are similar to the efficacy results in MOTION.

Data Quality and Integrity

Data:

All participant data relating to the study was entered into the electronic CRFs unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator was responsible for verifying that data entries were accurate and correct by electronically signing the CRF. The investigator maintained accurate documentation (source data) that supported the information entered in the CRF. The investigator permitted study-related monitoring, audits, Institutional Review Board (IRB) / Independent Ethics Committee (IEC) review, and regulatory agency inspections and provided direct access to source data documents. Monitoring details describing strategy methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (on-site, remote monitoring) were indicated in the monitoring plan to ensure the protocol and GCP was followed.

The sponsor or designee was responsible for the data management of this study including quality checking of the data. The sponsor assumed accountability for actions delegated to other individuals (e.g., Contract Research Organizations).

Study monitors performed ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel were accurate, complete, and verifiable from source documents; that the safety and rights of participants were being protected; and that the study was being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Records and documents, including signed ICFs, pertaining to the conduct of this study were retained by the investigator according to specifications in the ICH guidelines, local regulations, or as specified in the clinical trial agreement, whichever was longer. No records were to be destroyed during the retention period without the written approval of the sponsor. No records were to be transferred to another location or party without written notification to the sponsor. Deciphera conducts clinical studies according to procedures that incorporate the ethical principles of GCP. To ensure compliance with these procedures and to assess the adequacy of quality control procedures, Deciphera undertakes a GCP audit program. Audits were performed by Deciphera Quality Assurance (or designees) operating independently of the study monitors. The audits were aimed at study documentation, investigator sites, and CSRs. The audit program, together with Deciphera's internal quality control procedures, provide reassurance that study conclusions were based on valid procedures for data management and analysis, and that the clinical study program was carried out in accordance with GCP guidelines.

The Applicant's Position:

No issues were identified that could potentially impact data integrity, prevent an adequate assessment of the data, or change the conclusions drawn.

The FDA's Assessment:

Based on the results presented by the Applicant, FDA agrees with Applicant's assessment that no issues were identified that would impact data integrity or conclusions drawn.

Efficacy Results – Secondary and other relevant endpoints

Data:

Objective Tumor Response at Week 25 (C7D1) by IRR Using TVS (Expansion Cohort A)

In Cohort A, ORR at Week 25 (C7D1) assessed by IRR using TVS was 51% (95% CI: 36%, 66%); 0 participants had achieved CR, and 23 had achieved PR. During the overall treatment period, ORR assessed by IRR using TVS was 64% (95% CI: 49%, 78%) in Cohort A; 0 participants experienced CR, and 29 experienced PR. Median DOR could not be estimated by Kaplan-Meier for TVS as no participants had progressed or died using TVS at the data cutoff.

Functional Assessment (Expansion Cohort A)

Active relative ROM across a variety of joints increased by 19.74 (STD: 43.483) percentage points from Baseline to Week 25 (C7D1) in participants in Cohort A.

Patient-reported Outcomes (Expansion Cohort A)

BPI Worst Pain Response (Expansion Cohort A)

In Cohort A, at Week 25 (C7D1) 50.0% (95% CI: 34.9%, 65.1%) of participants were considered BPI worst pain responders (i.e., experienced a decrease of at least 30% in the mean BPI worst pain item and did not experience a 30% or greater increase in narcotic analgesic use).

PROMIS-PF Questionnaire (Expansion Cohort A)

Mean (STD) improvement from Baseline in PROMIS-PF for all participants with TGCT in Cohort A was 3.9 (7.83) points at Week 25 (C7D1).

Worst Stiffness NRS (Expansion Cohort A)

Participants with TGCT in Cohort A showed a mean (STD) improvement in worst stiffness in the last 24 hours by NRS of 1.81 (2.676) points by Week 25 (C7D1).

The Applicant's Position:

Using TVS, ORR was 51.1% (23 participants with PR) at 30 mg twice weekly, in participants with TGCT with no prior specific anti-CSF1/CSF1R therapy (except imatinib or nilotinib).

Analysis of functional assessments showed a mean 19.74 percentage point increase in active relative ROM from baseline in participants with TGCT.

Analysis of PRO endpoints showed an improvement in worst pain based on BPI, physical function based on PROMIS-PF, and Worst Stiffness NRS.

The FDA's Assessment:

FDA did not independently verify the results of the supportive study. PRO data is uninterpretable in a single-arm study.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

See FDA assessment in Section 8.1.6.

8.1.6. Assessment of Efficacy Across Trials

Data from MOTION and the Phase 1/2 study were not pooled because of the differences in study designs and efficacy endpoint assessments between these studies. Side-by-side efficacy data for the primary, key secondary, and other secondary endpoints (other secondary: limited to ORR per RECIST v1.1 and TVS, DOR per RECIST v1.1 and TVS) from MOTION and the corresponding endpoints (as applicable) from the Phase 1/2 study were presented. The Phase 1/2 study included a Dose Escalation Phase and enrolled participants with other solid tumors. Therefore, only efficacy results from participants with TGCT who received the recommended dose of 30 mg twice weekly from this study are presented. This includes:

- Participants with TGCT and without prior anti-CSF1/CSF1R treatment (Cohort A; Phase 2 Dose Expansion)
- Participants with TGCT and with prior anti-CSF1/CSF1R treatment (Cohort B; Phase 2 Dose Expansion)
- Participants with TGCT who received vimseltinib loading dose (30 mg × 5 days) followed by 30 mg twice weekly (Cohort 5 TGCT; Phase 1 Dose Escalation)

The analysis presented is based on the data extracted at the data cutoff dates (22 Aug 2023 for MOTION and 27 Jun 2023 for Phase 1/2). The data cutoff for MOTION reflects the primary analysis at Week 25 (Part 1, double-blind) as defined per

protocol. In addition, updated DOR for the responders at Week 25 with 6 additional months of follow-up after the primary analysis (data cutoff: 22 Feb 2024) are presented for MOTION.

Primary Endpoints

Data:

Objective Response Rate per RECIST v1.1 at Week 25

The ORR per RECIST v1.1 at Week 25 from MOTION and Phase 1/2 cohorts A, B, and 5 (TGCT) is presented in Table 37.

Table 37 Objective Response Rate per RECIST v1.1 Based on IRR at Week 25 From MOTION and Phase 1/2 Cohorts A, B, and 5 (TGCT)

Categories	MOTION (Part 1)		Phase 1/2		
	Vimseltinib (N=83)	Placebo (N=40)	Cohort A (N=45)	Cohort B (N=18)	Cohort 5 (TGCT) (N=8)
OR at Week 25, n1 ^a	83	40	45	14	8
CR, n (%)	4 (5)	0	0	0	0
PR, n (%)	29 (35)	0	17 (38)	5 (36)	4 (50)
ORR, n (%) [95% CI]	33 (40) [29, 51]	0 [0, 9]	17 (38) [24, 53]	5 (36) [13, 65]	4 (50) [16, 84]
CMH test stratification factors based on IRT ^{b,c}			n/a	n/a	n/a
Difference in ORR (vimseltinib vs placebo), % (95% CI)	39 (28, 50)		n/a	n/a	n/a
p-value	<0.0001		n/a	n/a	n/a

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; IRR=independent radiological review; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in the category; N=sample size; n/a=not applicable; NE=not evaluable; OR=overall response; ORR=objective response rate; PD=progressive disease; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1; SAP=statistical analysis plan; SD=stable disease; TGCT=tenosynovial giant cell tumor; U.S.=United States.

^a n1=all participants in the ITT Set (MOTION)/Per-Protocol Population (Phase 1/2) who have reached the timepoint for which data are being summarized or have discontinued from the study prior to that timepoint. Percentage is based on n1 at each timepoint.

^b For MOTION, the determination of the tumor response status for each participant at Week 25 (End of Part 1 Visit) with respect to the primary efficacy endpoint was based on definitions of response for the primary efficacy endpoint in MOTION.

^c Stratified by tumor location (lower limb/all other) and region (U.S./non-U.S.) based on IRT.

Note 1: For MOTION, participants who did not have an End of Part 1 assessment for any reason or whose Week 25 assessment was after the first dose in the open-label extension or outside of the visit window of ±14 days were assessed as NE and a

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nonresponder. A participant who had a scan performed in visit window but was not evaluable by IRR was NE due to “No adequate scan at Week 25”.

Note 2: Two-sided 95% Exact CI is computed using Clopper-Pearson method.

Note 3: Adjudication was performed in MOTION to identify the reader of record, while in Phase 1/2 adjudication was performed by averaging the readers’ response assessment in Phase 1/2.

Data cutoff dates: 22 Aug 2023 (MOTION); 27 Jun 2023 (Phase 1/2)

Sources: Module 5.3.5.1 DCC-3014-03-001 Table 14.2.1.1.1.1, Module 5.3.5.2 DCC-3014-01-001 Table 14.2.1.1.2, ADRS1.

The Applicant’s Position:

In MOTION, the primary endpoint of ORR per RECIST v1.1 at Week 25 by blinded IRR was met; the ORR was significantly higher in the vimseltinib arm compared to the placebo arm (40% versus 0%; $p < 0.0001$). Of the 33 participants in the vimseltinib arm who responded to treatment in MOTION, 4 (5%) had CR and 29 (35%) had PR.

The ORR per RECIST v1.1 at Week 25 by blinded IRR was comparable across the MOTION vimseltinib arm (40%) and Phase 1/2 Dose Expansion Cohorts A (38%) and B (36%).

The FDA’s Assessment:

FDA agrees that the ORR per RECIST v1.1 at Week 25 by blinded IRR was comparable to the MOTION vimseltinib arm (40%) and in DCC-3014-01-001 Dose Expansion Cohorts A (38%) which included patients with TGCT treated with 30 mg twice weekly. Cohort A includes patients with no prior treatment with a CSF1 or CSF1R targeted agent. FDA did not independently verify the efficacy results of DCC-3014-01-001, as the efficacy of vimseltinib in patients with TGCT is based on MOTION.

Secondary and Other Endpoints

Data:

Objective Response Rate per Tumor Volume Score at Week 25

In MOTION, the ORR per TVS at Week 25 based on IRR was significantly higher in the vimseltinib arm compared with the placebo arm (67% versus 0%; $p < 0.0001$). Of the 56 participants in the vimseltinib arm who responded to treatment in MOTION, 4 (5%) had CR and 52 (63%) had PR.

The ORR per TVS at Week 25 based on IRR was high in both MOTION vimseltinib arm (67%) and Phase 1/2 Dose Expansion Cohort A (51%). The ORR per TVS at Week 25 by blinded IRR in Phase 1/2 Dose Escalation Cohort 5 was 38% and in Dose Expansion Cohort B was 29%.

Duration of Response

DOR per RECIST 1.1 and TVS for the MOTION double-blind period, primary analysis with a cutoff of 22 Aug 2023, are presented in Section 8.1.2. Tumor responses were long lasting based on ORR per RECIST v1.1 and per TVS with vimseltinib 30 mg twice weekly. A primary analysis from the double-blind part of MOTION (22 Aug 2023) and an updated analysis with 6 months of additional follow-up (22 Feb 2024) demonstrated long-lasting response with vimseltinib. The Kaplan-Meier estimated median DOR for responders to vimseltinib at Week 25 per RECIST v1.1 was not reached at either analysis, with responses lasting up to 84.4+ weeks and with all but 1 response ongoing at the time of the updated analysis (Table 38).

In the Phase 1/2 study, up to the data cutoff date (27 Jun 2023), the Kaplan-Meier estimated median DOR for responders to vimseltinib per RECIST v1.1 was not reached across all TGCT 30 mg twice weekly cohorts (Cohorts A, B, and 5), with responses lasting up to 196+ weeks; all responses were ongoing, and most responses were maintained for at least 12 months.

The updated analysis of MOTION DOR with a median nearly 49 weeks of follow-up was conducted at a similar median follow-up duration as the Phase 1/2 study (ranged from 48.7 weeks to 56.1 weeks) and similarly demonstrated ongoing responses with approximately 12 months of on-study treatment. Given participants in Phase 1/2 initiated treatment before MOTION and had more opportunity to receive treatment past Week 25, response duration in Phase 1/2 may be considered as an early indicator for patients who have responded to vimseltinib treatment during the MOTION study.

The DOR per TVS demonstrated a trend similar to those per RECIST v1.1.

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Table 38 Duration of Response for Responders at Week 25 Based on IRR per RECIST v1.1 in MOTION

Categories	MOTION (Primary Analysis)		MOTION (Updated Analysis) ^a	
	Vimseltinib (N=83)	Placebo (N=40)	Vimseltinib (N=83)	Placebo (N=40)
Participants with objective response (CR+PR) at Week 25, n (%)	33 (40)	0	33 (40)	0
Number of participants with events (PD or Death), n (%) ^b	1 (3)	0	1 (3)	0
PD	1 (3)	0	1 (3)	0
Death	0	0	0	0
Number censored	32 (97)	0	32 (97)	0
K-M estimate of DOR in responders, weeks ^c				
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.1 ⁺ , 50.9 ⁺	NE	11.0 ⁺ , 84.4 ⁺	NE
Median (95% CI) duration of follow-up (weeks) ^d	24.14 (13.29, 35.29)	NE (NE, NE)	48.57 (36.14, 58.29)	NE (NE, NE)

Abbreviations: CI=confidence interval; CR=complete response; DOR=duration of response; IRR=independent radiological review; ITT=intent-to-treat; K-M=Kaplan-Meier; max=maximum; min=minimum; n=number of participants in the category; N=sample size; NE=not evaluable; OL=open-label; PD=progressive disease; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1; SAP=statistical analysis plan.

^a Twelve months from last participant randomized, ie, 6 months of additional follow-up from the primary analysis.

^b Percentage is calculated among participants in the ITT Population (MOTION) with an objective response according to RECIST v1.1.

^c DOR is defined as the time from the first documented objective response (CR or PR) until the time of disease progression or death by any cause, whichever occurs earlier. DOR in weeks is calculated as (earlier of date of PD or death, or censoring–date of first response+1)/7. Participants who do not have disease progression (per radiologic assessment) or death was censored according to the rules in SAP. The plus (+) sign for the Min or Max indicates that the participant is still in response.

^d Summary based on reverse Kaplan-Meier method reversing the event/censoring flag as specified in [Schemper and Smith, 1996](#).

Data cutoff dates: 22 Aug 2023 (MOTION primary analysis data); 22 Feb 2024 (MOTION updated analysis data).

Source: Sources: Module 5.3.5.1 DCC-3014-03-001 (primary analysis) Table 14.2.1.5.1.3 and DCC-3014-03-001 (updated analysis) Table 14.2.1.5.1.3, ADTTE1.

Functional and Patient-reported Endpoints

Collectively, assessment of key secondary ROM and PRO endpoints at Week 25 in MOTION demonstrated statistically significant and clinically meaningful improvement with vimseltinib treatment over placebo (Table 31). The change from baseline in ROM and PRO endpoints were consistent across the vimseltinib arm in MOTION and Phase 1/2 expansion cohorts.

The Applicant's Position:

Assessment of the key secondary endpoint ORR by TVS at Week 25 was planned to provide an early indicator of tumor response with vimseltinib 30 mg twice weekly. The TVS measures volumetric changes in irregularly shaped tumors like TGCT, which may not be captured with single dimension measurements per RECIST v1.1 at a given time point (Tap et al, 2015). Thus, changes in TGCT size may be observed earlier with TVS than with RECIST v1.1.

ORR per TVS was high in both MOTION vimseltinib arm (67%) and Phase 1/2 expansion Cohort A (51%).

Among objective responders in the vimseltinib arm at Week 25 per RECIST v1.1, the median DOR was not reached at either the primary or updated analysis with additional 6 months of follow-up, with responses lasting up to 84.4+ weeks and with all but 1 response ongoing at the time of the updated analysis. The updated MOTION DOR data demonstrate prolonged durability of response in participants with TGCT with further follow-up.

MOTION met all key secondary endpoints demonstrating statistically significant and clinically meaningful improvements in TVS, ROM, physical function, worst stiffness, QoL, and worst pain compared to placebo. The totality of efficacy data demonstrates a robust, statistically significant, and clinically meaningful efficacy response. The efficacy and PRO responses in MOTION were consistent with what was observed in participants with TGCT who received vimseltinib at the recommended dose of 30 mg twice weekly in the Phase 1/2 study.

The FDA's Assessment:

FDA did not independently verify the results of DCC-01-001 presented here, as the efficacy of vimseltinib was based on MOTION. FDA agrees that based on the data presented here, ORR per TVS was similar in the MOTION study (67%) and Cohort A of DCC-3014-01-001.

PRO endpoints in a single-arm study are uninterpretable.

Subpopulations

Data:

In MOTION, participants treated with vimseltinib achieved consistent benefit at Week 25 for the primary efficacy endpoint and key secondary efficacy endpoints in the subgroup analyses listed below. An additional subgroup analysis of ORR per RECIST v1.1 at Week 25 by primary joint location (knee, ankle, hip, all other) was also conducted. These results demonstrated consistent benefit across variables including tumor location, disease subtype, and prior treatment.

- Tumor location (lower limb versus all other)
- Region (U.S. versus non-U.S.)
- Participants with disease located in large joints (shoulder, elbow, hip, or knee) versus small joints (joints other than the shoulder, elbow, hip, or knee)
- Participants with disease located in the knee
- Disease subtype (localized versus diffuse)
- Participants at sites in the EU region only
- Age ($18 \leq \text{age} < 50$, $50 \leq \text{age} < 65$, $\text{age} \geq 65$)
- [REDACTED] (female versus male)
- Prior surgery (yes versus no)
- Prior imatinib/nilotinib (yes versus no)

Subgroup analyses were not performed in the Phase 1/2 study.

The Applicant's Position:

These results suggested no difference in efficacy across the broader population including age, sex, disease subtype, and prior treatment.

The FDA's Assessment:

The efficacy results in subpopulations with small sample size should be interpreted with caution.

Additional Efficacy Considerations

The FDA's Assessment:

There are no other efficacy considerations.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

There is no formal integrated assessment of efficacy. The data from MOTION, supported by data from the Phase 1/2 study, demonstrate vimseltinib provides statistically significant and long-lasting tumor response based on ORR per RECIST v1.1 and ORR by TVS in participants with symptomatic TGCT. Vimseltinib treatment also resulted in significant and meaningful improvements based on predetermined MCIDs in function as measured by active ROM and PROMIS-PF; in symptomatic improvements as measured by Worst Stiffness NRS and Worst Pain NRS; and in QoL as measured by EQ-VAS. Responses were observed across subgroups including age, sex, tumor location, and prior therapies, suggesting generalizability in the intended patient population. The results support approval of vimseltinib for the treatment of adult patients with symptomatic at the recommended dose of 30 mg twice weekly.

The FDA's Assessment:

FDA agrees that despite no formal integrated assessment of efficacy, the data from MOTION are statistically and clinically significant to support approval and are consistent with the results observed in the supportive study DCC-3014-01-001 Cohort A, which was not independently confirmed by the FDA. The ORR in MOTION per RECIST v1.1 performed at Week 25 shows a clinically significant benefit to patients (MOTION: 40%, DCC-3014-01-001 Cohort A 30 mg Vimseltinib twice weekly in patients not pre-treated with anti-CSF1/CSF1R therapy: 38%). In MOTION, the median DOR was not reached, with a range of 2.5+ to 19.4+ months. A total of 28 (85%) patients experienced a DOR of ≥ 6 months and 19 (58%) patients experienced a DOR of ≥ 9 months. Additionally, patients experienced clinically meaningful improvements on key secondary endpoints, including change from baseline ROM of affected joint and change from baseline in the PROs (PROMIS-PF and BPI-30 response) which further supported the efficacy endpoint. Therefore, in addition to inclusion of ORR and DOR in product labeling, the review team also included results of these secondary endpoints.

The Applicant originally proposed an indication which stated that vimseltinib was indicated for adult patients with symptomatic TGCT. During review of the NDA submission, FDA amended the proposed indication to state that it is indicated for the treatment of patients with symptomatic TGCT for whom surgical resection will potentially cause worsening functional limitations or severe morbidity which more accurately reflects the patient population enrolled in MOTION. The Applicant agreed.

ROMVIMZA is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).	ROMVIMZA is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity.
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These data support the efficacy of vimseltinib in the treatment of patients with TGCT.

8.2. Review of Safety

Data:

Refer to Section 8.2.4 for summaries of deaths, SAEs, AEs leading to discontinuations, and other safety data.

The Applicant's Position:

Vimseltinib has a manageable and acceptable safety profile in participants with TGCT.

The FDA's Assessment:

Although, FDA generally agrees with Applicant's assessment that vimseltinib has an overall manageable safety profile and an acceptable risk:benefit assessment, a known adverse reaction with another CSFR1 inhibitor, pexidartinib is hepatotoxicity and pexidartinib has a BOXED Warning for this toxicity and is only available through a REMS program.

Cases of serious and fatal liver injury have occurred with the use pexidartinib. Therefore, FDA conducted a comprehensive review of hepatotoxicity with the use of vimseltinib. During FDA review, serious and fatal liver injury were not observed with vimseltinib. Cases of $\leq$ Grade 2 AST and ALT elevations were common in patients who received vimseltinib, though no patients developed bilirubin elevations. FDA did not identify any cases of Hy's law or drug-induced liver injury (DILI). Due to this known risk of in class hepatotoxicity, sections 2.2 and 5.1 of product labeling addresses specific guidelines for managing potential hepatotoxicity in patients, including guidelines for routine laboratory surveillance.

After multidisciplinary review of clinical and nonclinical data, FDA determined that a REMS program was not required for vimseltinib. However, FDA will continue to collect further data on hepatotoxicity through a PMR registry study enrolling at least 100 patients in the postmarketing setting. There is nonclinical evidence to suggest small molecule inhibitors of CSFR1 lead to a higher incidence of elevated transaminases, but also may cause hepatic damage. FDA will continue to reevaluate the safety data for hepatotoxicity.

Additional warnings and precautions included in section 5.1 of product labeling are for potential embryo-fetal toxicity, allergic reactions to FD&C Yellow No.5 (Tartazine) and No. 6 (Sunset Yellow FCF) and increased creatinine without affecting renal function.

8.2.1. Safety Review Approach

The Applicant's Position:

The clinical review of safety of vimseltinib as a treatment for patients with symptomatic TGCT was based on the MOTION study (details of study design are in Section 8.1.1). The majority of the safety evaluation is based on the first 25 weeks of treatment to allow for comparison between the 83 participants randomized to vimseltinib and the 39 participants randomized to placebo.

The integrated safety database comprises data from participants included in the safety analysis set from the Phase 1/2 study and MOTION, including participants from MOTION originally randomized to vimseltinib and participants who crossed over to vimseltinib after receiving placebo. The safety analysis set consists of participants who have received at least 1 dose of vimseltinib.

The safety analysis set included the following populations:

- **Pool 1 (All participants with TGCT at 30 mg twice weekly dose):** All participants with TGCT in the Phase 1/2 study and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly are included. Data are summarized by Expansion Cohorts and MOTION (Cohort A, Cohort B, MOTION, Cohort A + MOTION) and overall (Cohort A + Cohort B + MOTION).
 - Phase 1/2 Cohort A is comprised of participants with TGCT who are not amenable to surgery and who have not received prior CSF1 or CSF1R therapy (excluding imatinib and/or nilotinib); a population similar to that of the target patient population of the ongoing pivotal MOTION study. Thus, for the pooled analysis, Cohort A and MOTION are grouped together.
 - Phase 1/2 Cohort B is comprised of participants with TGCT who were not amenable to surgery and who received prior CSF1 or CSF1R therapy and is presented separately in the pooled analysis.
- **Pool 2 (All participants with TGCT, any dose):** All participants with TGCT in the Phase 1/2 study and MOTION who received at least 1 dose of vimseltinib are included. Data are summarized by study phase (Escalation, Expansion, and MOTION) and overall.
- **Pool 3 (All participants, any dose):** All participants who received at least 1 dose of vimseltinib in the Phase 1/2 study and MOTION regardless of tumor type or dose of vimseltinib are included. Data are summarized by tumor type (MST versus TGCT) and overall.

- **Pool 4 (All participants at 30 mg twice weekly dose):** All participants in the Phase 1/2 study and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly, including those participants who received a loading dose. Data are summarized by tumor type (MST versus TGCT) and overall.

For all analysis pools, the analysis period comprises the duration from the first dose of vimseltinib through all available follow-up until the data cutoff (22 Feb 2024 and 27 Dec 2023 for MOTION and the Phase 1/2 study, respectively).

In order to better understand the safety of vimseltinib in the indicated population, a review of adverse events, laboratory assessments, vital signs, physical findings, and other observations related to safety was completed for Pool 1. A brief summary of data from participants in Pool 3 (including participants with MST) was also provided, as this is the largest safety pool.

In addition, 211 healthy participants received at least one dose of vimseltinib in the clinical pharmacology studies DCC-3014-01-002, DCC-3014-01-003, DCC-3014-01-004, and DCC-3014-01-006.

The FDA's Assessment:

The review team agrees with the safety Pools as stated above were agreed upon in the preNDA meeting held on January 16, 2024. During the meeting, FDA stated that although the safety assessment would be based on all patients with any tumor type who received at least one dose of vimseltinib (Pool 3 n=253), the focus of safety would be on the 83 patients who received vimseltinib 30 mg twice weekly in the double-blind portion of MOTION. The use of the larger data set was to assess any low incidence occurring serious adverse events and to contribute to the Warnings and Precautions section of the labeling. Section 6 of product labeling is thus based on the 83 patients who received vimseltinib in the double-blind portion of MOTION. Warnings and Precautions evaluated in product labeling was based on 253 patients who received any dose of vimseltinib in the double-blind portion of MOTION (n=83), the open-label portion of MOTION (n=35) and in DCC-3014-01-001 which included patients with TGCT as well as other solid tumors (n=135). These datasets were independently reviewed by the review team. The safety analysis within this section will mainly reflect the patients in the double-blind portion of MOTION unless otherwise stated.

The review team for did not independently evaluate the 211 healthy participants who received a single-dose of vimseltinib in the clinical pharmacology studies DCC-3014-01-002, DCC-3014-01-003, DCC-3014-01-004, and DCC-3014-01-006.

8.2.2. Review of the Safety Database

Overall Exposure

Data:

Table 39 summarizes exposure to vimseltinib in participants across the clinical studies supporting safety, including any exposure to vimseltinib, and exposure in the target indication at the proposed dose. A total of 464 participants received at least one dose of vimseltinib in the clinical development program.

Table 39 Exposure to Vimseltinib in Participants Across Clinical Studies Supporting Safety

Clinical Study	Any Exposure to Vimseltinib	Participants With TGCT Exposed to Vimseltinib 30 mg Twice Weekly
Pivotal Study		
Study DCC-3014-03-001 (MOTION)	118	83 (randomized to vimseltinib during double-blind period) 35 (crossed over from placebo to vimseltinib during open-label period)
Supportive Study		
Study DCC-3014-01-001 (Phase 1/2, Dose Escalation/Dose Expansion ^a)	135	46 (Cohort A) 20 (Cohort B)
Clinical Pharmacology Studies		
Study DCC-3014-01-002 (Phase 1, PK, Food Effect, QTc)	98	0
Study DCC-3014-01-003 (Phase 1 hAME)	8	0
Study DCC-3014-01-004 (Hepatic Impairment)	16 (of 48 planned)	0
Study DCC-3014-01-006 (DDI, P-gp)	89	0
Total Exposure	464	184

Abbreviations: CSF1=colony-stimulating factor 1; CSF1R=colony-stimulating factor 1 receptor; DDI=drug-drug interaction; hAME=human absorption, metabolism, and excretion; P-gp=P-glycoprotein; PK=pharmacokinetic(s); QTc=QT interval corrected for heart rate; TGCT=tenosynovial giant cell tumor.

^a In the Expansion Phase, Cohort A was comprised of participants with TGCT who were not amenable to surgery and who did not receive prior CSF1 or CSF1R therapy; Cohort B enrolled participants with TGCT who were not amenable to surgery and who received prior CSF1 or CSF1R therapy.

Sources: DCC-3014-03-001 Tables 14.1.5.1.1 and 14.1.5.2.1; DCC-3014-01-001 Table 14.1.1.1; ISS Table 10.1; Study DCC-3014-01-002 Table 34; Study DCC-3014-01-003 CSR Section 12.1; Study DCC-3014-01-006 CSR Section 12.1; Study DCC 3014-01-004 (protocol and data on file).

Drug exposure in the double-blind period of MOTION is presented in Table 40.

Table 40 Drug Exposure, Double-blind Period, MOTION Safety Set

Parameter	DB Vimseltinib N=83	DB Placebo N=39	Total Vimseltinib (DB and OL Period) N=118
Treatment duration (months) ^a			
Mean (STD)	5.2 (0.93)	5.2 (1.01)	8.2 (4.62)
Median	5.5	5.5	7.8
Min, max	1, 6	0, 7	0, 19
Treatment duration by category, n (%) ^a			
<1 month	1 (1.2)	1 (2.6)	5 (4.2)
1 to <3 months	3 (3.6)	1 (2.6)	15 (12.7)
3 to <6 months	78 (94.0)	36 (92.3)	20 (16.9)
≥6 months	1 (1.2)	1 (2.6)	78 (66.1)

Abbreviations: DB=double blind; max=maximum; min=minimum; n=number of participants in a category; N=sample size; OL=open label; STD=standard deviation.

^a Treatment duration (months) = (last dose date-first dose date+1)/30.4375.

Note: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.1.5.1.1 and Table 14.1.5.2.1, ADEX.

Drug exposure in Pool 1 is presented in Table 41. Considering the long treatment duration in the Phase 1/2 study Expansion Phase and the percent of dose reductions and interruptions, the relative dose intensity was high (≥75%).

Similar to Pool 1, in Pool 3 the mean (STD) exposure to vimseltinib was 14.0 months (11.61) in the overall population and 16.1 months (11.29) in participants with TGCT. The percentage of participants exposed to vimseltinib for 12 to <15 months was 10.3% (26/253), for 15 to <18 months was 7.9% (20/253), for 18 to <21 months was 7.1% (18/253), for 21 to <24 months was 4.7% (12/253), and for ≥24 months was 18.2% (46/253).

Table 41 Drug Exposure to Vimseltinib – Pool 1 (All Participants with TGCT at 30 mg Twice Weekly)

Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
Treatment duration (months) ^a					
Mean (STD)	19.6 (12.50)	15.4 (12.09)	12.4 (6.04)	14.4 (8.92)	14.5 (9.28)
Median	22.2	9.9	12.9	13.1	13.0

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Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
Min, max	0, 36	1, 36	1, 25	0, 36	0, 36
Treatment duration (months) by category, n (%) ^a					
<1 month	1 (2.2)	1 (5.0)	2 (1.7)	3 (1.8)	4 (2.2)
1 - <3 months	3 (6.5)	1 (5.0)	7 (5.9)	10 (6.1)	11 (6.0)
3 - <6 months	6 (13.0)	3 (15.0)	13 (11.0)	19 (11.6)	22 (12.0)
6 - <9 months	6 (13.0)	4 (20.0)	15 (12.7)	21 (12.8)	25 (13.6)
9 - <12 months	2 (4.3)	2 (10.0)	17 (14.4)	19 (11.6)	21 (11.4)
12 - <15 months	2 (4.3)	1 (5.0)	23 (19.5)	25 (15.2)	26 (14.1)
15 - <18 months	1 (2.2)	0	15 (12.7)	16 (9.8)	16 (8.7)
18 - <21 months	1 (2.2)	1 (5.0)	16 (13.6)	17 (10.4)	18 (9.8)
21 - <24 months	2 (4.3)	2 (10.0)	8 (6.8)	10 (6.1)	12 (6.5)
≥24 months	22 (47.8)	5 (25.0)	2 (1.7)	24 (14.6)	29 (15.8)
Number of cycles initiated ^b					
Mean (STD)	21.7 (13.63)	17.3 (13.25)	14.0 (6.58)	16.2 (9.72)	16.3 (10.12)
Median	24.5	11.5	14.5	15.0	15.0
Min, max	1, 40	1, 40	1, 28	1, 40	1, 40
Total number of doses received					
Mean (STD)	155.2 (100.84)	122.8 (103.91)	99.5 (51.66)	115.2 (73.16)	116.0 (76.77)
Median	176.0	74.5	100.0	106.0	102.5
Min, max	2, 311	7, 308	8, 214	2, 311	2, 311
Total planned dose (mg) ^c					
Mean (STD)	5212.2 (3271.08)	4140.0 (3180.98)	3360.0 (1579.56)	3879.5 (2332.69)	3907.8 (2429.80)
Median	5880.0	2760.0	3480.0	3600.0	3600.0
Min, max	240, 9600	240, 9600	240, 6720	240, 9600	240, 9600
Total administered dose (mg) ^d					
Mean (STD)	3737.2 (2655.32)	3228.6 (2702.39)	2618.7 (1457.10)	2932.4 (1929.90)	2964.6 (2020.95)
Median	3653.0	2006.0	2526.0	2580.0	2525.0

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Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
Min, max	60, 9330	210, 9240	240, 6420	60, 9330	60, 9330
Relative dose intensity (%) ^c					
Mean (STD)	71.32 (20.128)	78.52 (16.020)	77.27 (18.672)	75.60 (19.217)	75.92 (18.879)
Median	70.65	80.14	78.60	77.50	77.69
Min, max	25.0, 100.0	47.9, 106.3	25.0, 100.0	25.0, 100.0	25.0, 106.3
Participants with dose reduction or dose interruption, n (%)	36 (78.3)	15 (75.0)	86 (72.9)	122 (74.4)	137 (74.5)
Any dose reduction	28 (60.9)	10 (50.0)	60 (50.8)	88 (53.7)	98 (53.3)
Any dose interruption	33 (71.7)	13 (65.0)	74 (62.7)	107 (65.2)	120 (65.2)

Abbreviations: ISS=Integrated Summary of Safety; max=maximum; min=minimum; n=number of participants in a category; N=sample size; STD=standard deviation; TGCT=tenosynovial giant cell tumor.

^a Treatment duration (months): date of last vimseltinib dose - date of first vimseltinib dose +1/30.4375.

^b Number of cycles initiated: taking treatment duration (days)/28, round up to integer to get number of cycles.

^c Total planned dose (mg) was defined as the sum of the prescribed doses (mg).

^d Total administered dose (mg) was defined as the sum of the actual doses (mg) administered.

^e Relative dose intensity (%) was defined as total administered dose (mg)/total planned dose (mg) x 100.

Note 1: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Note 2: Data cutoff for Phase 1/2 study is 27 Dec 2023 and for MOTION is 22 Feb 2024.

Source: ISS Table 10.1, ADEX.

The Applicant's Position:

Treatment exposure was similar for the vimseltinib and placebo arms in MOTION (5.2 [0.93] months and 5.2 [1.01] months, respectively). In Pool 1, the mean (STD) duration of exposure to vimseltinib was 14.5 (9.28) months in 184 participants with TGCT who received 30 mg twice weekly.

Exposure to study treatment was considered appropriate to allow for an adequate assessment of safety in participants who were representative of the intended target population.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of treatment exposure for patients enrolled in the double-blind phase of MOTION in Table 40.

For clarification, the following define each patient population listed by the Applicant in Table 41.

- Cohort A: Patients with TGCT in the expansion phase of DCC-3014-01-001 with no prior anti-CSF1 or anti-CSF1R
- Cohort B: Patients with TGCT in the expansion phase of DCC-3014-01-001 no prior anti-CSF1 or anti-CSF1R
- MOTION: Patients who received at least one dose of vimseltinib in the double-blind (n=83) and in the open-label portion (n=35)

Relevant characteristics of the safety population:

Data:

Population characteristics were similar between treatment arms in the double-blind period of MOTION. The mean (STD) age of participants was 43.4 (13.80) years. The participants were generally White (65.0%), non-Hispanic (69.1%), and female (59.3%). The mean (STD) baseline BMI was 27.37 (5.974) kg/m². Majority of participants were non-U.S. (89.4%) and presented with tumor in the lower limb (88.6%) as recorded per interactive response technology. Table 25 shows an overall summary of demographic characteristics and baseline characteristics in MOTION.

Demographic characteristics for Pool 1 are presented in Table 42.

Pool 3 demographic characteristics were similar to those of Pool 1.

Table 42 Demographic Characteristics – Pool 1 (All Participants with TGCT at 30 mg Twice Weekly)

Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
Age (years) ^a					
n	46	20	118	164	184
Mean (STD)	43.4 (13.71)	47.7 (12.35)	43.5 (13.66)	43.4 (13.63)	43.9 (13.53)
Median	44.0	45.0	44.0	44.0	44.0
Min, max	21, 71	26, 65	20, 78	20, 78	20, 78
Age Group (years), n (%)					
≥18 to <50	27 (58.7)	11 (55.0)	77 (65.3)	104 (63.4)	115 (62.5)
≥50 to <65	17 (37.0)	8 (40.0)	33 (28.0)	50 (30.5)	58 (31.5)

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Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
≥65 to <75	2 (4.3)	1 (5.0)	6 (5.1)	8 (4.9)	9 (4.9)
≥75 to <85	0	0	2 (1.7)	2 (1.2)	2 (1.1)
Sex, n (%)					
Male	15 (32.6)	10 (50.0)	49 (41.5)	64 (39.0)	74 (40.2)
Female	31 (67.4)	10 (50.0)	69 (58.5)	100 (61.0)	110 (59.8)
Race, n (%)					
Asian	2 (4.3)	0	5 (4.2)	7 (4.3)	7 (3.8)
Black or African American	0	1 (5.0)	4 (3.4)	4 (2.4)	5 (2.7)
Native Hawaiian or Other Pacific Islander	0	1 (5.0)	0	0	1 (0.5)
White	36 (78.3)	17 (85.0)	79 (66.9)	115 (70.1)	132 (71.7)
Other	5 (10.9)	1 (5.0)	0	5 (3.0)	6 (3.3)
Not Reported	3 (6.5)	0	30 (25.4)	33 (20.1)	33 (17.9)

Abbreviations: ISS=Integrated Summary of Safety; max=maximum; min=minimum; n=number of participants in a category; N=sample size; STD=standard deviation; TGCT=tenosynovial giant cell tumor.

^a Age (years) was calculated as (date of informed consent - date of birth +1)/365.25 if age at informed consent was not collected on the case report form.

Note 1: Baseline weight, height, and body mass index were summarized using the last nonmissing value before the first dose of vimseltinib.

Note 2: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Note 3: Data cutoff for Phase 1/2 study is 27 Dec 2023 and for MOTION is 22 Feb 2024.

Source: ISS Table 2.1, ADSL.

The Applicant's Position:

Demographic characteristics were consistent in Pool 1, Pool 3, and the double-blind period of MOTION, thereby providing reassurance regarding the interpretation of the treatment comparison and the validity of the safety conclusions.

The FDA's Assessment:

FDA agrees with the Applicant's assessment of demographic characteristics for patients treated in the double-blind portion of MOTION as shown in Table 25.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data from the Phase 3 pivotal study, MOTION, and Cohorts A and B of the supportive Phase 1/2 study. Further details are provided in Section 8.2.1. This population allows for a thorough assessment of the vimseltinib safety data and a judgment of the overall benefit-risk in subjects with TGCT. The duration of the treatment is adequate to allow assessment of adverse reactions over time. The safety database represents the sex, age, and race consistent with that observed in the population of patients with TGCT.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the adequacy of the safety database. The primary safety analyses to support approval was based on the 83 patients who received vimseltinib in the double-blind portion of MOTION. An additional 135 patients treated on DCC-3014-01-001 and 35 patients who were treated with vimseltinib in the open-label portion of MOTION were evaluated, for a total of 253 patients who received at least one dose of vimseltinib.

8.2.3. Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following a completion of site inspections; data in the case report forms and AE databases were consistent.

The FDA's Assessment:

FDA agrees with Applicant's assessment.

Categorization of Adverse Event

The Applicant's Position:

A TEAE was defined as any AE that occurred or worsened after the administration of the first dose of vimseltinib and through 30 days after the last dose of vimseltinib or the day before the start of a new anti-tumor therapy. Drug-related AEs reported after 30 days following the last dose of vimseltinib were also considered as treatment-emergent.

Adverse events were classified using Medical Dictionary for Regulatory Activities (MedDRA) v26.0.

The severity grade of the AEs for the Phase 1/2 study was assessed by National Cancer Institute Common Terminology Criteria for Adverse Event (NCI-CTCAE) v4.03 and for MOTION by NCI-CTCAE v5.0.

The FDA's Assessment:

FDA agrees with the categorization of TEAEs and severity. The Applicant provided appropriate definitions and reporting requirements for AEs and serious AEs (SAEs). AE evaluation was performed at the time of informed consent up to 30 days after the last dose of study treatment.

Routine Clinical Tests

Data:

Routine clinical tests, including vital signs, 12-lead ECG, hematology, chemistry, coagulation, and urinalysis, were performed according to the Schedules of Assessments in the study protocols for the MOTION and Phase 1/2 studies.

The Applicant's Position:

The tests and frequency of testing are considered adequate to assess the safety of vimseltinib in the MOTION and Phase 1/2 studies.

The FDA's Assessment:

FDA agrees that the frequency and type of testing used in these studies was adequate to assess the safety of vimseltinib.

8.2.4. Safety Results

Deaths

Data:

No participants died in the double-blind period of MOTION.

In Pool 1, one participant in the open-label period of MOTION died from a fall that was assessed as unrelated to vimseltinib.

In addition, 8 participants with MST in DCC-3014-01-001 experienced TEAEs leading to death. All were assessed as unrelated to vimseltinib.

The Applicant's Position:

Vimseltinib was not considered as a cause of death for any reported event.

The FDA's Assessment:

FDA reviewed all the death narratives and agrees that vimseltinib was not considered a cause of death for any event. No deaths are therefore reported in Section 6 of product labeling.

Serious Adverse Events

Data:

Table 43 presents all SAEs reported in the double-blind period of MOTION by PT. (b) (4)

Table 43 Treatment-emergent SAEs in Double-blind Period by Preferred Term, MOTION Safety Set

Preferred term, n (%)	Vimseltinib N=83	Placebo N=39	Total N=122
Any SAE	6 (7.2)	1 (2.6)	7 (5.7)
Cellulitis	1 (1.2)	0	1 (0.8)
Fall	1 (1.2)	0	1 (0.8)
Papillary thyroid cancer	1 (1.2)	0	1 (0.8)
Plasma cell myeloma	1 (1.2)	0	1 (0.8)
Subcutaneous abscess	1 (1.2)	0	1 (0.8)
Uveitis	1 (1.2)	0	1 (0.8)
Diarrhoea	0	1 (2.6)	1 (0.8)
Vomiting	0	1 (2.6)	1 (0.8)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; SAE=serious adverse event.

Note 1: SAEs were coded per MedDRA v26.0.

Note 2: If a preferred term was reported more than once for a participant, the participant would only be counted once.

Note 3: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.3.2.3.1.1, ADAE.

Serious AEs experienced by >1 participant in Pool 1 are presented in Table 44. All drug-related SAEs were reported in 1 participant each.

Similar to Pool 1, in Pool 3 the most frequently reported SAE was cellulitis (2.0% [5/251]). All drug-related SAEs were reported in 1 participant each.

Table 44 Treatment-emergent Serious Adverse Events Occurring in >1 Participant by System Organ Class and Preferred Term – Pool 1 (All Participants with TGCT at 30 mg Twice Weekly)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183) ^a n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Any serious TEAE	9 (19.6)	3 (15.0)	21 (17.8)	30 (18.3)	33 (18.0)
Infections and infestations	4 (8.7)	0	8 (6.8)	12 (7.3)	12 (6.6)
Cellulitis	0	0	5 (4.2)	5 (3.0)	5 (2.7)
Injury, poisoning and procedural complications	0	0	3 (2.5)	3 (1.8)	3 (1.6)

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System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183) ^a n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Fall	0	0	2 (1.7)	2 (1.2)	2 (1.1)

Abbreviations: AE=adverse event; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; TGCT=tenosynovial giant cell tumor.

^a One participant from the Expansion Phase (Cohort A) re-enrolled into Cohort B. This participant was counted as 1 participant for the total column.

Note 1: MedDRA v26.0 was used. TEAE was defined as any AE that occurred or worsened after the administration of the first dose of vimseltinib and through 30 days after the last dose of vimseltinib or the day before the start of new anti-tumor therapy.

Note 2: Drug-related AEs reported after 30 days following the last dose of vimseltinib were considered treatment emergent.

Note 3: If an SOC or PT was reported more than once for a participant, the participant was counted only once in the incidence for that SOC or PT.

Note 4: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Note 5: Data cutoff for Phase 1/2 study is 27 Dec 2023 and for MOTION is 22 Feb 2024.

Source: ISS Table 12.3.1, ADAE.

The Applicant's Position:

Participants in the vimseltinib arm experienced more SAEs than those in the placebo arm in the double-blind period of MOTION; (b) (4)

Serious AEs including drug-related SAEs were generally consistent across the different pooled populations. No individual drug-related SAE was reported in more than participant.

The FDA's Assessment:

FDA does not agree with Applicant's assessment, as all SAEs are considered attributable regardless of causality. Patients who received vimseltinib experienced more SAEs than those in the placebo arm (7% vs. 2.6%, respectively) with each SAE occurring in one patient only. FDA reviewed the narratives for all patients who experienced an SAE. Based on the reviewer assessment, only cellulitis (1 patient) and sub-cutaneous abscess (1 patient) were considered SAEs (2.4%). The original proposed labeling from the Applicant did not include SAEs but through negotiations, an incidence of 2.4% was included in product labeling.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

In the double-blind period of MOTION, 5 (6.0%) participants in the vimseltinib arm discontinued vimseltinib treatment due to a TEAE compared to 0% in the placebo arm. The TEAEs were periorbital oedema, (b) (4) peripheral sensory neuropathy, rash, and hypertension. None of these TEAEs led to discontinuation in >1 participant.

Treatment-emergent AEs leading to treatment discontinuation occurred in 9.3% (17/183) of participants in Pool 1. In Pool 1, the most frequently reported TEAEs leading to treatment discontinuation were rash and periorbital edema (each reported in 1.6% of participants [3/183]).

Similar to Pool 1, in Pool 3 the most frequently reported TEAEs leading to treatment discontinuation were rash and periorbital edema (each reported in 1.2% of participants [3/251]).

The Applicant's Position:

More vimseltinib-treated participants discontinued study drug treatment than placebo-treated participants in the double-blind period of MOTION. However, the rate of discontinuation was still low in vimseltinib-treated participants.

Treatment-emergent AEs leading to treatment discontinuation were generally consistent across the different pooled populations. TEAEs leading to discontinuation were similar to those that were managed with interruptions and dose reductions.

The FDA's Assessment:

FDA does not agree with applicant's assessment. A total of 4.8% of patients receiving vimseltinib discontinued treatment due to a TEAE, including one patient with each of the following: periorbital edema, peripheral sensory neuropathy, rash and hypertension. FDA does not consider (b) (4) to be an adverse reaction at least possibly attributable to the use of vimseltinib.

Dose Interruptions, Delays, and/or Reductions Due to Adverse Effects

Data:

In the double-blind period of MOTION, TEAEs leading to dose modification (including dose reduction or interruption) were experienced by 62.7% of participants in the vimseltinib arm versus 10.3% in the placebo arm. The most frequently reported TEAEs leading to dose modification in the vimseltinib arm were periorbital edema (9.6%); COVID-19, pruritus, asthenia, and blood CPK increased (8.4% each); and rash maculo-papular (7.2%).

In Pool 1, treatment-emergent AEs leading to dose modification occurred in 74.3% of participants. The most frequently reported TEAEs leading to dose modification were blood creatine phosphokinase (CPK) increased (16.9% [31/183]), periorbital edema (13.7% [25/183]), asthenia (12.0% [22/183]), pruritus (9.8% [18/183]), rash maculo-papular (9.3% [17/183]), and COVID-19 (8.2% [15/183]).

Similar to Pool 1, in Pool 3 the most frequently reported TEAEs leading to dose modification were blood CPK increased (14.3% [36/251]), periorbital edema (12.0% [30/251]), and asthenia (8.8% [22/251]).

The Applicant's Position:

TEAEs leading to dose modification were generally consistent across the different pooled populations and were similar to those seen in the double-blind period of MOTION. Although most participants experienced a TEAE leading to dose modification, the RDI was high ($\geq 75\%$), as discussed in Section 8.1.2

The FDA's Assessment:

FDA analyzed the dose interruptions or reductions in patients on the double-blind portion of MOTION. Dose reductions due to an adverse reaction occurred in 39% of patients who received vimseltinib. Adverse reactions leading to dose reductions in $\geq 2\%$ of patients were rash, periorbital edema, peripheral edema, fatigue, pruritus, face edema, increased CPK, neuropathy, and hypertension. Dose interruptions due to adverse reaction abnormality occurred in 40% of patients who received vimseltinib. Adverse reactions leading to interruptions in $\geq 2\%$ of patients included rash, fatigue, peripheral edema, increased CPK, periorbital edema, face edema, pruritus, neuropathy, and hypertension. The Applicant's statement above that "TEAEs leading to dose modification (including dose reduction or interruption) were experienced by 62.7% of participants in the vimseltinib" includes overlap between some patients who experienced both dose reductions and dose interruptions.

Table 48 displays the agreed upon adverse reactions in product labeling for vimseltinib.

Significant Adverse Events

The Applicant's Position:

Deaths, SAEs, TEAEs leading to discontinuation, and TEAEs leading to dose modification are discussed above. No adverse events of special interest or other significant adverse events were identified. For adverse reactions, see the following subsection.

The FDA's Assessment:

See Section 8.2.5 below for details on hepatotoxicity.

Treatment Emergent Adverse Events and Adverse Reactions

Data:

Treatment-emergent Adverse Events

Table 45 presents TEAEs with $\geq 10\%$ of total for the double-blind period of MOTION.

Table 45 Treatment-emergent Adverse Events With $\geq 10\%$ of Total by Preferred Term in MOTION Double-Blind Period, Safety Set

Preferred Term, n (%)	Vimseltinib N=83	Placebo N=39	Total N=122
Any TEAE	83 (100.0)	37 (94.9)	120 (98.4)
Periorbital oedema	37 (44.6)	5 (12.8)	42 (34.4)
Fatigue	27 (32.5)	6 (15.4)	33 (27.0)
Headache	23 (27.7)	10 (25.6)	33 (27.0)
Asthenia	22 (26.5)	9 (23.1)	31 (25.4)
Face oedema	26 (31.3)	3 (7.7)	29 (23.8)
Nausea	21 (25.3)	8 (20.5)	29 (23.8)
Pruritus	24 (28.9)	3 (7.7)	27 (22.1)
Arthralgia	16 (19.3)	6 (15.4)	22 (18.0)
Blood CPK increased	20 (24.1)	0	20 (16.4)
AST increased	19 (22.9)	1 (2.6)	20 (16.4)
Rash	16 (19.3)	2 (5.1)	18 (14.8)
Oedema peripheral	15 (18.1)	3 (7.7)	18 (14.8)
Hypertension	14 (16.9)	4 (10.3)	18 (14.8)
Diarrhoea	10 (12.0)	8 (20.5)	18 (14.8)
Rash maculo-papular	16 (19.3)	0	16 (13.1)
Eyelid oedema	11 (13.3)	2 (5.1)	13 (10.7)

Abbreviations: AST=aspartate aminotransferase; CPK=creatinine phosphokinase; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; TEAE=treatment-emergent adverse event.

Note 1: TEAEs were coded per MedDRA v26.0. If a preferred term was reported more than once for a participant, the participant would be counted only once.

Note 2: Table cut-off was based on $\geq 10\%$ of total participants by preferred term in double-blind period.

Note 3: Data cutoff date was 22 Aug 2023.

Source: Module 5.3.5.1 DCC-3014-03-001 Table 14.3.1.4.2.1, ADAE.

Table 46 presents the TEAEs reported in $\geq 10\%$ of participants in Pool 1. Among the most frequently reported TEAEs ($\geq 25\%$ of participants) in Pool 1, the majority of these TEAEs were experienced during the first year of vimseltinib exposure, and the incidence did not increase over time.

Similar to Pool 1, in Pool 3 the TEAEs reported in $\geq 25\%$ of participants were periorbital edema (43.0% [108/251]), blood CPK increased (41.4% [104/251]), fatigue (31.9% [80/251]), headache (29.1% [73/251]), arthralgia (27.1% [68/251]), nausea (27.1% [68/251]), AST increased (26.3% [66/251]), and asthenia (25.5% [64/251]).

Table 46 Treatment-emergent Adverse Events Occurring in $\geq 10\%$ of Participants by System Organ Class and Preferred Term – Pool 1 (All Participants with TGCT at 30 mg Twice Weekly)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183) ^a n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Any TEAE	46 (100.0)	20 (100.0)	117 (99.2)	163 (99.4)	182 (99.5)
General disorders and administration site conditions	38 (82.6)	16 (80.0)	94 (79.7)	132 (80.5)	147 (80.3)
Asthenia	17 (37.0)	3 (15.0)	35 (29.7)	52 (31.7)	55 (30.1)
Fatigue	10 (21.7)	11 (55.0)	34 (28.8)	44 (26.8)	55 (30.1)
Face oedema	10 (21.7)	2 (10.0)	35 (29.7)	45 (27.4)	47 (25.7)
Oedema peripheral	11 (23.9)	4 (20.0)	24 (20.3)	35 (21.3)	39 (21.3)
Generalised oedema	7 (15.2)	2 (10.0)	18 (15.3)	25 (15.2)	26 (14.2)
Eye disorders	30 (65.2)	15 (75.0)	91 (77.1)	121 (73.8)	136 (74.3)
Periorbital oedema	18 (39.1)	9 (45.0)	56 (47.5)	74 (45.1)	83 (45.4)
Eyelid oedema	8 (17.4)	2 (10.0)	13 (11.0)	21 (12.8)	23 (12.6)
Lacrimation increased	5 (10.9)	2 (10.0)	12 (10.2)	17 (10.4)	19 (10.4)
Skin and subcutaneous tissue disorders	31 (67.4)	15 (75.0)	80 (67.8)	111 (67.7)	125 (68.3)
Pruritus	8 (17.4)	3 (15.0)	39 (33.1)	47 (28.7)	50 (27.3)
Rash maculo-papular	11 (23.9)	6 (30.0)	26 (22.0)	37 (22.6)	43 (23.5)
Rash	8 (17.4)	4 (20.0)	27 (22.9)	35 (21.3)	39 (21.3)
Dry skin	4 (8.7)	2 (10.0)	15 (12.7)	19 (11.6)	21 (11.5)
Investigations	34 (73.9)	15 (75.0)	62 (52.5)	96 (58.5)	111 (60.7)
Blood CPK increased	32 (69.6)	12 (60.0)	34 (28.8)	66 (40.2)	78 (42.6)
AST increased	9 (19.6)	8 (40.0)	33 (28.0)	42 (25.6)	50 (27.3)
ALT increased	4 (8.7)	4 (20.0)	21 (17.8)	25 (15.2)	29 (15.8)
Gastrointestinal disorders	31 (67.4)	13 (65.0)	52 (44.1)	83 (50.6)	96 (52.5)
Nausea	16 (34.8)	6 (30.0)	27 (22.9)	43 (26.2)	49 (26.8)
Diarrhoea	6 (13.0)	7 (35.0)	22 (18.6)	28 (17.1)	35 (19.1)
Vomiting	8 (17.4)	2 (10.0)	15 (12.7)	23 (14.0)	25 (13.7)

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System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183) ^a n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Nervous system disorders	25 (54.3)	13 (65.0)	57 (48.3)	82 (50.0)	95 (51.9)
Headache	19 (41.3)	11 (55.0)	32 (27.1)	51 (31.1)	62 (33.9)
Musculoskeletal and connective tissue disorders	29 (63.0)	12 (60.0)	54 (45.8)	83 (50.6)	95 (51.9)
Arthralgia	13 (28.3)	5 (25.0)	32 (27.1)	45 (27.4)	50 (27.3)
Myalgia	14 (30.4)	5 (25.0)	12 (10.2)	26 (15.9)	31 (16.9)
Infections and infestations	18 (39.1)	6 (30.0)	55 (46.6)	73 (44.5)	79 (43.2)
COVID-19	7 (15.2)	2 (10.0)	19 (16.1)	26 (15.9)	28 (15.3)
Vascular disorders	9 (19.6)	5 (25.0)	35 (29.7)	44 (26.8)	48 (26.2)
Hypertension	6 (13.0)	5 (25.0)	28 (23.7)	34 (20.7)	38 (20.8)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19= coronavirus disease-19; CPK=creatine phosphokinase; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; TGCT=tenosynovial giant cell tumor.

^a One participant from the Expansion Phase (Cohort A) re-enrolled into Cohort B. This participant was counted as 1 participant for the total column.

Note 1: MedDRA v26.0 was used. TEAE was defined as any AE that occurred or worsened after the administration of the first dose of vimseltinib and through 30 days after the last dose of vimseltinib or the day before the start of new anti-tumor therapy.

Note 2: Drug-related AEs reported after 30 days following the last dose of vimseltinib were considered treatment-emergent.

Note 3: If an SOC or PT was reported more than once for a participant, the participant was counted only once in the incidence for that SOC or PT.

Note 4: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Note 5: Data cutoff for Phase 1/2 study is 27 Dec 2023 and for MOTION is 22 Feb 2024.

Source: ISS Table 12.1.1, ADAE.

Drug-related TEAEs

In the double-blind period of MOTION, drug-related TEAEs with $\geq 5\%$ higher incidence with vimseltinib than placebo were periorbital edema, fatigue, face edema, asthenia, pruritus, blood CPK increased, AST increased, rash, rash maculo-papular, peripheral edema, hypertension, and eyelid edema.

In Pool 1, the drug-related TEAEs reported in $\geq 25\%$ of participants were periorbital edema (44.8% [82/183]), blood CPK increased (42.1% [77/183]), fatigue (28.4% [52/183]), asthenia (27.9% [51/183]), headache (27.3% [50/183]), AST increased (26.2% [48/183]), pruritus (26.2% [48/183]), and face edema (25.1% [46/183]).

Similar to Pool 1, in Pool 3 the drug-related TEAEs reported in $\geq 25\%$ of participants were periorbital edema (42.2% [106/251]), blood CPK increased (40.2% [101/251]), and fatigue (29.1% [73/251]).

Grade 3/4 TEAEs

In the double-blind period of MOTION, Grade 3/4 TEAEs were experienced by 37.3% in the vimseltinib arm and 10.3% in the placebo arm. Grade 3/4 TEAEs experienced by >1 participant in the vimseltinib arm included blood CPK increased, hypertension, periorbital edema, pruritus, and asthenia.

In Pool 1, 53.0% (97/183) of participants reported Grade 3/4 TEAEs. The most frequently reported Grade 3/4 TEAEs were blood CPK increased (23.5% [43/183]), hypertension (8.7% [16/183]), and pruritus (2.7% [5/183]).

Similar to Pool 1, in Pool 3, 53.8% (135/251) of participants reported Grade 3/4 TEAEs. The most frequently reported Grade 3/4 TEAEs were blood CPK increased (21.1% [53/251]), hypertension (7.2% [18/251]), and AST increased, lipase increased, and fatigue (2.4% [6/251] each)

Adverse Drug Reactions

All reported TEAEs from both MOTION and the Phase 1/2 study were evaluated to identify those that were reasonably associated with the use of vimseltinib. Adverse drug reactions were identified based on event incidence, difference between the vimseltinib and placebo arms in MOTION, temporal relationship, seriousness, severity, consistency across studies, nonclinical findings, and plausible mechanism of action.

Placebo-controlled data from the double-blind period of MOTION (DCO date 22 August 2023) were selected as the best available data for the presentation of adverse drug reactions in the label. Participants were counted once for each adverse drug reaction term, and incidence rates were based on the number of participants who initially received placebo or vimseltinib.

Table 47 summarizes the adverse reactions observed in MOTION through Week 25. Events that were coded under different terms in the database but that represent the same phenomenon were grouped together as a single adverse drug reaction. Preferred terms included within each grouped term are captured in the footnotes.

Table 47 Adverse Reactions Observed in MOTION Through Week 25

System organ class	Frequency category	Adverse reaction	Incidence and CTCAE Grades ^a			
			Vimseltinib N=83		Placebo N=39	
			All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Eye disorders	Very common	Periorbital edema ^b	60%	4%	21%	0%
	Very common	Lacrimation increased	12%	0%	0%	0%

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ROMVIMZA (vimseltinib)

System organ class	Frequency category	Adverse reaction	Incidence and CTCAE Grades ^a			
			Vimseltinib N=83		Placebo N=39	
			All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
	Common	Dry eye ^c	10%	0%	0%	0%
	Common	Vision blurred	6%	0%	0%	0%
Skin and subcutaneous tissue disorders	Very common	Rash ^d	43%	2%	5%	0%
	Very common	Pruritus	29%	2%	8%	0%
	Common	Dry skin	8%	0%	0%	0%
General disorders and administration site conditions	Very common	Fatigue	33%	0%	15%	0%
	Very common	Face edema	31%	1%	8%	0%
	Very common	Peripheral edema ^e	18%	0%	8%	0%
	Very Common	Generalized edema	13%	1%	0%	0%
Vascular disorders	Very Common	Hypertension	17%	5%	10%	3%
Nervous system disorders	Very common	Neuropathy ^f	12%	1%	3%	0%

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; N=sample size.

^a The severity of adverse drug reactions was assessed using CTCAE v5.0.

^b Periorbital edema comprises eye oedema, eyelid oedema, periorbital oedema.

^c Dry eye comprises dry eye, xerophthalmia.

^d Rash comprises rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, dermatitis acneiform, erythema.

^e Peripheral edema comprises peripheral oedema, peripheral swelling.

^f Neuropathy comprises peripheral neuropathy, paraesthesia, hypoaesthesia, peripheral sensory neuropathy.

Source: DCC-3014-03-001 ADAE.

The Applicant's Position:

Adverse drug reactions were identified based on comprehensive assessment of available data and are presented above.

TEAEs, including drug-related TEAEs and Grade 3/4 TEAEs were consistent across the different pooled populations. The TEAE profiles in the pooled populations were similar to those observed in the double-blind period of MOTION.

Review of all TEAEs occurring in Years 2 through 4 did not reveal an increased incidence of events typically occurring with longer latency. No new or worsening cardiovascular toxicities,

secondary malignancies, renal or hepatic toxicities, or other clinically significant AEs were observed with long-term vimseltinib exposure.

The FDA’s Assessment:

The reviewer and the Applicant used alternative methodology of grouping of TEAEs which led to difference in incidences of some composite terms. In addition, the reviewer does not agree with the reporting of drug-related TEAEs and has evaluated all TEAEs regardless of causality. This is reflected in the labeling for vimseltinib. Table 48 includes the adverse reaction with the agreed upon composite terms and incidence of adverse reactions that occurred in $\geq 10\%$ of patients receiving vimseltinib with a difference between arms of $>5\%$.

FDA initially proposed the use of the group term edema to include the preferred terms periorbital edema, face edema, eye edema, eyelid edema, generalized edema, edema peripheral, and localized edema. The Applicant did not agree and requested the use of the group terms periorbital edema (eye edema, eyelid edema, periorbital edema), facial edema (face edema) and peripheral edema (generalized edema, peripheral edema, localized edema). The Applicant stated that the use of these separate grouped terms best reflected clinical presentation and management. FDA agreed to the use of these group terms.

The agreed upon preferred terms for each group term were as follows:

- Periorbital edema: eye edema, eyelid edema, periorbital edema
- Dry eye: dry eye, xerophthalmia
- Fatigue: Fatigue and asthenia
- Peripheral edema: generalized edema, peripheral edema, localized edema
- Rash: urticarial dermatitis, eczema, rash, rash pruritic, rash maculo-papular, palmar-plantar erythrodysesthesia syndrome, dermatitis acneiform, eyelid rash, rash erythematous, rash pustular, dermatitis, rash macular
- Neuropathy: peripheral neuropathy, paresthesia, hypoesthesia, peripheral sensory neuropathy

Table 48 FDA: Adverse Reactions Occurring in 10% of Patients Receiving Vimseltinib with a Difference Between Arms of $>5\%$ Compared to Placebo Through Week 25, MOTION

Adverse Reaction*	Vimseltinib N=83		Placebo N=39	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Eye disorders				
Periorbital edema ¹	60	3.6	21	0

Adverse Reaction*	Vimseltinib N=83		Placebo N=39	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Lacrimation increased	12	0	0	0
Dry eye ¹	10	0	0	0
General disorders and administration site conditions				
Fatigue ¹	59	1.2	38	2.6
Peripheral edema ¹	33	1.2	8	0
Face edema	31	1.2	8	0
Skin and subcutaneous tissue disorders				
Rash ¹	47	3.6	5	0
Pruritus	29	2.4	8	0
Vascular disorders				
Hypertension	17	4.8	10	2.6
Nervous system disorders				
Neuropathy ¹	12	1.2	2.6	0
*The severity of adverse drug reactions was assessed using CTCAE v5.0. ¹ Includes multiple related terms Source: USPI for vimseltinib				

Laboratory Findings

Data:

Chemistry

During the double-blind period of MOTION, notable differences between vimseltinib and placebo were observed for alanine aminotransferase (ALT), AST, Alkaline phosphatase (ALP), creatinine, and cholesterol. The majority of shifts in serum chemistry parameters from baseline to worst post-baseline CTCAE Grade were normal to Grade 1. No other clinically meaningful abnormalities in serum chemistry parameters were observed.

Across all pools, the most frequently reported shifts in chemistry laboratory parameters (worsening from baseline in $\geq 20\%$ of participants) were ALT increased, AST increased, cholesterol high, creatinine increased, hypertriglyceridemia, and hypoglycemia. Most of these reported shifts were worsening to $< \text{Grade } 3$.

In Pool 1, the parameters that showed any shift in $\geq 20\%$ of participants were ALT increased (27.2% [50/184]), AST increased (92.4% [170/184]), cholesterol high (52.7% [97/184])

creatinine increased (42.9% [79/184]), hypertriglyceridemia (27.2% [50/184]), and hypoglycemia (22.8% [42/184]). Of these, the parameters that showed worsening to Grade 3/4 were AST increased (0.5% [1/184]), cholesterol high (1.1% [2/184]), and hypertriglyceridemia (1.1% [2/184]).

Although ALT or AST increases were frequently observed in participants who received vimseltinib, a small proportion of elevations were $\geq 3\times$ upper limit of normal (ULN). None of these elevations were accompanied by $\geq 1\times$ ULN of total bilirubin. No Hy’s Law cases were identified.

Similarly, the cholestatic screening plot does not suggest any occurrence of cholestatic drug induced liver injury. Although an increase in ALP $>2\times$ ULN occurred in 2 participants, this increase was not accompanied by an increase in total bilirubin.

Results were similar in Pool 3.

Hematology

During the double-blind period of MOTION, notable differences between vimseltinib and placebo shifts in hematology parameters from baseline to worst post-baseline CTCAE Grade were reported for leukocytes (overall) and neutrophils. No other clinically meaningful shifts in hematology parameters from baseline to worst post-baseline CTCAE Grade were reported in the vimseltinib treatment period.

In Pool 1, the parameters that showed any worsening in $\geq 25\%$ of participants were neutrophil count decreased (36.4% [67/184]) and white blood cell decreased (33.2% [61/184]). Of these, few participants showed worsening to Grade 3/4 (2.7% [5/184] of participants with neutrophil count decreased and 0.5% [1/184] of participants with white blood cell decreased).

All observed laboratory abnormalities from both MOTION and pooled data were evaluated to identify those that were reasonably associated with the use of vimseltinib. Considering event incidence, difference between the vimseltinib and placebo arms in MOTION, temporal relationship, seriousness, severity, consistency across studies, nonclinical findings, and plausible mechanism of action, laboratory abnormalities observed through Week 25 in MOTION and considered reasonably associated with the use of vimseltinib are summarized in Table 49.

Table 49 Laboratory Abnormalities Observed in MOTION through Week 25

Frequency Category	Laboratory Abnormality	Incidence and CTCAE Grade			
		Vimseltinib N=83		Placebo N=39	
		Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Very common	Increased AST	92%	0%	10%	0%

Frequency Category	Laboratory Abnormality	Incidence and CTCAE Grade			
		Vimseltinib N=83		Placebo N=39	
		Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Very common	Increased cholesterol	43%	0%	15%	0%
Very common	Decreased neutrophils	31%	1%	3%	0%
Very common	Increased ALT	24%	0%	15%	0%
Very common	Increased creatinine	17%	0%	3%	0%
Very common	Increased ALP	14%	0%	8%	0%

Abbreviations: AST=aspartate aminotransferase; ALT=alanine transaminase; ALP=alkaline phosphatase; CTCAE=Common Terminology Criteria for Adverse Events.

Note: The severity was assessed using CTCAE v5.0.

Source: DCC-3014-03-001 ADLB.

In addition, increased CPK was identified as a laboratory abnormality reasonably associated with the use of vimseltinib. The frequency of increased CPK cannot be determined from MOTION because CPK was not assessed at baseline. In the Phase 1/2 study conducted in 65 participants receiving vimseltinib 30 mg twice weekly, increased CPK from baseline was observed in all participants. Skeletal muscle injury or other organ damage was not observed in patients with elevated CPK. There were no treatment discontinuations due to increased CPK reported in MOTION or the Phase 1/2 study.

The Applicant's Position:

Serum enzyme elevations are frequently observed in patients treated with CSF1R inhibitors, which are known to reduce Kupffer cells in the liver as part of the mechanism of action. None of the changes met Hy's Law criteria and there was no evidence of cholestatic hepatotoxicity, skeletal muscle injury, or other organ damage.

Decreased neutrophils were observed with vimseltinib treatment during double-blind period of MOTION but were not associated with symptoms.

The FDA's Assessment:

In general, the most clinically important laboratory abnormalities appear to be increases in liver enzymes, which occurred without associated elevations in bilirubin, as shown in lab shift table, Table 50. Overall, the worsening in baseline of AST or ALT elevation (92% and 24%, respectively) in patients treated with vimseltinib was higher than in patients treated with placebo (10% and 15%, respectively). No patients experienced a Grade 3 or higher elevation in AST or ALT in the vimseltinib arm. Refer to Section 8.2.5 for further discussion and overall conclusions regarding hepatotoxicity risk with vimseltinib.

The Applicant initially did not include magnesium increased, calcium decreased, or leukocyte decreased in the initial proposed label; however, during the review team’s assessment, these additional laboratory abnormalities were noted to occur at an incidence $\geq 10\%$ of patients and were added to the label in agreement by the Applicant.

Table 50 FDA: Laboratory Abnormalities Worsening from Baseline in $\geq 10\%$ of Patients Receiving ROMVIMZA with a Difference Between Arms of $>5\%$ Compared to Placebo Through Week 25 in MOTION

Laboratory Abnormality ^a	Vimseltinib N=83		Placebo N=38	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
AST increased	92	0	11	0
Cholesterol increased	43	0	16	0
ALT increased	24	0	16	0
Creatinine increased	17	0	2.6	0
ALP increased	14	0	8	0
Magnesium increased	13	1.2	2.6	0
Calcium decreased	13	0	2.6	0
Hematology				
Neutrophils decreased	31	1.2	2.6	0
Leukocytes decreased	29	0	8	0
AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase ^a The severity of adverse drug reactions was assessed using CTCAE v5.0 Source: USPI for vimseltinib				

In addition, the Applicant proposed adding information regarding increased CPK

(b) (4)

Data from DCC-3014-01-001 systematically collected CPK labs, as opposed to MOTION, which did not collect baseline CPK for patients and thus there were limited data on elevations in CPK in MOTION. In the supportive trial DCC-3014-01-001, 135 patients were included in the safety population. A total of 130 patients (96%) in this study developed CPK elevation, and 3 patients (2.2%) developed myalgia within 5 days of the worst CPK elevation and 19 patients (14%) developed myalgia within 5 days of any CPK elevation. There were no cases of rhabdomyolysis.

To further assess CPK elevation, FDA sent an information request regarding CPK data, including incidence of sequelae, such as myalgia, rhabdomyolysis, as well as detailed information on de-challenge/re-challenge in patients who experienced elevated CPK on January 7, 2025, and the Applicant responded on January 8, 2025. The Applicant provided CPK results

for Pool 3, which included all patients treated on vimseltinib at any dose. A total of 104 patients (41%) in Pool 3 experienced an AE of CPK elevation of any Grade, 32 patients had a dose interruption, and 0 patients withdrew treatment due to CPK increased. Although there were several cases of myalgia, there were no cases of rhabdomyolysis.

Ultimately, while the elevations in CPK did not appear to be clinically significant and (b) (4) the review team included a statement as mentioned about these elevations in Section 6 for awareness that this laboratory abnormality could be associated with vimseltinib treatment.

Vital Signs

Data:

In Pool 1, the mean (STD) baseline systolic and diastolic blood pressures for all participants were 123.9 (13.01) and 75.3 (9.38) mmHg, respectively. A total of 38.6% (71/184) of participants experienced no shift in post-baseline systolic blood pressure (BP) during treatment, and 10.9% (20/184) of participants experienced a maximum shift in systolic BP from baseline from <140 to ≥160 mmHg. A total of 46.2% (85/184) of participants experienced no shift in post-baseline diastolic BP, and 6.5% (12/184) of participants experienced a maximum shift in diastolic BP from baseline from <90 to ≥100 mmHg.

Results for Pool 3 were similar.

No other clinically meaningful changes from baseline in vital sign measurements were observed.

The Applicant's Position:

Hypertension was identified as an adverse drug reaction of vimseltinib. Hypertension can be managed in clinical practice and is not an important safety concern for vimseltinib. No other clinically meaningful changes from baseline in vital sign measurements were observed.

The FDA's Assessment:

FDA agrees with Applicant's assessment. Median baseline systolic blood pressure for the 83 patients who received vimseltinib was 124.1 (range: 100, 180) and the mean change from baseline at week 25 was +5.9 (range: -16, +36). Median diastolic blood pressure for the 83 patients who received vimseltinib was 76 (range: 51, 96) and the mean change from baseline at week 25 was +5 (range: -17, +24).

Electrocardiograms (ECGs)

Data:

During the double-blind period in MOTION, 1 participant in the vimseltinib arm had post-baseline QTcF >450 ms, and 13 (15.9%) participants had QTcF increase from baseline >30 ms.

None of the worst post-baseline ECG changes in the vimseltinib arm was interpreted as clinically significant.

In Pool 1, 15.4% (28/184) of participants experienced a QTcF increase from baseline >30 ms and 1.1% (2/184) of participants experienced a QTcF increase from baseline >60 ms.

In Pool 3, 14.9% (36/253) of participants experienced a QTcF increase from baseline >30 ms and 1.2% (3/253) of participants experienced a QTcF increase from baseline >60 ms.

No participant experienced QTcF prolongation >500 ms and only 3 participants experienced QTcF prolongation above the baseline >60 ms.

No participant experienced QTcF prolongation on multiple occasions. No observation was considered clinically significant, and none led to dose modification or treatment discontinuation.

The Applicant's Position:

Vimseltinib administration was not associated with clinically significant postbaseline changes in ECG parameters.

Based on the integrated analysis, vimseltinib did not appear to have an effect on the QTcF interval.

The FDA's Assessment:

FDA agrees with the Applicant's assessment. One patient each in the placebo and vimseltinib arms experienced a post-baseline QTcF of >450 ms. In the vimseltinib arm, 13 patients (16%) experienced a QTcF increase of >30 ms. In the placebo arm, 7 patients (18%) experienced a QTcF increase of >30 ms. These were not assessed as clinically relevant.

QT

Data:

A concentration QTc modeling analysis was performed based on the data from participants with MST in the Phase 1/2 study and healthy participants from Study DCC-3014-01-002 (who are physiologically similar to participants with TGCT). The results from the cardiodynamic evaluation of the 40 mg and 50 mg doses demonstrated that vimseltinib has no clinically relevant effect on heart rate or on cardiac conduction (the PR and QRS intervals). There was no clinically meaningful effect on the QTc interval, and an effect on $\Delta\Delta\text{QTcF}$ exceeding 10 ms can be excluded within the observed ranges of plasma concentrations of vimseltinib, up to 1774 ng/mL.

The Applicant's Position:

At exposures exceeding 2 times the mean maximum exposure of the recommended dosage, vimseltinib does not prolong the QTc interval to any clinically relevant extent.

The FDA's Assessment:

FDA review by the QT-IRT team determined that at the maximum recommended dose of vimseltinib, clinically significant QTc interval prolongation was not observed.

Immunogenicity

The Applicant's Position:

Not applicable to this submission.

The FDA's Assessment:

FDA agrees.

8.2.5. Analysis of Submission-Specific Safety Issues

The Applicant's Position:

Adverse drug reactions and laboratory abnormalities are discussed above. No additional submission-specific safety issues have been identified.

The FDA's Assessment:

As previously mentioned, worsening in baseline of AST or ALT elevation (92% and 24%, respectively) in patients treated with vimseltinib was higher than in patients treated with placebo (10% and 15%, respectively) however no patients experienced a Grade 3 or higher elevation in AST or ALT in the vimseltinib arm and there were no bilirubin elevations, Hy's Law cases or other signs of severe liver toxicity in the submitted safety datasets for MOTION.

Nonetheless, the risk of hepatotoxicity or liver injury was identified as serious risk during the development of pexidartinib which shares the same target; CSFR1. Pexidartinib was the first CSFR1 targeting inhibitor that was FDA-approved for systemic use in patients with TGCT. Pexidartinib was approved based on the clinical trial ENLIVEN, which treated 61 patients, and a total of 768 patients received pexidartinib during all clinical trials for which data was available at the time of pexidartinib approval.

To enroll on ENLIVEN, patients were required to have total bilirubin and AST/ALT ≤ 1.5 times the upper limit of normal (ULN). In ENLIVEN, serum transaminase elevations occurred in a majority of patients; elevations in ALT and AST occurred in 67% and 90% of patients, respectively; bilirubin increases occurred in 12% of patients. Grade 3 or higher elevations in ALT and AST occurred in 20% and 12% of patients, respectively. Grade 3 or higher bilirubin elevation occurred in 3.3%. Concerningly, approximately 5% of patients in the ENLIVEN trial experienced a pattern of serum transaminase and bilirubin elevation indicative of severe liver injury, characterized by AST or ALT greater than 3 times the ULN with concurrent bilirubin increases greater than 2 times the ULN.

Among the 768 patients in clinical trials, there were two cases of irreversible cholestatic liver injury; one patient with advanced cancer and ongoing liver toxicity died and one patient with a confirmed case of VBDS required a liver transplant. The review team thus instituted a boxed warning in product labeling for pexidartinib regarding serious and potentially fatal liver injury, and pexidartinib was made available only via the risk evaluation and mitigation (REMS) program with an Elements to Assure Safe Use (ETASU). The REMS program (n=609) revealed similar numbers observed of serious liver injury, with 32 patients (5.3%) developing liver toxicity within 71 days of the first dose of pexidartinib; ten required hospitalization, and two developing VBDS.

Because of the known risk of hepatotoxicity with pexidartinib as described above, FDA reviewed vimseltinib’s NDA carefully for evidence of similar toxicity and evaluated the possible need for a REMS and/or a boxed warning in product labeling. The evaluation of hepatotoxicity for vimseltinib was primarily based on MOTION but also includes data collected from DCC-3014-01-001 and is described below.

Hepatotoxicity in MOTION

In the original protocol for MOTION, the risk of hepatotoxicity was mitigated with selection of patients without baseline liver toxicity, laboratory and clinical monitoring for liver toxicity, dosage interruptions and management guidelines for hepatobiliary laboratory abnormalities.

Patients treated on MOTION had AST, ALT and bilirubin assessed prior to treatment initiation, and then at day 1 and 15 of the first cycle, and the first day of each 28-day cycle thereafter. Patients treated on ENLIVEN, the pivotal study of pexidartinib, had a similar evaluation schedule, with ALT, AST and bilirubin assessed prior to initiation of treatment, weekly during cycle 1, and then once per 28-day cycle thereafter. It is unlikely that clinically significant LFT elevation events would have been missed in MOTION, as the monitoring schedule was fairly rigorous.

Table 51 lists all observed cases of laboratory abnormalities related to liver function in patients enrolled in MOTION. While AST and ALT elevations from baseline were common, almost all were Grade 1 in severity with only 3.6% experiencing Grade 2 events of AST increase, and no Grade 3 or higher events observed in any patients. There were no dose reductions or discontinuations due to liver function elevations and no SAEs related to hepatotoxicity.

Table 51 FDA-Laboratory Values Related to Liver Function Worsening from Baseline in ≥10% of Patients Receiving Vimseltinib, MOTION

Laboratory Abnormality ^a	Vimseltinib N=83				Placebo N=39			
	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 or 4 (%)
AST increased	92	88	3.6	0	11	11	0	0

Laboratory Abnormality ^a	Vimseltinib N=83				Placebo N=39			
	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 or 4 (%)
ALT increased	24	24	0	0	16	16	0	0
ALP increased	14	14	0	0	8	8	0	0
Bilirubin increased	1.2	1.2	0	0	0	0	0	0

AST – aspartate aminotransferase, ALT – alanine aminotransferase, ALP – alkaline phosphatase

^a The severity of adverse drug reactions was assessed using CTCAE v5.0

Source: Reviewer generated table: ADLB, CSR

Table 52 displays adverse events that may be associated with liver toxicity from MOTION.

Table 52 FDA- Liver Enzyme Summary, MOTION

	Vimseltinib N=83 n (%)	Placebo N=40 n (%)
SAEs due to elevated liver enzymes	0	0
Discontinuation due to elevated liver enzymes	0	0
Dose reduction due to elevated liver enzymes	0	0
Dose interruptions due to elevated liver enzymes	1 (1.2)	2 (5)
Deaths due to elevated liver enzymes	0	0

Source: FDA generated table: ADAE, CSR

Hepatotoxicity in the overall clinical development program (Pool 3)

Additional analyses that include all 253 patients in Pool 3 are summarized below. This pool includes patients with solid tumors who may have had liver metastases and elevated liver chemistries at baseline. Overall, despite more liberal inclusion criteria in the broader database, very few Grade 3 events of AST elevation (2.4%) or ALT elevation (0.8%) were observed, with no Grade 3 bilirubin elevation and no Hy's Law cases.

Table 53 FDA-Laboratory Values Related to Liver Function Worsening from Baseline in ≥10% of Patients Receiving Vimseltinib, Pool 3

Laboratory Abnormality	Vimseltinib N=253				
	All Grades (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
AST increased	92	82	47.1	2.4	0
ALT increased	32	27	43.6	0.8	0
ALP increased	19	16	21.6	0.8	0
Bilirubin increased	2.0	1.6	0.4	0	0

Source: FDA generated table

In terms of timing and resolution of observed transaminase elevations, the median time to initial increase in AST/ALT was 2.1 weeks (range: 1.0-72.3) and 4.1 weeks (range 1.0, 151.6), respectively. Median time to initial increase in bilirubin was 16.1 (range 1.0-126.3) weeks. These data point to early onset of these mild transaminase increases, with median time to onset occurring within the first cycle of study drug. In Pool 3 (n=253), 26 patients had Grade ≥ 2 AST or ALT elevations. Of these, 21 patients returned to Grade 1 or baseline. Of the 5 remaining patients that did not return to Grade 1 or baseline, the elevations did not worsen beyond Grade 2. The median time to resolution to Grade 1 or baseline for Grade ≥ 2 ALT or AST elevation was 3.3 weeks.

In terms of reported management of these LFT elevations, among the 37 patients in Pool 3 with a reported AE of ALT increased, 2 patients experienced a dose modification (interruption and/or dose reduction) and none withdrew treatment due to ALT increased. Among the 66 patients in Pool 3 with a reported AE of AST increased, 9 experienced a dose modification and 1 withdrew treatment due to AST increased. There were only 2 patients with AEs of blood bilirubin increased, which did not lead to a dose modification or discontinuation. Among the 10 patients with dose interruptions due to an AE of ALT/AST increased, 9 were rechallenged, with 5 patients experiencing recurrent AEs of ALT/AST increased of the same or lower grade (positive rechallenge).

Review of the overall safety database was generally concordant with the data from patients treated in MOTION and did not raise concern that clinically significant hepatotoxicity had occurred across the larger development program, despite inclusion of some patients with liver metastases and/ or mildly elevated liver chemistries at baseline.

Overall Assessment

Given the relatively limited number of patients treated with vimseltinib and the known severe, irreversible liver toxicity observed with pexidartinib, FDA considered the need for a boxed warning or REMS program to ensure the safe use of vimseltinib. The primary review team discussed the safety findings and need for a REMS or boxed warning informally with FDA's Division of Risk Management (DRM), the Office of Oncologic Diseases (OOD) safety team, and the labeling team during the course of the evaluation of liver toxicity.

After extensive multidisciplinary discussions, review of nonclinical findings, presented safety data, and other literature, the review team determined that there is no current evidence of severe hepatotoxicity in patients treated with vimseltinib. Unlike in the pexidartinib development program, for patients treated with vimseltinib, there were no cases of Grade 3 or higher elevations in AST or ALT on MOTION, no cases of Hy's law or DILI, no patients required discontinuation of treatment due to elevated AST/ALT and no patients developed symptomatic liver toxicity. A total of 253 patients were treated with vimseltinib and there were no reported cases of liver injury. ENLIVEN, the registrational trial for pexidartinib, exhibited much more

concerning evidence for hepatotoxicity, for example with Grade 3 or higher elevations in ALT in 20% for patients and Hy's Law cases in 5% of patients. If vimseltinib was truly associated with concerning hepatotoxicity to the same extent, a similar percentage of patients would likely have exhibited evidence of hepatotoxicity in MOTION. In contrast, there were no Grade 3 elevations or HY's Law cases in MOTION, which is reassuring regarding the likely absence of severe risk for hepatotoxicity with vimseltinib.

In discussion regarding the use of a boxed warning, the review team did not find evidence to suggest that there was a risk of serious, fatal, or life-threatening consequences that would require alerting patients and providers in an enhanced manner. Regarding a discussion of the need for a REMS, given the low-grade events, the review team did not feel that patient selection, careful monitoring, avoiding, certain concomitant therapy, addition of another drug or managing patients in a manner, or avoiding use in a specific clinical situation was required for administration of vimseltinib. Although class labeling could be considered based on the known risk of pexidartinib, the safety signal for hepatotoxicity was much higher and more severe with the available clinical trial data on pexidartinib at the time of approval action compared with the data available at the time of approval for vimseltinib.

The Applicant did not originally propose to include any mention of hepatotoxicity in product labeling for vimseltinib. To further clarify the Applicant's stance, FDA sent an information request to the Applicant on October 24, 2025, requesting additional information to support the Applicant's position that hepatotoxicity with pexidartinib does not reflect a class effect and that no labelled warning was required for safe use of vimseltinib. The Applicant provided review of published literature that suggested that the molecular structure of pexidartinib undergoes extensive metabolism involving the formation of reactive intermediates with potential to modify biological macromolecules. The Applicant argued that formation of such reactive species has previously been associated with drug induced liver injury (DILI) and overt hepatotoxicity in humans across a range of chemotypes and pharmacological mechanisms unrelated to CSF1R inhibition. The mechanism of hepatotoxicity may be related to metabolism of the pyrrole ring of pexidartinib by CYP3A-mediated oxidation, which is not generalizable to all CSF1R inhibitors and non-clinical data via published literature suggested that pexidartinib-induced hepatotoxicity may be due to mitochondrial injury. The Applicant thus argued that this mechanism of hepatotoxicity was specific to pexidartinib and was not relevant to vimseltinib. While the FDA review team, including nonclinical pharmacology/ toxicology, reviewed the referenced literature and thought that the argument advanced by the Applicant might be plausible, the team concluded that the risk of hepatotoxicity related to agents targeting CSF1R could not be fully ruled out based on clinical and non-clinical data (See Section 5).

Given that there is some degree of residual uncertainty of the potential for hepatotoxicity based on the reviewed vimseltinib data given its relatively small safety database, enrollment of patients with no baseline hepatic liver abnormalities or disease on MOTION, observed low-grade LFT elevations in the majority of patients, and unclear definitive mechanism of hepatotoxicity with the CSF1R inhibitor pexidartinib, the review team determined that a Warnings and Precautions

for hepatotoxicity was warranted. Within the warning, the review team included a statement to avoid use of vimseltinib in patients with pre-existing increased serum transaminases, total bilirubin or direct bilirubin (>ULN), or active liver or biliary tract disease, including ALP. This is consistent with inclusion criteria for MOTION. In addition, the review team added recommended monitoring for LFTs to product labeling, including AST, ALT, total bilirubin, direct bilirubin, ALP and gamma-glutamyl transferase (GGT), prior to initiation of vimseltinib, twice a month for the first two months and once every 3 months for the first year of therapy and as clinically indicated thereafter. This schedule was instituted accounting for the observation that toxicity generally occurs early in the administration of pexidartinib, with most (96%) of cases of pexidartinib-induced liver injury occurring in the first two months of administration, thus presumably any cases of liver injury occurring with vimseltinib would be accounted for with the recommended schedule. The review team also added a table of recommended dose modifications for vimseltinib in cases of elevated AST, ALT, bilirubin, INR, or ALP.

To further assess the potential risk for hepatotoxicity, a PMR (see section 13) was issued that will include a patient registry to provide additional information to further characterize the risk of hepatotoxicity in the indicated population outside of the clinical trial setting and to elucidate the potential long-term risk of liver injury associated with vimseltinib treatment. In addition, an enhanced pharmacovigilance program will be instituted to capture patients who may not be included in the PMR registry.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

COAs are discussed in Section 8.1.2 and Section 8.1.4.

The FDA's Assessment:

See FDA's assessment in Section 8.1.2 and Section 8.1.4.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Intrinsic factors

Subgroup analyses of TEAEs and SAEs by age, sex, and race were performed for each analysis pool in the integrated analysis of the MOTION and Phase 1/2 studies. Overall, the results observed for subgroup analysis were similar to the overall safety results observed for each analysis pool. No major differences were observed by age, sex, or race.

Extrinsic factors

Subgroup analyses of TEAEs and SAEs by geographic region and prior systemic therapy were performed for each analysis pool in the integrated analysis of the MOTION and Phase 1/2 studies. Overall, the results observed for subgroup analysis were similar to the overall safety results observed for each analysis pool. No major differences were observed by geographic region or prior systemic therapy.

The FDA's Assessment:

In MOTION, there were too few patients in demographics subgroups to assess whether clinically meaningful differences in safety exist.

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

No studies have been conducted with vimseltinib specifically to address safety concerns.

The FDA's Assessment:

FDA agrees with this statement.

8.2.9. FDA agrees with applicant's assessment. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

No human carcinogenicity studies have been conducted with vimseltinib.

The FDA's Assessment:

FDA agrees with this statement.

Human Reproduction and Pregnancy

Data:

No clinical studies have been performed to assess use of vimseltinib during pregnancy or lactation.

In animals, malformations of the cardiovascular and skeletal systems along with additional indications of developmental perturbation, including structural anatomic variations and indications of developmental delay, occurred at 15 mg/kg/day (~20 times the exposure at the recommended human dose). There were no adverse findings in the pregnant animals and the maternal NOAEL (no adverse effect level) was 15 mg/kg/day, the highest dose evaluated. Due to the adverse malformations in the fetuses at 15 mg/kg/day, the developmental NOAEL was 5 mg/kg/day.

One pregnancy was reported in the Phase 1/2 study. One additional pregnancy was reported in a female partner of a male participant in the open-label period in MOTION. No evidence of birth

defects was noted in prenatal testing, and a healthy male newborn was delivered via cesarian section.

The Applicant's Position:

Pregnant women should be advised of the potential risk to the fetus.

Women should be advised not to breastfeed during treatment with vimseltinib.

Women of reproductive potential should be advised to use effective contraception during treatment with vimseltinib and for (b) (4) days after the final dose.

The FDA's Assessment:

FDA agrees that women of childbearing potential should be advised to use effective contraception during treatment and for at least (b) (4) days after the final dose due to the potential risk to the fetus and that women should be advised not to breastfeed during treatment.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

Vimseltinib has not been assessed in pediatric studies. See Section 10.

The FDA's Assessment:

FDA agrees with this statement and there is no current plan to study vimseltinib in pediatric patients. The pediatric section of product labeling will contain a statement that the safety and effectiveness of vimseltinib have not been established in pediatric patients. Refer to non-clinical Section 5 for discussion regarding potential risks of vimseltinib in skeletally immature patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Based on the mechanism of action, drug abuse, withdrawal, or rebound effects are not anticipated with vimseltinib. There have been no cases of treatment overdose reported in any clinical study of vimseltinib. Treatment of overdose consists of observation and general supportive measures.

The FDA's Assessment:

FDA agrees with this statement.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable. Vimseltinib has not been marketed in any country.

The FDA's Assessment:

FDA agrees with this statement.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Very common and common toxicities appear to have been adequately represented in the studies with vimseltinib. Potential safety concerns with uncommon or rare occurrence may be detected during the postmarketing period. Routine pharmacovigilance will be conducted to monitor for these adverse events.

The FDA's Assessment:

FDA does not agree. Because uncertainty exists with respect to hepatotoxicity, a postmarketing requirement will be issued to assess the potential risk of severe hepatotoxicity. (See Section 13). An enhanced pharmacovigilance plan to collect data on events in the postmarketing setting for patients not captured in the registry was instituted.

8.2.11. Integrated Assessment of Safety

Data:

A total of 253 participants constituted the vimseltinib safety database from the MOTION and Phase 1/2 studies, of whom 216 were participants with TGCT. The safety profile of participants with TGCT enrolled in the Phase 1/2 study were similar to those enrolled in MOTION.

In Pool 1 of the integrated analysis (184 participants), the mean (STD) duration of exposure to vimseltinib was 14.5 months (9.28).

Most participants (99.5%) reported at least 1 TEAE. The most frequently reported ($\geq 25\%$ of participants) TEAEs in participants receiving vimseltinib were periorbital edema (45.4%), blood CPK increased (42.6%), and headache (33.9%). Of these, most were low grade in severity, nonserious, and considered drug-related.

The most frequently reported Grade 3/4 TEAEs were blood CPK increased (23.5%), hypertension (8.7%), and pruritus (2.7%).

Serious AEs were reported in 18.0% of participants. The most frequently reported SAEs were cellulitis (2.7%) and fall (1.1%). Most SAEs were considered unrelated to vimseltinib, and no related SAEs were experienced by >1 participant.

Treatment-emergent AEs leading to dose modification (reduction or interruption) were reported in 74.3% of participants. The most frequently reported TEAEs leading to dose modification were blood CPK increased (16.9%), periorbital edema (13.7%), asthenia (12.0%), pruritus (9.8%), rash maculo-papular (9.3%), and COVID19 (8.2%).

Treatment-emergent AEs leading to treatment discontinuation were reported in 9.3% of participants. The most frequently reported TEAEs leading to treatment discontinuation were rash and periorbital edema (each reported in 1.6% of participants).

Review of all TEAEs occurring in Years 2 through 4 did not reveal an increased incidence of events typically occurring with long latency. No new or worsening cardiovascular toxicities, secondary malignancies, renal or hepatic toxicities, or other clinically significant AEs were observed with long-term vimseltinib exposure.

No drug-related events leading to death occurred in the entire safety population.

Serum enzyme elevations including ALT, AST, ALP, and CPK were observed. None of the changes met Hy's Law criteria and there was no evidence of cholestatic hepatotoxicity, skeletal muscle injury, or other organ damage.

Decreased neutrophils were observed but were not associated with symptoms.

Overall, vimseltinib was generally safe with a manageable AE profile in participants with TGCT.

The Applicant's Position:

The evaluation of the safety data from participants with TGCT who received vimseltinib treatment at the recommended dose of 30 mg twice weekly in MOTION and Phase 1/2 demonstrated an acceptable safety profile.

Most of the TEAEs observed were nonserious, Grade 1 or Grade 2 in severity, and manageable in clinical practice.

The FDA's Assessment:

In general, FDA agrees with Applicant's assessment. FDA reviewed the following:

- 83 patients who received vimseltinib in MOTION at the proposed dose.
- 218 patients who were treated in clinical studies, including the 83 patients in MOTION and included 135 in DCC-2013-01-001, and
- 253 patients including the 218 above and 35 patients who received vimseltinib in the open-label period.

FDA specifically reviewed data regarding hepatotoxicity and noted no cases of Hy's law in this

safety population. Refer to section 5.1 of product labeling for additional information. In review of the 253 patients who received vimseltinib (Pool 3) no additional safety findings, signals or serious adverse reaction were identified.

Patients treated on MOTION had AST, ALT and bilirubin assessed prior to treatment initiation, and then at day 1 and 15 of the first cycle, and the first day of each 28-day cycle thereafter. Patients treated on ENLIVEN, the pivotal study of pexidartinib for treatment of TGCT, had ALT, AST and bilirubin assessed prior to initiation of treatment, weekly during cycle 1, and then once per 28-day cycle thereafter.

Treatment with vimseltinib resulted in frequent AST and ALT elevations, without Hy's law or evidence of other liver dysfunction, and after extensive multidisciplinary review of the safety data, nonclinical findings and literature, it is FDA's opinion that there is no evidence to date of severe hepatotoxicity in patients treated with vimseltinib. However, post-marketing monitoring will be required, given the small sample size treated.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

The MOTION trial demonstrated a statistically significant improvement in ORR, BPI-30 response rates, mean change from baseline to Week 25 in active ROM, and PROMIS-PF. The robustness of results was established based on extensive sensitivity analysis corresponding to each of these endpoints as presented in the "Study results" section of this review.

The results of the key secondary endpoint of ORR at Week 25 per TVS was statistically significant; however, this endpoint has not been validated as a surrogate for any of the established endpoints for clinical benefit claims in oncology, and therefore FDA considers ORR by TVS as supportive.

FDA concludes that MOTION demonstrated a statistically significant improvement in ROM for vimseltinib compared to placebo. The magnitude of improvement (difference in LS means) from baseline for patients on the vimseltinib arm compared to placebo arm was estimated to be 14.6% (4.0, 25.3). Although a treatment benefit was demonstrated for ROM, interpretation of the effect is unclear due to limited information on clinical meaningfulness for the target patient population in study MOTION. Based on the exploratory responder analysis using Applicant's proposed clinically meaningful threshold of 10%, there appears to be clinical benefit of vimseltinib on active ROM because more patients in the vimseltinib arm (48%) had a clinically meaningful improvement in ROM in the affected joints compared to the placebo arm (20%).

The results for 15-item PROMIS-PF in vimseltinib arm were statistically significant compared to placebo arm (Difference in LS means for change from baseline to Week 25: 3.3 [95% CI: 1.4, 5.2]). Due to limited information provided by the Applicant for evaluation of proposed clinical meaningful change, a definitive conclusion regarding the clinically meaningful difference cannot be made. However, based on FDA's assessment, a plausible clinical meaningful change may range from 3 to 7-points, and the observed effect of 3.3 points was covered by the range.

BPI-30 response rate was significantly different between the arms. Additional sensitivity analyses were performed to assess the robustness of the observed results and also beyond the Applicant specified definition. The sensitivity analyses support the primary analyses results and concludes that there is a substantial improvement(decrease) in the pain experienced by the patients treated with vimseltinib when compared to placebo.

Results from the Worst Stiffness NRS and EQ-VAS are not considered as part of improvement in quality-of-life assessments.

8.4. Conclusions and Recommendations

The FDA's Assessment:

Based on the totality of evidence, the multidisciplinary review teams recommend granting regular approval of vimseltinib 30 mg BIW for the treatment of adult patients with symptomatic TGCT for which surgical resection will potentially cause worsening functional limitation or severe morbidity.

The Applicant submitted substantial evidence of safety and effectiveness from the pivotal MOTION Study to support approval. MOTION demonstrated that vimseltinib provided clinically meaningful and statistically significant improvement in ORR. The ORR was also statistically different between the two arms with 40% (95% CI: 29, 51) and 0% (95% CI: 0, 9) in the vimseltinib, and placebo arms, respectively. The responses were durable with a median duration that was NR in the vimseltinib arm with a range from 2.5+ to 19.4+ months. Of the 33 patients who treated with vimseltinib who experienced an objective response, duration of response was ≥ 6 months for 85% of patients and ≥ 9 months for 58%. These results were further supported by improvements in ROM and clinical outcome assessment data of patient-reported pain, and patient-reported physical functioning data.

In general, the safety findings were consistent with the known adverse reactions commonly seen with the use of other CSFR1 inhibitors. The reviewer did not find evidence of severe or life-threatening hepatotoxicity with the use of vimseltinib at the proposed dose in an overall small sample size. Low-Grade elevation of AST and/or ALT were noted without a concurrent increase in bilirubin. There were no deaths, or cases of Hy's law or DILI. A Warnings and Precautions and dose modifications for hepatotoxicity were added to the USPI for vimseltinib. A PMR and enhanced pharmacovigilance plane for further assessment of hepatotoxicity were issued.

8.4.1. Approach to Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (*enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response*):

ROMVIMZA is a kinase inhibitor indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity.

2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)
 - a. Adequate and well-controlled clinical investigation(s):

- i. ☐ Two or more adequate and well-controlled clinical investigations, **OR**

- ii. ☒ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

- c. ☐ Evidence that supported SEE from a prior approval (*e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch*)²

3. Complete response, if applicable

- a. ☒ SEE was established
b. ☐ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)]

X

X

Sirisha Mushti
Primary Statistical Reviewer

Chi Song
Statistical Team Leader

X

X

Jennifer Stundon

Primary Clinical Reviewer

Leslie Doros

Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

No advisory committee meeting was held for this application.

10 Pediatrics

The Applicant's Position:

On 12 March 2021, the Sponsor submitted an iPSP requesting a full drug-specific waiver for vimseltinib for the treatment of symptomatic TGCT not amendable to surgery for all pediatric age groups (0 < ^(b)₍₄₎ years) on the basis that clinical studies would be impossible or highly impracticable to conduct in the pediatric population. On 16 July 2021, FDA issued an Agreed iPSP Agreement letter for a full waiver for vimseltinib in all subsets of the pediatric population.

The FDA's Assessment:

FDA agrees that a full waiver for vimseltinib in the pediatric population is appropriate.

11 Labeling Recommendations

Data:

The Applicant's Position: This is an original application. The proposed labeling is included in the NDA, Module 1.14.

Not applicable.

The FDA's Assessment:

The format, language, and content of the proposed labeling was evaluated and revised for consistency with 21 Code of Federal Regulations (CFR), labeling guidances and current labeling practices of the Office of Oncologic Diseases. The table below summarizes key changes.

(b) (4)

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

Pexidartinib was approved by the FDA for patients with TGCT associated with severe morbidity or functional limitations and not amenable to surgery. However, in the pivotal study to support approval, ENLIVEN, 3 of 61 (5%) patients who received pexidartinib developed signs of serious liver injury. Hepatotoxicity including liver failure and life-threatening vanishing bile duct syndrome (VBDS), ductopenia, and symptomatic cholestasis can occur and can occur despite monitoring and prompt drug cessation. Thus, pexidartinib has a boxed warning for hepatotoxicity and a REMS mitigate the risk of serious and potentially fatal liver injury. Given the important identified risk of severe hepatotoxicity observed with the use of pexidartinib, the review team performed a comprehensive analysis of the risk of hepatotoxicity for vimseltinib. The review team considered the need for a REMS based on a class effect and the identified risk for hepatotoxicity with use of pexidartinib. However, the safety data from the 253 patients who received at least one dose of vimseltinib in MOTION or the supportive study, DCC-3014-01-001, did not identify a risk of serious or significant hepatotoxicity that would require a REMS. While transient AST and ALT elevations were common in MOTION, there were no cases of bilirubin elevation and no cases of Hy's law.

The safe use of vimseltinib can be adequately implemented in the postmarketing setting without issuing a REMS for this drug product. The product labeling for vimseltinib includes information on common and clinically significant adverse reactions that have been observed across the drug class including hepatotoxicity, and trained oncologists have experience in the monitoring and management of these adverse reactions. Product labeling also includes dose modification and management guidelines any events as well as specific guidelines for hepatotoxicity. Risk management based on labeling, routine pharmacovigilance, and a PMR for hepatotoxicity is expected to ensure the safe use of vimseltinib.

13 Postmarketing Requirements and Commitment

The FDA’s Assessment:

The following postmarketing requirement with milestone goal dates were issued to the Applicant.

Clinical

4791-2 Conduct a prospective clinical registry to evaluate the potential risk of serious hepatotoxicity in patients receiving vimseltinib for the treatment of tenosynovial giant cell tumor. Analyses should include evaluation of alanine aminotransferase, aspartate aminotransferase, bilirubin, symptoms suggestive of hepatotoxicity, and dose reduction and treatment discontinuation related to hepatotoxicity. Include investigations of time to event and severity, and potential risk factors such as age, race, and comorbidities. The registry should aim to enroll at least 100 patients. Monitor patients until discontinuation of study treatment or a minimum of 5 years from start of treatment, whichever occurs first. Interim safety analyses should be performed yearly beginning one year after the first patient has received vimseltinib to characterize the long-term risk of hepatotoxicity with vimseltinib.

Draft Protocol Submission:	06/2025
Final Protocol Submission:	10/2025
Interim Report Submission #1:	05/2026
Interim Report Submission #2:	05/2027
Interim Report Submission #3:	05/2028
Interim Report Submission #4:	05/2029
Interim Report Submission #5:	05/2030
Study Completion:	12/2030
Final Report Submission:	05/2031

Clinical Pharmacology

4791-3 Conduct a clinical pharmacokinetic trial to evaluate the serious potential risk of increased drug toxicity and determine an appropriate dose of vimseltinib to minimize potential serious toxicity, in patients with moderate hepatic impairment using the NCI-ODWG criteria. Design and conduct the trial in accordance with the FDA Guidance for Industry entitled “Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling.”

Draft Protocol Submission:	03/2025
Final Protocol Submission:	07/2025

Trial Completion: 07/2026
Final Report Submission: 02/2027

4791-4 Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of vimseltinib on the single dose pharmacokinetics of a sensitive BCRP substrate to evaluate the serious potential risk of increased drug toxicity. Design and conduct the trial in accordance with the ICH Harmonized Guidance entitled “M12 Drug Interaction Studies.”

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Trial Completion: 06/2026
Final Report Submission: 12/2026

4791-5 Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of vimseltinib on the single dose pharmacokinetics of sensitive OATP1B1 and OATP1B3 substrates to evaluate the serious potential risk of increased drug toxicity. Design and conduct the trial in accordance with the ICH Harmonized Guidance entitled “M12 Drug Interaction Studies.”

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Trial Completion: 06/2026
Final Report Submission: 12/2026

4791-6 Conduct a clinical pharmacokinetic trial to evaluate the effect of multiple doses of vimseltinib on the single dose pharmacokinetics of a sensitive OCT2 substrate to evaluate the serious potential risk of increased drug toxicity. Design and conduct the trial in accordance with the ICH Harmonized Guidance entitled “M12 Drug Interaction Studies.”

Draft Protocol Submission: 04/2025
Final Protocol Submission: 08/2025
Trial Completion: 06/2026
Final Report Submission: 12/2026

Nonclinical

4791-1 Complete the ongoing 104-week rat carcinogenicity study (Study No. DCC-3014-04-0025) to evaluate the potential for carcinogenicity.

Study Completion: 05/2025
Final Report Submission: 06/2025

FDA PMC/PMR Checklist for U.S. Population Representativeness

The following were evaluated and considered as part of FDA's review:		Is a PMC/PMR needed?
☐	The patients enrolled in the clinical trial are representative of the racial, ethnic, and age group of the U.S. population for the proposed indication.	☐ Yes ☒ No
☐	Does the FDA review indicate uncertainties in the safety and/or efficacy findings by demographic factors (e.g. race, ethnicity, sex, age, etc.) to warrant further investigation as part of a PMR/PMC?	☐ Yes ☒ No
☐	Other considerations (e.g.: PK/PD), if applicable:	☐ Yes ☒ No

14 Division Director (DHOT) (NME ONLY)

X

15 Division Director (OCP)

X

16 Division Director (OB)

X

17 Division Director (Clinical)

X

Chana Weinstock

18 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Paul Kluetz

19 Appendices

19.1. References

The Applicant's References:

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The FDA's References:

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19.2. Financial Disclosure

The Applicant's Position:

See Sections 8.1.2 and 8.1.4 for financial disclosure information.

Covered Clinical Study (Name and/or Number):* DCC-3014-01-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>255</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in study: Sponsor of covered study:		

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>250</u>		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

Covered Clinical Study (Name and/or Number):* DCC-3014-03-001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>261</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: Proprietary interest in the product tested held by investigator: Significant equity interest held by investigator in study: Sponsor of covered study:		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>256</u>		

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)
--	---	--

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

FDA reviewed the submitted financial agreement and notes that five investigators for the MOTION trial did not provide signed financial disclosures (see section 8.1.2). The Applicant made attempts to contact these investigators and independently reviewed internal records and confirmed there were no direct payments to these investigators.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

See Section 5.

The FDA's Assessment:

Findings from 13-week studies are similar to general toxicology findings described in Section 5.

Report Title: DCC-3014: A 13-Week Oral Gavage Toxicity and Toxicokinetic Study in Rats with a 4-Week Recovery Phase Study No. 8403647-1 (DCC-3014-004-0008)

Species/Strain: SPRAGUE-DAWLEY RAT **GLP Compliance:** Yes

10/sex/group for dosing phase

5/sex/group for recovery (except n=0 at low dose; n=4 high dose females)

Vehicle / Formulation: 0.4% (w/v) hydroxypropyl methylcellulose in reverse osmosis water

Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1.876	3.75	7.5	0	1.876	3.75	7.5
Alanine Aminotransferase (U/L)								
Day 92	45.9	+163	+240	+234	34.9	+201	+235	+252
Aspartate Aminotransferase (U/L)								
Day 92	97.7	+133	+186	+218	103.2	+180	+199	+201
Calcium (mg/dL)								
Day 92	10.67	-1	-10	-15	10.51	-2	-11	-14
Phosphate (mg/dL)								
Day 92	6.51	-22	-36	-44	5.57	-26	-38	-38
Activated Partial Thromboplastin Time (sec)								
Day 92	16.72	-9	-10	-12	14.95	-0	-4	-5
Hematocrit (%)								
Day 92	50.93	-5	-5	-8	47.18	-3	-9	-13
Hemoglobin (g/dL)								
Day 92	16.74	-4	-5	-8	15.90	-4	-10	-14
Neutrophils (10 ⁹ /L)								
Day 92	1.915	+108	+86	+65	0.631	+311	+442	+439
Platelets (10 ⁹ /L)								
Day 92	933.3	+14	+10	+28	1010.1	+17	+20	+30

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1.876	3.75	7.5	0	1.876	3.75	7.5
Erythrocytes (10 ¹² /L)								
Day 92	9.435	-1	-3	-11	8.449	-0	-11	-20
Reticulocytes (10 ⁹ /L)								
Day 92	219.55	-25	-26	-21	199.31	-22	-14	-14
KIDNEY to Body Weight Ratio (%)								
Day 92	0.58940	+1	-1	+3	0.59251	-1	+10	+14
Histopathology								
TERMINAL SACRIFICE / MORIBUND								
SACRIFICE								
BONE, FEMUR								
PHYSIS THICKNESS, INCREASED								
1 OF 5	0	0	3	0	0	0	0	0
2 OF 5	0	0	1	0	0	0	1	1
3 OF 5	0	0	4	10	0	0	9	10
EPIDIDYMIS								
DEGENERATION/NECROSIS								
1 OF 5	0	1	0	1	0	0	0	0
2 OF 5	0	0	2	2	0	0	0	0
3 OF 5	0	0	2	0	0	0	0	0
ESOPHAGUS								
EDEMA								
1 OF 5	0	6	7	8	0	9	7	6
EYELID, LEFT								
CRUST								
1 OF 5	0	0	0	0	0	0	0	1
HYPERPLASIA								
1 OF 5	1	0	0	4	0	0	0	3
2 OF 5	0	0	0	8	0	0	0	1
3 OF 5	0	0	0	2	0	0	0	0
HYPERTROPHY								
1 OF 5	0	0	0	3	0	0	1	1
2 OF 5	1	0	0	3	0	0	0	3
3 OF 5	1	0	0	4	0	0	0	0
INFILTRATE								
1 OF 5	0	0	0	1	0	0	0	0
INFLAMMATION								
3 OF 5	0	0	0	0	0	0	0	2
ULCER								
3 OF 5	0	0	0	0	0	0	0	2
EYELID, RIGHT								
CRUST								
2 OF 5	0	0	1	0	0	0	0	1
3 OF 5	0	0	0	0	0	0	0	1
HYPERPLASIA								
1 OF 5	0	0	2	3	0	0	0	3
2 OF 5	0	0	3	8	0	0	1	1
3 OF 5	0	0	0	1	0	0	0	0
HYPERTROPHY								
1 OF 5	0	0	2	0	0	0	1	3
2 OF 5	0	0	0	3	0	0	0	1
3 OF 5	0	0	0	4	0	0	0	0
INFILTRATE								

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ROMVIMZA (vimseltinib)

Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1.876	3.75	7.5	0	1.876	3.75	7.5
1 OF 5 INFLAMMATION	0	0	0	1	0	0	0	0
2 OF 5	0	0	1	0	0	0	0	1
3 OF 5	0	0	0	0	0	0	0	1
ULCER								
1 OF 5	0	0	0	0	0	0	0	1
GLAND, ADRENAL, Cortex DEGENERATION/NECROSIS								
1 OF 5	0	0	0	0	0	2	3	4
HYPERTROPHY								
1 OF 5	0	0	0	0	0	3	7	7
INFILTRATE								
1 OF 5	0	0	0	0	0	1	1	1
GLAND, LACRIMAL INFILTRATE								
2 OF 5	0	0	0	1	0	0	0	0
GLAND, PREPUTIAL INFLAMMATION								
3 OF 5	0	0	0	1	0	0	0	0
GLAND, PROSTATE DEGENERATION/NECROSIS								
1 OF 5	0	0	0	2	0	0	0	0
GUT-ASSOCIATED LYMPHOID TISSUE CELLULARITY, DECREASED								
1 OF 5	0	4	7	3	0	2	3	5
2 OF 5	0	0	1	7	0	0	2	3
HEART EDEMA								
1 OF 5	0	0	0	4	0	0	0	0
RODENT PROGRESSIVE CARDIOMYOPATHY								
1 OF 5	5	0	0	1	0	0	0	1
KIDNEY CAST								
1 OF 5	3	8	4	5	1	9	7	5
2 OF 5	3	1	4	5	0	0	2	4
3 OF 5	0	0	0	0	0	0	0	1
DEGENERATION								
1 OF 5	4	8	4	7	0	3	3	7
2 OF 5	1	1	1	3	0	0	2	1
3 OF 5	0	0	0	0	0	0	0	1
DEGENERATION/NECROSIS								
1 OF 5	0	0	0	0	0	0	1	0
INFILTRATE								
1 OF 5	0	1	0	0	0	0	0	0
3 OF 5	0	0	0	0	0	0	0	1
LARGE INTESTINE, CECUM EDEMA								
1 OF 5	0	0	1	2	0	2	3	3
INFILTRATE								
1 OF 5	0	0	0	0	0	0	0	1
LARGE INTESTINE, RECTUM DEGENERATION/NECROSIS								

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1.876	3.75	7.5	0	1.876	3.75	7.5
1 OF 5	0	1	2	0	0	0	0	1
2 OF 5	0	0	0	3	0	0	0	0
EROSION								
2 OF 5	0	0	0	1	0	0	0	0
INFLAMMATION								
2 OF 5	0	0	0	1	0	0	0	0
LIVER								
HYPERTROPHY								
1 OF 5	0	0	0	0	0	6	6	6
INFILTRATE								
1 OF 5	0	0	0	0	1	0	1	1
2 OF 5	0	0	0	0	0	0	0	1
NECROSIS								
1 OF 5	1	0	0	0	0	0	0	0
2 OF 5	0	0	0	0	0	0	0	1
LUNG								
INFILTRATE								
1 OF 5	2	0	0	1	0	0	0	2
LYMPH NODE, AXILLARY	0	0	0	0	0	0	0	2
CELLULARITY, INCREASED								
2 OF 5	0	0	0	0	0	0	0	1
3 OF 5	0	0	0	0	0	0	0	1
LYMPH NODE, INGUINAL								
CELLULARITY, INCREASED								
3 OF 5	0	0	0	0	0	0	1	1
LYMPH NODE, INGUINAL, LEFT								
CELLULARITY, INCREASED								
2 OF 5	0	0	0	1	0	0	0	1
LYMPH NODE, MANDIBULAR								
CELLULARITY, INCREASED								
1 OF 5	0	0	1	0	0	0	0	0
2 OF 5	0	7	4	1	0	8	6	3
3 OF 5	0	3	4	5	0	2	4	3
4 OF 5	0	0	1	4	0	0	0	5
LYMPH NODE, MESENTERIC								
CELLULARITY, INCREASED								
1 OF 5	2	8	5	4	3	10	8	2
2 OF 5	0	1	3	3	0	0	2	9
3 OF 5	0	0	0	2	0	0	0	0
PANCREAS								
DEGENERATION/NECROSIS								
1 OF 5	0	0	0	0	0	0	0	1
SKIN/SUBCUTIS								
CRUST								
3 OF 5	0	0	0	0	0	0	0	1
DEGENERATION/NECROSIS								
2 OF 5	0	0	1	0	0	0	0	0
3 OF 5	0	0	0	2	0	0	0	0
EDEMA								
2 OF 5	0	0	2	2	0	0	0	0
3 OF 5	0	0	0	1	0	0	0	1
HYPERPLASIA								
1 OF 5	0	0	0	0	0	0	0	1

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ROMVIMZA (vimseltinib)

Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1.876	3.75	7.5	0	1.876	3.75	7.5
INFLAMMATION								
1 OF 5	0	1	0	0	0	0	0	0
3 OF 5	0	0	0	1	0	0	0	2
ULCER								
3 OF 5	0	0	0	0	0	0	0	1
SPLEEN								
CELLULARITY, DECREASED								
1 OF 5	0	3	4	0	0	3	5	5
2 OF 5	0	0	0	7	0	0	3	1
3 OF 5	0	0	0	1	0	0	0	1
CONGESTION								
1 OF 5	1	3	2	6	0	3	6	6
2 OF 5	0	0	0	0	0	0	2	4
FIBROSIS								
1 OF 5	0	0	0	0	0	0	0	1
STOMACH, GLANDULAR								
DEGENERATION/NECROSIS								
1 OF 5	0	0	0	0	0	0	1	0
EROSION								
1 OF 5	0	0	1	0	0	0	0	0
2 OF 5	0	0	0	0	0	0	0	1
HEMORRHAGE								
1 OF 5	0	0	0	1	0	0	0	0
2 OF 5	0	0	0	1	0	0	0	0
INFILTRATE								
1 OF 5	0	0	0	1	0	0	0	2
2 OF 5	0	0	0	1	0	0	0	0
TESTIS								
DEGENERATION/ATROPHY								
1 OF 5	1	0	0	0	0	0	0	0
THYMUS								
APOPTOSIS								
1 OF 5	0	0	3	9	0	4	8	8
DEGENERATION/NECROSIS								
2 OF 5	0	0	0	2	0	0	0	0
Recovery Evaluation								
Clinical Pathology								
Hematocrit (%)								
Day 120	55.22	-	-3	-4	50.30	-	0	-1
Hemoglobin (g/dL)								
Day 120	16.74	-	-3	-4	15.96	-	-1	-2
Neutrophils (10 ⁹ /L)								
Day 120	1.922	-	+21	+59	0.766	-	+31	+21
Histopathology								
RECOVERY SACRIFICE								
BONE, FEMUR								
PHYSIS THICKNESS, INCREASED								
1 OF 5	0	0	2	4	0	0	4	2
2 OF 5	0	0	0	1	0	0	0	2
EPIDIDYMIS								
DEGENERATION/NECROSIS								
1 OF 5	0	0	0	1	0	0	0	0

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ROMVIMZA (vimseltinib)

Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	1.876	3.75	7.5	0	1.876	3.75	7.5
2 OF 5 SPERM GRANULOMA	0	0	0	1	0	0	0	0
3 OF 5 EYELID, LEFT CRUST	0	0	0	2	0	0	0	0
1 OF 5 GLAND, THYROID COLLOID, INCREASED	0	0	0	1	0	0	0	0
1 OF 5 HEART DEGENERATION/NECROSIS	0	0	2	2	0	0	3	3
2 OF 5 RODENT PROGRESSIVE CARDIOMYOPATHY	0	0	0	1	0	0	0	0
1 OF 5 KIDNEY CAST	1	0	0	0	0	0	0	0
1 OF 5 2 OF 5 DEGENERATION	3	0	0	5	2	0	0	3
1 OF 5 LARGE INTESTINE, RECTUM DEGENERATION/NECROSIS	1	0	0	0	0	0	0	0
2 OF 5 LYMPH NODE, MANDIBULAR CELLULARITY, INCREASED	3	0	0	4	3	0	0	3
1 OF 5 2 OF 5 LYMPH NODE, MESENTERIC CELLULARITY, INCREASED	0	0	0	1	0	0	0	0
1 OF 5 2 OF 5 LYMPH NODE, MESENTERIC CELLULARITY, INCREASED	0	0	2	1	0	0	1	3
2 OF 5 MUSCLE, BICEPS FEMORIS DEGENERATION/NECROSIS	0	0	3	4	0	0	4	1
1 OF 5 2 OF 5 PANCREAS DEGENERATION/NECROSIS	2	0	5	3	1	0	5	4
2 OF 5 2 OF 5 PANCREAS DEGENERATION/NECROSIS	0	0	0	2	0	0	0	0
2 OF 5 SPLEEN CONGESTION	0	0	0	1	0	0	0	0
1 OF 5 TESTIS DEGENERATION/ATROPHY	0	0	0	0	0	0	1	4
1 OF 5 TRACHEA DEGENERATION/NECROSIS	0	0	0	1	0	0	0	0
1 OF 5	0	0	0	1	0	0	0	0

Report Title: 13-Week Oral Gavage Toxicity and Toxicokinetic Study with DCC-3014 in Beagles with a 4-Week Recovery Phase Study No. 8403702 (DCC-3014-04-0007)

GLP Compliance: Yes

5/sex/group for dosing phase (except n=3 at low dose)

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Version date: March 1, 2024 (ALL NDA/ BLA reviews)

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

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ROMVIMZA (vimseltinib)

Vehicle / Formulation: 0.4% (w/v) hydroxypropyl methylcellulose in reverse osmosis water

DCC-3014 (DP-6865)								
Treatment	DCC-3014 (DP-6865)							
Sex	M				F			
Group #	1	2	3	4	1	2	3	4
Dose (mg/kg/day)	0	2	4	8	0	2	4	8
CLINICAL CHEMISTRY / SERUM								
Alanine Aminotransferase (U/L)								
Day 92	51.6	+19	+25	+5	38.0	+32	+5	+19
Aspartate Aminotransferase (U/L)								
Day 92	30.6	+42	+59	+178	41.2	+22	+29	+105
Creatine Kinase (U/L)								
Day 92	185.4	+81	+80	+298	511.4	-39	-16	+41
Lactate Dehydrogenase (U/L)								
Day 92	69.6	+47	+34	+91	97.4	-29	-18	+3
Phosphate (mg/dL)								
Day 92	4.58	-5	-9	-28	4.30	-6	-7	-36
HEMATOLOGY / WHOLE BLOOD								
Platelets (10 ⁹ /L)								
Day 92	270.0	-1	+39	+102	354.6	+5	+11	+50
Reticulocytes (10 ⁹ /L)								
Day 92	29.36	-31	+22	+125	37.72	+13	+12	+31
ORGAN WEIGHT								
HEART								
Organ to Body Weight Ratio (%)								
Day 92	0.9517	-12	-13	-13	0.9870	-1	-13	-4
OVARY								
Organ to Body Weight Ratio (%)								
Day 92	-	-	-	-	0.0247	-46	-16	-45
UTERUS/CERVIX								
Organ to Body Weight Ratio (%)								
Day 92	-	-	-	-	0.1230	-1	+12	+133
HISTOPATHOLOGY								
EYE								
INFILTRATE								
1 OF 5	0	1	1	0	0	0	0	0
GLAND, PROSTATE								
INFILTRATE								
1 OF 5	0	1	1	1	0	0	0	0
HEART								
INFILTRATE								
1 OF 5	0	0	1	0	0	0	0	0
MINERALIZATION								
1 OF 5	0	0	1	0	0	0	0	0
LIVER								
FIBROSIS/ADHESION								
1 OF 5	0	0	1	1	0	0	0	0
2 OF 5	0	0	0	1	0	0	0	0

LUNG	HYPERPLASIA								
	1 OF 5	1	0	0	0	1	2	0	0
	2 OF 5	0	0	0	1	0	0	0	0
PANCREAS	ATROPHY								
	2 OF 5	0	0	0	0	0	0	0	1
TESTIS	DEGENERATION								
	1 OF 5	0	0	2	0	0	0	0	0
	2 OF 5	1	0	0	0	0	0	0	0
	HYPOPLASIA								
	2 OF 5	0	0	0	2	0	0	0	0
	3 OF 5	0	0	0	2	0	0	0	0
UTERUS	HYPERPLASIA								
	3 OF 5	0	0	0	0	0	0	0	1

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

19.4.1.1. Executive Summary

The FDA's Assessment:

The PK of vimseltinib in adult population was characterized by a 2-compartment model with sequential zero- and first-order absorption followed by first-order elimination. The population PK model described the observed data reasonably well.

The proposed dosage of 30 mg biw is considered acceptable for the proposed patient population.

19.4.1.2. PPK Assessment Summary

The Applicant's Position:

[Highlight the key findings in the white cells.]

General Information	
Objectives of PPK Analysis	The aim of this analysis was to characterize the population PK of vimseltinib in healthy volunteers, patients with malignant solid tumors, and patients with TGCT.
Studies Included	DCC-3014-01-001, DCC-3014-01-002, and DCC-3014-03-001
Dose(s) Included	Treatment range: 4- 50 mg Regimens: daily, 5 days daily and twice weekly after, 5 days daily and twice weekly after, twice weekly and single dose

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ROMVIMZA (vimseltinib)

Population Included		98 Healthy volunteers (28%), 37 Malignant solid tumor patients (11 %), 214 Tenosynovial giant cell tumor patients (61%)
Population Characteristics (PopPK Report Table 1)	General	Age (year) [median (min, max)]: 45.0 (20.0, 91.0) Weight (kg) [median (min, max)]: 76.0 (43.0, 150) Sex: 204 Female (58%), 145 Male (42%) Subject type (N [%]): 98 Healthy volunteers (28%), 37 Malignant solid tumor patients (11 %), 214 Tenosynovial giant cell tumor patients (61%) Race (N [%]): 19 Black or African American (5%), 272 White (78%), 30 Unknown or not reported (9%), 28 Other (8%)
	Organ Impairment	Hepatic impairment – Liver function based on National Cancer Institute classification was not identified as a covariate in the PopPK analysis. Renal impairment – eGFR was not identified as a covariate and no relevant differences in steady state exposure are anticipated for mild and moderate renal function (eGFR ≥ 37.7 mL/min/1.73 m ²).
	Pediatrics (if any)	None
No. of Patients, PK Samples, and BLQ		349 adult participants; 6199 PK samples (excluding LLOQ (739 records), Dose of 0 (11 records) and duplicates (5 records))
Sampling Schedule	Rich Sampling	DCC-3014-01-001: Predose and at 0.5, 1, 2, 4, 6, 8, 10-12, 24 hours post-dose on Day -7, Day 1 (Cycle 1), Day 8 (Cycle 1) and Day 1 (Cycle 2) DCC-3014-01-002: - Arm Ia-c (Period 1), Ann 2 (Period 1 and 2): Predose (Day 1) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 96, 120, 144, 168, 216, 264, 312, 480 hours post-dose. - Arm Ib. (Period 2): Predose (Day 1), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72 hours post-dose. - Arm Id: Day 1 Predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours post-dose. Day 2 Predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 264, 312 hours post Day 2 dose. - Arm le: Predose (Day 1), and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours post-dose. Predose (Day 5), 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 60, 72, 84, 96, 120, 144, 168, 192, 216, 264, 312 hours post Day 5 dose.
	In ITT population	DCC-3014-03-001: Double-blind period: - Predose (within 60 min before dosing) Day 1 (Cycle 1, Week 1), Day 15 (Cycle 1, Week 3), Day 1 (Cycle 2, Week 5), Day 1 (Cycle 3, Week 9), Day 1 (Cycle 5, Week 17), or the end of treatment visit (Week 25) whichever occurs first. 2 hours post-dose on Day 1 (Cycle 1, Week 1), Day 15 (Cycle 1, Week 3), Day 1 (Cycle 2, Week 5), Day 1 (Cycle 3, Week 9). Crossover period:

4NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

		- Predose (within 60 min before dosing) Day 1 (Cycle 1, Week 25), Day 15 (Cycle 1, Week 27), Day 1 (Cycle 2, Week 29), Day 1 (Cycle 3, Week 33), Day 1 (Cycle 5, Week 41), Day 1 (Cycle 7, Week 49), Day 1 (Cycle 10, Week 61), Day 1 (Cycle 13, Week 73) or the end of treatment visit, whichever occurs first. 2 hours post-dose on Day 1 (Cycle 1, Week 25), Day 15 (Cycle 1, Week 27), Day 1 (Cycle 2, Week 29), Day 1 (Cycle 3, Week 33). Open-label period: - Predose (within 60 min before dosing) on Day 1 (Cycle 7, Week 25), Day 1 (Cycle 10, Week 37) and Day 1 (Cycle 13, Week 49) or the end of treatment visit.
Covariates Evaluated	Static	See Table 54 below for all covariates evaluated in the PopPK model development.
	Time- varying	See above.
Final Model	Summary	Acceptability [FDA's comments]
Software and Version	NONMEM (Version 7.5)	Yes
Model Structure	2-compartment model with sequential zero- and first-order absorption and first-order elimination from the central compartment.	Yes
Model Parameter Estimates	See Table 55 below for model parameter estimates.	Yes
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	All model parameters were estimated with good precision ($RSE \leq 18.3\%$). IIV was small to moderate for most of the parameters and relatively high for MAT. Shrinkage was low for most of the parameters ($\leq 30.7\%$) and moderate for IIV on V_p/F . See Table 55 for details.	Yes
BLQ for Parameter Accuracy	The number of post-first-dose below limit of quantification (BLQ) observations relative to the total number of Vimseltinib plasma observation records in the derived data file was low and no alternative modelling approaches for handling these observations were deemed necessary. These records were excluded from model development.	Yes
GOF, VPC	Model diagnostics for the final model indicate a satisfactory predictive performance for vimseltinib plasma concentrations.	Yes

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	See Figure 23 below for VPC.	
Significant Covariates and Clinical Relevance	Body weight and food status were the most influential covariates on the primary parameters in the final PK model. Body weight was included using allometric scaling with fixed exponents, thus steady state exposure increased with lower body weight. The covariate-parameter relation of food status on MAT suggests that fed subjects had an approximately 6-fold longer mean absorption time than fasted subjects; however, this had a limited effect on steady state exposure metrics. Several exploratory covariate-parameter relationships were identified during covariate analysis: Healthy volunteers had a lower Vc/F, and higher Vp/F, compared to TGCT patients. Subjects of Black or African American race had a higher Vp/F compared to non-Black or African American subjects. However, the effect of all structural and exploratory covariates on steady state exposure parameters were within the 80%-125% limits.	Yes The significant covariates on PK are not expected to have a clinically meaningful impact.
Analysis Based on Simulation (optional)	Predicted exposures provided in Table 54 below.	Yes
Labeling Language	Description	Acceptability [FDA's comments]
12.3 PK	Refer to Section 12.3 of USPI	Yes

Table 54 Covariate-parameter relationships evaluated in the vimseltinib PK model development

Parameter	Type	Covariate ^a
Clearance	Mechanistic	body weight ^b
	Structural	food status, serum albumin, NCI liver function classification ^c , alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), weight normalized creatinine clearance (CRCL)
Volumes of distribution	Exploratory	age, sex, race, ethnicity, dosing regimen, body mass index, disease population ^d
	Mechanistic	body weight ^e
	Structural	serum albumin
Mean absorption time	Exploratory	age, sex, race, ethnicity, dosing regimen, body mass index, disease population ^d
	Mechanistic	
	Structural	food status ^f
Bioavailability	Exploratory	age, sex, race, ethnicity, dosing regimen, body mass index, disease population ^d
	Mechanistic	
	Structural	food status ^f , serum albumin
	Exploratory	age, sex, race, ethnicity, dosing regimen, body mass index, disease population ^d

^a Covariates evaluated with the SCM method will only be considered for parameters that are associated with IIV.

^bIncluded allometrically with a fixed exponent of 0.75 if included in the model, the same allometric exponent will be used for inter-compartmental clearance (Q).

^c In case of high correlations between NCI liver function classification and transaminases and bilirubin, NCI will be prioritized in the covariate analysis.

^d Divided into healthy volunteers, patients with MST, and patients with TGCT.

^eIncluded allometrically with a fixed exponent of 1. If included in the model, the same allometric exponent will be used for peripheral volume of distribution (V_p).

^f Food status will be considered as time-varying for each dose.

Abbreviations: IIV: inter-individual variability; NCI: national cancer institute; SCM: stepwise covariate model building procedure

Table 55 Parameter estimates of the final vimseltinib PK model

Final model				
Run		301		
OFV		-7990.65		
Condition number		58.81		
	Unit	Value	RSE (%)	SHR (%)
CL/F	(L/h)	0.612	2.41	
V _c /F	(L)	88.0	2.25	
V _p /F	(L)	28.9	4.36	
MAT ^a	(h)	0.713	1.56	
Q/F	(L/h)	17.1	4.98	
MAT _{fr} ^a		0.434	2.25	
Effect of fed food status on MAT ^a		4.77	2.62	
Baseline albumin on V _c /F		-0.0261	18.6	
Healthy volunteers on V _c /F		-0.293	10.9	
Healthy volunteers on V _p /F		1.15	8.49	
Black or African American race on V _p /F		0.334	23.6	
WT on CL/F		0.750		
WT on V _c /F		1.00		
WT on V _p /F		1.00		
WT on Q/F		0.750		
F _{rel}		1.00		
IIV RUV	(CV)	0.451	4.04	1.15
IIV CL/F	(CV)	0.440	3.18	1.83
IIV V _c /F	(CV)	0.430	3.74	8.34
Correlation CL/F-V _c /F	(correlation)	0.637	4.80	
IIV V _p /F	(CV)	0.150	18.3	62.6
IIV MAT	(CV)	1.17	5.09	30.7
RUV	(CV)	0.240	2.16	1.11

The RSE for IIV and RUV parameters are reported on the approximate SD scale.

RSEs reported were computed based on results file from a SIR output of the final vimseltinib PK model with non-fixed absorption parameters (MAT, MAT_{fr}, and the effect of food status).

^a The point estimate for this parameter was fixed in the final model.

Abbreviations: CL/F=apparent clearance; IIV=inter-individual variability; F_{rel}=relative bioavailability; MAT=mean absorption time; MAT_{fr}= fraction of mean absorption time associated with first order absorption; RSE=relative standard error; SHR=shrinkage; Q/F=apparent inter-compartmental clearance; V_c/F=apparent central volume of distribution; V_p/F=apparent peripheral volume of distribution WT=body weight

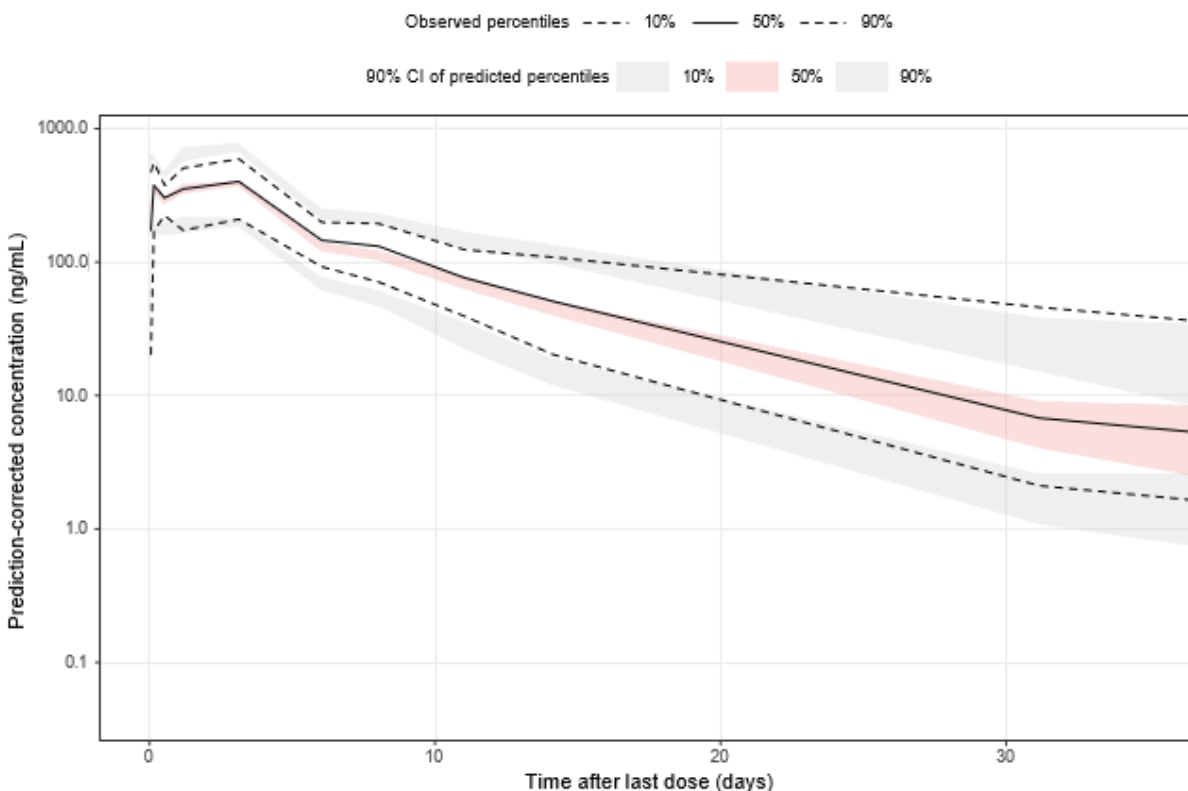
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Table 56 Exposure metrics for the 30 mg BIW regimen based on EBEs from the final vimseltinib PK model and analysis population, stratified by disease population

	Healthy volunteers	Malignant solid tumor patients	Tenosynovial giant cell tumor patients	Overall
	N=98	N=37	N=214	N=349
C_{max,ss} (ng/mL)				
Mean (SD, CV%)	887 (264, 29.8)	905 (595, 65.8)	801 (325, 40.6)	836 (350, 41.9)
Median (min, max)	860 (163, 1500)	783 (259, 3370)	751 (158, 3440)	791 (158, 3440)
gMean (gCV, gCI)	835 (40.9, 773 - 903)	792 (51.9, 677 - 927)	747 (39.4, 710 - 786)	776 (41.4, 744 - 809)
C_{avg,ss} (ng/mL)				
Mean (SD, CV%)	639 (207, 32.4)	744 (561, 75.4)	610 (288, 47.2)	632 (311, 49.2)
Median (min, max)	612 (141, 1120)	634 (198, 3240)	561 (94.5, 3190)	583 (94.5, 3240)
gMean (gCV, gCI)	599 (40.6, 555 - 648)	634 (56.7, 535 - 751)	559 (45.1, 527 - 592)	577 (45.3, 552 - 604)
C_{min,ss} (ng/mL)				
Mean (SD, CV%)	501 (179, 35.8)	605 (482, 79.5)	468 (251, 53.7)	492 (271, 55.1)
Median (min, max)	481 (111, 945)	510 (125, 2730)	429 (11.2, 2710)	446 (11.2, 2730)
gMean (gCV, gCI)	465 (43.5, 429 - 505)	502 (64.3, 415 - 606)	415 (57.9, 386 - 446)	437 (55.2, 414 - 461)
AUC_{τ,ss} (mg*h/L)				
Mean (SD, CV%)	53.7 (17.4, 32.4)	62.5 (47.1, 75.4)	51.2 (24.2, 47.2)	53.1 (26.1, 49.2)
Median (min, max)	51.4 (11.9, 94.2)	53.2 (16.7, 272)	47.2 (7.94, 268)	49.0 (7.94, 272)
gMean (gCV, gCI)	50.4 (40.6, 46.6 - 54.4)	53.2 (56.7, 44.9 - 63.1)	46.9 (45.1, 44.3 - 49.7)	48.5 (45.3, 46.4 - 50.8)

Abbreviations: AUC_{τ,ss}=area under the concentration-time curve during a dosing interval at steady state; biw=twice every week; C_{avg,ss}=average concentration during a dosing interval at steady state; C_{max,ss}=maximum concentration during a dosing interval at steady state; C_{min,ss}=minimum concentration during a dosing interval at steady state; gCI=geometric 95% confidence interval; gCV=geometric CV; gMean=geometric mean; CV=coefficient of variation; SD=standard deviation.

Figure 23 Prediction-corrected visual predictive check of vimseltinib PK plasma concentrations versus time after dose, for the vimseltinib PK analysis data set using the final vimseltinib PK model, presented on a semi-logarithmic scale



Time points associated with BLQ observations were included in the pcVPC. The x-axis is limited to 35 days after the last dose. Abbreviations: BLQ=below limit of quantification; CI=confidence interval; pcVPC=prediction-corrected visual predictive check.

The FDA's Assessment:

The population PK analysis is considered adequate.

19.4.1.3. PPK Review Issues

The impact of hepatic function on PK was evaluated using popPK analysis to support labelling. There was no hepatic impairment other than mild by NCI ODWG classification in a total of 11 patients (7 with TGCT) from Ph1/2 study DCC-3014-01-001 and MOTION study. The mild hepatic impairment was not identified as a significant covariate based on 159 observations from these 11 patients. Despite small patient number, the number of observations and the coverage for time after dose is considered adequate to characterize the effect of mild hepatic impairment on PK.

The baseline characteristics used in popPK analysis was provided in Table 57.

Table 57. Baseline characteristics of the subjects in the vimseltinib PK analysis data set, stratified by study.

	DCC-3014-01-001	DCC-3014-01-002	DCC-3014-03-001	Overall
	N=134	N=98	N=117	N=349
Body weight (kg)				
Mean (SD)	79.6 (19.5)	73.8 (13.2)	79.5 (18.8)	78.0 (17.8)
Median (min, max)	78.0 (44.0, 150)	72.2 (46.1, 110)	78.0 (43.0, 142)	76.0 (43.0, 150)
Age (year)				
Mean (SD)	49.8 (15.0)	38.3 (10.8)	43.4 (13.7)	44.4 (14.2)
Median (min, max)	52.0 (21.0, 91.0)	38.0 (20.0, 60.0)	44.0 (20.0, 78.0)	45.0 (20.0, 91.0)
Albumin (g/L)				
Mean (SD)	41.6 (4.42)	44.9 (2.88)	45.2 (2.88)	43.7 (3.92)
Median (min, max)	42.3 (29.0, 51.0)	45.0 (39.0, 51.0)	45.0 (37.0, 52.0)	44.0 (29.0, 52.0)
Alanine aminotransferase (U/L)				
Mean (SD)	21.4 (12.1)	19.0 (9.62)	17.2 (8.52)	19.3 (10.5)
Median (min, max)	18.5 (5.00, 91.0)	16.5 (4.00, 54.0)	15.0 (6.00, 48.0)	17.0 (4.00, 91.0)
Aspartate aminotransferase (U/L)				
Mean (SD)	21.9 (8.50)	18.3 (4.91)	18.3 (6.17)	19.6 (7.08)
Median (min, max)	20.0 (8.00, 66.0)	18.0 (9.00, 34.0)	18.0 (8.00, 61.0)	18.0 (8.00, 66.0)
Total bilirubin (µmol/L)				
Mean (SD)	8.43 (3.98)	8.53 (3.94)	7.41 (3.37)	8.12 (3.80)
Median (min, max)	7.45 (3.00, 21.0)	8.55 (3.40, 20.5)	7.00 (3.00, 22.0)	7.00 (3.00, 22.0)
Estimated glomerular filtration rate (mL/min/1.73 m²)_a				
Mean (SD)	98.3 (18.5)	106 (14.8)	101 (16.3)	101 (17.0)
Median (min, max)	99.3 (37.7, 134)	105 (63.8, 144)	103 (58.2, 138)	103 (37.7, 144)
Missing (N (%))	3 (2.2%)	0 (0%)	0 (0%)	3 (0.86%)
Body mass index (kg/m²)				
Mean (SD)	27.5 (5.66)	26.0 (2.99)	27.2 (5.77)	27.0 (5.11)
Median (min, max)	26.4 (16.5, 50.3)	26.6 (19.0, 30.4)	26.2 (17.2, 46.0)	26.4 (16.5, 50.3)
Missing (N (%))	8 (6.0%)	0 (0%)	2 (1.7%)	10 (2.9%)
Sex				
Female	82 (61%)	53 (54%)	69 (59%)	204 (58%)
Male	52 (39%)	45 (46%)	48 (41%)	145 (42%)

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Hispanic ethnicity				
Hispanic	9 (6.7%)	42 (43%)	3 (2.6%)	54 (15%)
Non-hispanic	117 (87%)	55 (56%)	84 (72%)	256 (73%)
(Missing)	8 (6.0%)	1 (1.0%)	30 (26%)	39 (11%)
Race				
Black or African American	2 (1.5%)	13 (13%)	4 (3.4%)	19 (5.4%)
Asian	3 (2.2%)	6 (6.1%)	4 (3.4%)	13 (3.7%)
Native Hawaiian or other Pacific Islander	1 (0.75%)	0 (0%)	0 (0%)	1 (0.29%)
White	115 (86%)	78 (80%)	79 (68%)	272 (78%)
Multiple or other	10 (7.5%)	1 (1.0%)	0 (0%)	11 (3.2%)
Unknown or not reported	0 (0%)	0 (0%)	30 (26%)	30 (8.6%)
(Missing)	3 (2.2%)	0 (0%)	0 (0%)	3 (0.86%)
Treatment regimen				
qd	39 (29%)	35 (36%)	0 (0%)	74 (21%)
5 days qd and biw after	27 (20%)	0 (0%)	0 (0%)	27 (7.7%)
5 days qd and qw after	4 (3.0%)	0 (0%)	0 (0%)	4 (1.1%)
Single dose	0 (0%)	63 (64%)	0 (0%)	63 (18%)
biw	64 (48%)	0 (0%)	117 (100%)	181 (52%)
Disease population				
Healthy volunteers	0 (0%)	98 (100%)	0 (0%)	98 (28%)
Malignant solid tumor patients	37 (28%)	0 (0%)	0 (0%)	37 (11%)
Tenosynovial giant cell tumor patients	97 (72%)	0 (0%)	117 (100%)	214 (61%)
NCI ODWG classification				
No dysfunction	125 (93%)	94 (96%)	115 (98%)	334 (96%)
Mild dysfunction	9 (6.7%)	0 (0%)	2 (1.7%)	11 (3.2%)
(Missing)	0 (0%)	4 (4.1%)	0 (0%)	4 (1.1%)
P-gp inhibitor used at baseline				
No	124 (93%)	98 (100%)	112 (96%)	334 (96%)
Yes	10 (7.5%)	0 (0%)	5 (4.3%)	15 (4.3%)
P-gp inducer used at baseline				
No	134 (100%)	98 (100%)	116 (99%)	348 (100%)
Yes	0 (0%)	0 (0%)	1 (0.85%)	1 (0.29%)
Anti-acid agent used at baseline				
No	121 (90%)	98 (100%)	111 (95%)	330 (95%)
Yes	13 (9.7%)	0 (0%)	6 (5.1%)	19 (5.4%)

Source: Table 3 of Applicant's population PK report (REP-3-PK-DECI-VIM-PMX-1).

19.4.1.4. Reviewer's Independent Analysis

None.

19.4.2. Exposure-Response Analysis

19.4.2.1. ER (efficacy) Executive Summary

The FDA's Assessment:

Lack of positive E-R relationships for efficacy endpoints was observed across steady-state exposure with a planned fixed dosage of 30 mg biw (median relative dose intensity of 74%). Similar ORR was observed between patients with and without dosage reduction that suggested the efficacy in patients who needed dose modifications was not impacted as a result of dose reduction.

19.4.2.2. ER (efficacy) Assessment Summary

The Applicant's Position:

General Information		
Goal of ER analysis		The aim of this analysis was to characterize the population ER relationships between vimseltinib exposure and efficacy endpoints in patients with TGCT.
Study Included		DCC-3014-03-001
Endpoint		ORR per RECIST v1.1 at Week 25; ORR per TVS at Week 25
No. of Patients (total, and with individual PK)		83 total patients with TGCT (all 83 patients included individual PK)
Population Characteristics (Exposure-Response Modeling Table S1)	General	Age (year) [median (min, max)]: 45 (20, 78) Weight (kg) [median (min, max)]: 80.0 (46.7, 142) Sex: 46 females, 37 males Race: 59 White, 4 Black or African American, 1 Asian, 19 unknown or not reported
	Pediatrics (if any)	None
Dose(s) Included		30 mg twice weekly
Exposure Metrics Explored (range)		Both ORR per RECIST v1.1 and ORR per TVS: $C_{avg,ss}$ (113 to 1470 ng/mL) $C_{max,ss}$ (169, 1710 ng/mL), $C_{min,ss}$ 450 (61.2, 1250 ng/mL)
Covariates Evaluated		age, sex, race, baseline tumor size and tumor location
Final Model Parameters		Summary Acceptability [FDA's]

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		comments]
Model Structure	The final ORR per RECIST v1.1 model is a logistic regression model with a linear effect of $C_{avg,ss}$, and a linear effect of baseline tumor size. The final ORR per TVS model is a logistic regression model with a linear effect of $C_{avg,ss}$.	Yes
Model Parameter Estimates	ORR per RECIST v1.1: Table 58 below. ORR per TVS: Table 59 below.	Yes
Model Evaluation	Model diagnostics for the final ORR per RECIST v1.1 and ORR per TVS models indicated a satisfactory predictive performance for the observed data.	yes
Covariates and Clinical Relevance	ORR per RECIST v1.1: A covariate effect of baseline tumor size on ORR per RECIST v1.1 was included, where lower baseline tumor size was associated with higher ORR per RECIST v1.1. ORR per TVS at Week 25: No covariates were identified.	Yes
Simulation for Specific Population	Following vimseltinib 30 mg twice weekly dosing, ORR per RECIST v1.1 and ORR per TVS at Week 25 were predicted to be 41.4% and 68.5%, respectively (Figure 24, below). The predicted proportions were similar across body weight subgroups.	Yes
Visualization of E-R relationships	Proportion of responders versus $C_{avg,ss}$, is plotted for the final ORR per RECIST v1.1 model, based on the ORR per RECIST v1.1 analysis data set.in Figure 25 below. Proportion of responders versus $C_{avg,ss}$ is plotted for the final ORR per TVS model, based on the ORR per TVS analysis data set in Figure 26 below.	Yes
Overall Clinical Relevance for ER	The available ORR per RECIST v1.1 and ORR per TVS data showed that part of the TGCT patients treated with vimseltinib responded to treatment, while there were no responders in the placebo group. The ER analyses did not show differences in response of ORR per RECIST v1.1 and ORR per TVS at different levels of exposure within the evaluated 30 mg BIW dose group.	Yes. Interpret with caution for single dose data used in E-R analysis.
Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	The exposure-response relationship for efficacy of vimseltinib has not been fully characterized.	Yes

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Table 58 Parameter estimates for the ORR per RECIST v1.1 final and covariate models

Parameter	Unit	Covariate model for ORR per RECIST v1.1			Final model for ORR per RECIST v1.1		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
Population values							
Base ^a	Probability	0.429	1.27×10 ²	0.430	0.405	63.0	0.112
Slope _{Cavg,ss}	LO per ng/mL	-1.5×10 ⁻⁴	7.38×10 ²	0.892	-3.34×10 ⁻⁵	3.04×10 ³	0.974
Baseline age effect	LO per year	-0.0287	64.8	0.123			
Baseline tumor size effect	LO per mm	-0.0159	48.4	0.0389	-0.0171	41.1	0.0151
Sex: Male	LO ^b	-0.460	1.1×10 ²	0.362			
Race: Non-White	LO ^b	-0.469	2.17×10 ²	0.645			
Tumor location: Other than lower limb	LO ^b	0.631	1.2×10 ²	0.405			
Residual error							
Sigma		1.15			1.14		

RSEs are reported on the LO scale.
^a The base parameter reflects the probability of response for a reference patient treated with C_{avg,ss} of 576 ng/mL, and with age (year): 45.0; tumor size (mm): 63.4 and sex: female; race: white or missing; tumor location: lower limb.
^b Compared to the reference patient.

Abbreviations: LO=log odds; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors; RSE=relative standard error.

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Table 59 Parameter estimates for ORR per TVS base, final and covariate models

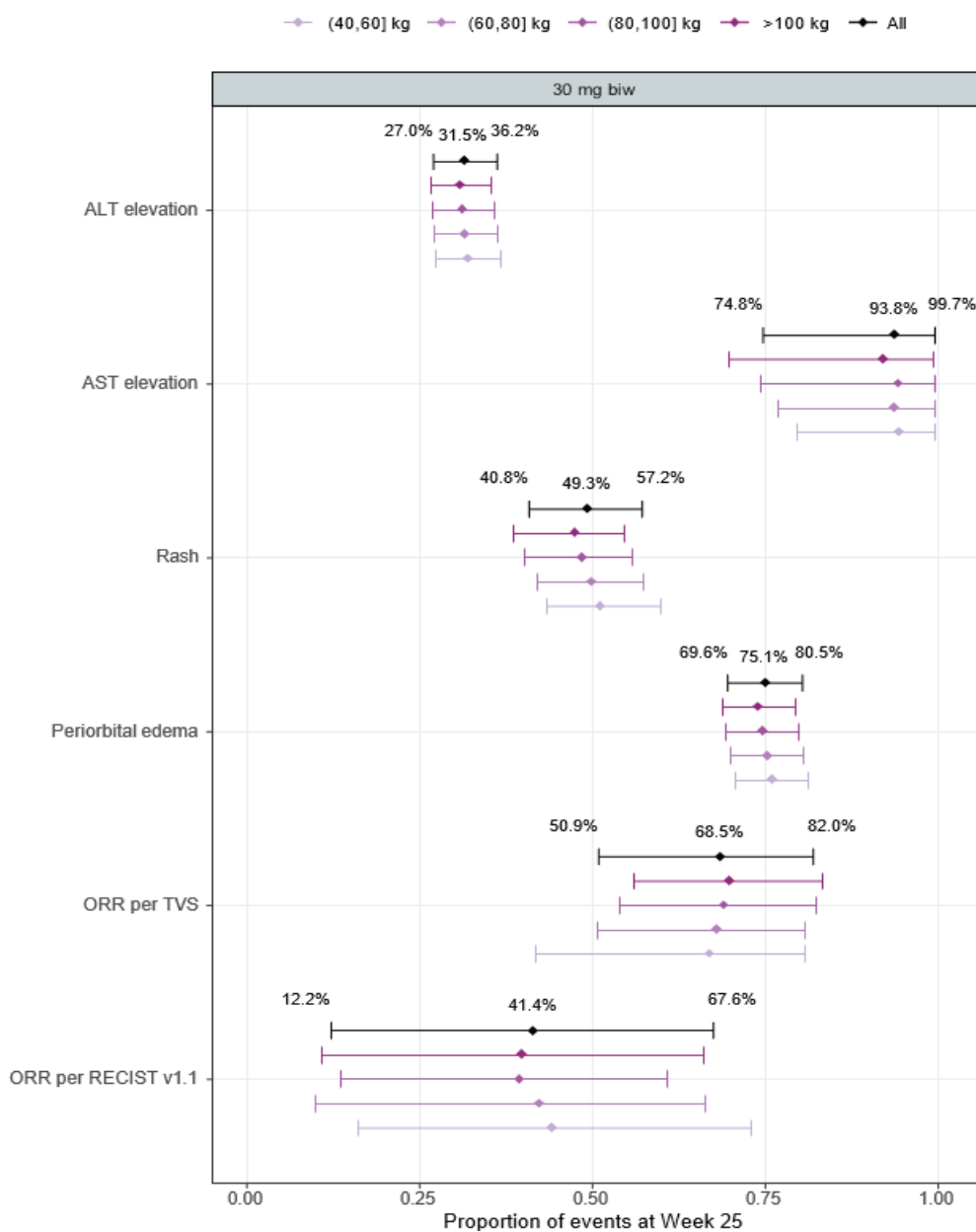
Parameter	Unit	Base and final model			Covariate model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
Population values							
Base ^a	Probability	0.682	32.3	0.00194	0.732	39.4	0.0112
Slope _{Cavg,ss}	LO per ng/mL	-4.48×10 ⁻⁴	2.17×10 ²	0.646	-3.61×10 ⁻⁴	3.02×10 ²	0.741
Baseline age effect	LO per year				-0.0336	56.7	0.0780
Baseline TVS effect	LO				0.0260	88.0	0.256
Sex: Male	LO ^b				-0.621	82.6	0.226
Race: Non-White	LO ^b				-0.247	4.02×10 ²	0.803
Tumor location: Other than lower limb	LO ^b				-0.348	2.17×10 ²	0.644
Residual error							
Sigma		1.14			1.14		

RSEs are reported on the LO scale.
^a The base parameter reflects the probability of response for a reference patient treated with vimseltinib with C_{avg,ss} of 576 ng/mL, and with age (year): 45.0; tvs: 6.00 and sex: female; race: white or missing; tumor location: lower limb.
^b Compared to the reference patient.

Abbreviations: LO=log odds; ORR=objective response rate; RSE=relative standard error; TVS=Tumor volume score.

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

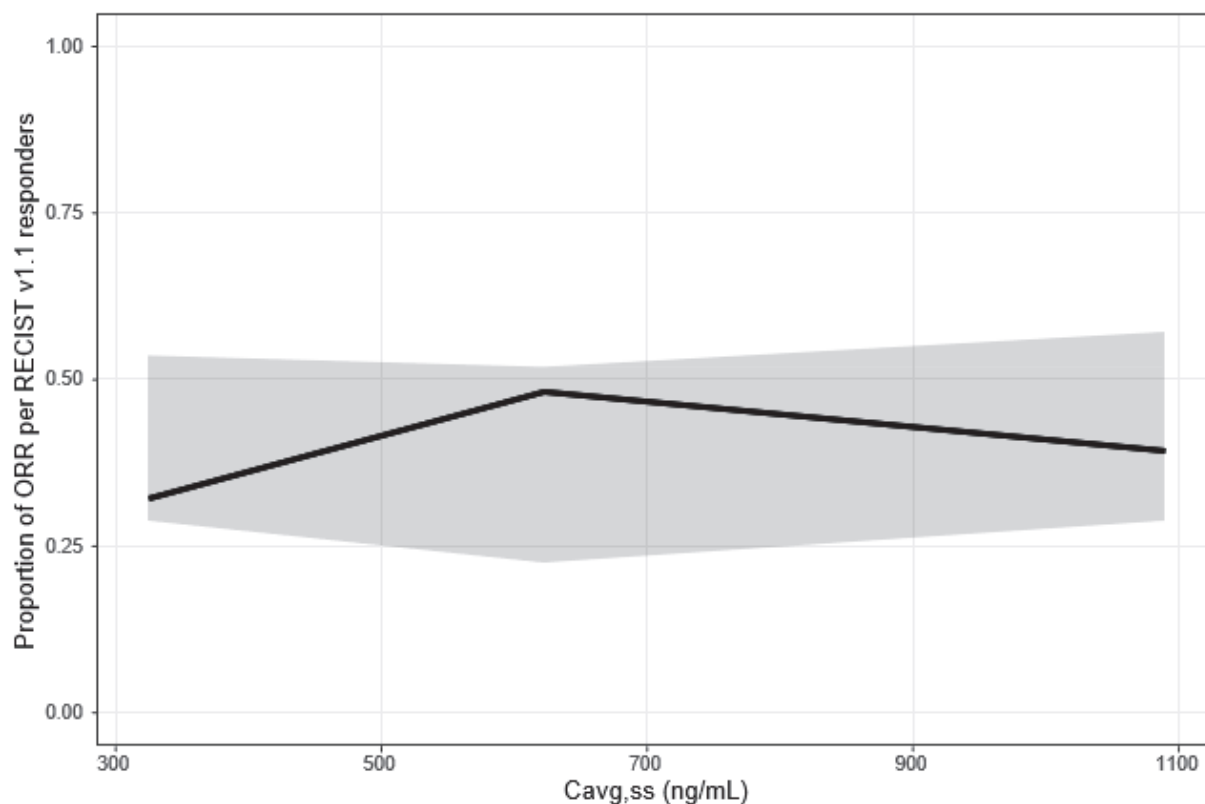
Figure 24 Predicted proportion of ORR per RECIST v1.1, ORR per TVS, and periorbital edema, rash, AST elevation, and ALT elevation events at Week 25, following 30 mg BIW dosing



Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; biw=twice every week ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors; TVS=Tumor volume score; WT=body weight.

Data are colored by WT group. Closed dots represent the median of the predicted proportions and the error bars correspond to the 90% CI. The numbers in text indicate the median and 90% CI for the overall population.

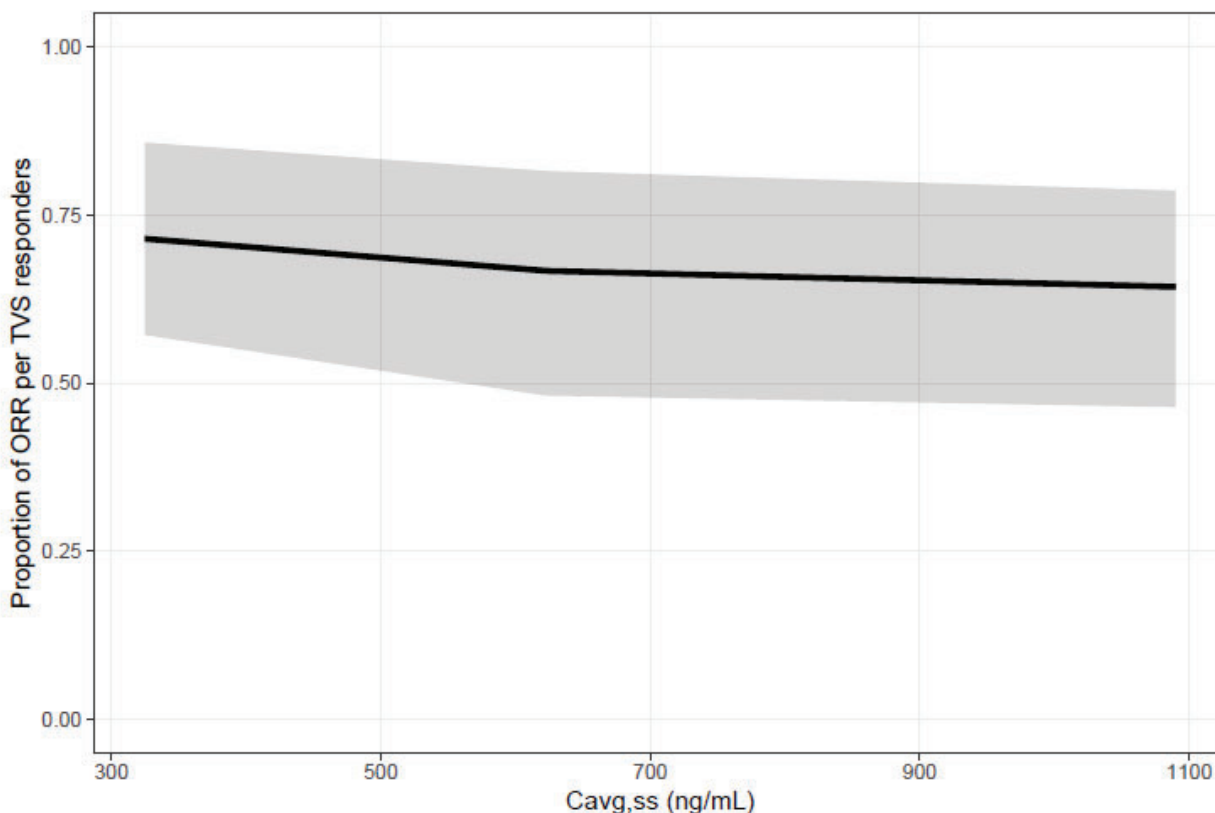
Figure 25 Visual predictive check of the proportion of responders versus $C_{avg,ss}$, for the final ORR per RECIST v1.1 model, based on the ORR per RECIST v1.1 analysis data set



Abbreviations: $C_{avg,ss}$ =average concentration during a dosing interval at steady state; CI=confidence interval; ORR=objective response rate; RECIST=Response Evaluation Criteria in Solid Tumors.

The thick line corresponds to the observed fractions of responders, and the shaded area corresponds to the associated predicted 90% CI. The x-axis positions are centered between the corresponding tertile boundaries.

Figure 26 Visual predictive check of the proportion of responders versus $C_{avg,ss}$, for the base and the final ORR per TVS model, based on the ORR per TVS analysis data set



Abbreviations: $C_{avg,ss}$ =average concentration during a dosing interval at steady state; CI=confidence interval; ORR=objective response rate; TVS=Tumor volume score.

The thick line corresponds to the observed fractions of responders, and the shaded area corresponds to the associated predicted 90% CI. The x-axis positions are centered between the corresponding tertile boundaries.

19.4.2.3. ER (safety) Executive Summary

The FDA's Assessment:

Positive E-R relationships was observed across steady-state exposure for periorbital edema, rash, and AST/ALT elevation. The lower dosage (i.e., 20 mg biw) is predicted to marginally improve safety.

19.4.2.4. ER (safety) Assessment Summary

The Applicant's Position:

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General Information		
Goal of ER analysis		The aim of this analysis was to characterize the population ER relationships between vimseltinib exposure and safety endpoints in patients with TGCT and malignant solid tumors.
Study Included		DCC-3014-01-001 and DCC-3014-03-001
Population Included		Patients with TGCT or malignant solid tumors
Endpoint		Time to first event of periorbital edema of any grade; Time to first event of rash of any grade; Time to first event of AST elevation of any grade; Time to first event of ALT elevation of any grade
No. of Patients (total, and with individual PK)		285 patients with TGCT or malignant solid tumors (all 285 patients included individual PK)
Population Characteristics (Exposure-Response Modeling Table S1)	General	Age (year) [median (min, max)]: 48 (20, 91) Weight (kg) [median (min, max)]: 76.9 (43.0, 150) Sex: 174 females, 111 males Race: 214 White, 6 Black or African American, 10 Asian, 1 Native Hawaiian or other Pacific Islander, 10 Multiple or other, 44 unknown or not reported or missing
	Pediatrics (if any)	None
Dose(s) Included		Various randomized vimseltinib doses ranging from 6 to 50 mg (once daily (twice weekly) or placebo
Exposure Metrics Explored (range)		All safety endpoints: $C_{avg,ss}$ (85.0, 3780 ng/mL), $C_{max,ss}$ (94.8, 3640 ng/mL), $C_{min,ss}$ 450 (11.2, 3460 ng/mL)
Covariates Evaluated		age, sex, race, and tumor type (TGCT or malignant solid tumor)
Final Model Parameters		Acceptability [FDA's Comments]
Model Structure		Yes
Model Parameter Estimates		Yes

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	Time to first event of ALT elevation of any grade: Table 63 below	
Model Evaluation	Model diagnostics for the final time to first event models indicated a satisfactory predictive performance of the observed data.	
Covariates and Clinical Relevance	Time to first event of periorbital edema: All covariates except tumor type were not found to be statistically significant. The probability of having a periorbital edema event was decreased for subjects with MST, compared to subjects with TGCT. Time to first event of AST elevation: The effects of sex and tumor type were found to be statistically significant. The probability of having an AST elevation event was increased in males, compared to females, and was increased for subjects with MST, compared to subjects with TGCT. No covariates were identified for time to first event of rash or ALT.	Yes. Despite that male sex is associated with a higher risk of AST elevation, the incidence of AST elevation is marginally increased in male TGCT patients who received 30 mg biw at steady state (95% in males vs 91% in females), likely due to lower exposures with heavier weights in males.
Simulation for Specific Population	Following vimseltinib 30 mg twice weekly dosing, the median predicted proportion of events at Week 25 were 75.1%, 49.3%, 93.8%, and 31.5%, for periorbital edema, rash, AST elevation, and ALT elevation, respectively (Figure 24, above). The predicted proportions were similar across WT subgroups.	Yes.
Visualization of E-R relationships	The predicted proportions of safety events increased with increasing C _{max,ss} , with an initial increase for low C _{max,ss} , followed by a plateau. The initial increase was steep for AST elevation events, while it was less the case for other endpoints, leading to a relatively flat relationship between C _{max,ss} and periorbital edema, rash and ALT elevation events (Figure 27).	Yes. CPK elevation (see 19.4.2.5) was evaluated whose incidence was not found to be increased with increasing exposures.
Overall Clinical Relevance for ER	Following vimseltinib 30 mg twice weekly dosing, the median predicted proportion of events at Week 25 were 75.1%, 49.3%, 93.8%, and 31.5%, for periorbital edema, rash, AST elevation, d ALT elevation, respectively (Figure 28). Following vimseltinib 20 mg twice weekly dosing, the simulated difference in the median predicted proportions of events compared to 30 mg twice weekly dosing was <5% for periorbital edema, rash, and ALT elevation. For AST elevation, the difference was 7.3%.	Yes. AST elevation shows a steep E-R relationship which led to dose reduction in 2.5% of patients. Dose modification is considered an appropriate measure to manage this AE.

Labeling Language	Description	Acceptability [FDA's comments]
12.2 Pharmacodynamics	<u>Exposure-Response Relationship</u> Positive exposure-response relationships were observed between vimseltinib exposure and all grades of edema, rash, AST and ALT elevations.	Editorial edits for E-R relationship (see the labeling).

Table 60 Parameter estimates for periorbital edema final and covariate models

Parameter	Unit	Covariate Model			Final Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
C _{max,ss}	LH per ng/mL	0.0932	22.2	6.67×10^{-6}	0.0929	22.4	7.92×10^{-6}
Baseline age	LH per year	0.00926	58.4	0.0870			
Sex: Male	LH ^a	-0.163	95.5	0.295			
Race: Non-White	LH ^a	0.0421	6.12×10^2	0.870			
Tumor type: MST	LH ^a	-1.80	20.9	1.65×10^{-6}	-1.62	22.4	7.79×10^{-6}

RSEs are reported on the LH scale.

^a Compared to the associated reference levels: Sex: Female; Race: White or missing; Tumor type: TGCT.

Abbreviations: C_{max,ss}=maximum concentration during a dosing interval at steady state; LH=log hazard; MST=malignant solid tumor; RSE=relative standard error; TGCT=tenosynovial giant cell tumor.

Table 61 Parameter estimates for rash base, final and covariate models

Parameter	Unit	Base and Final Model			Covariate Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
C _{max,ss}	LH per ng/mL	0.144	30.1	9.01×10^{-4}	0.149	28.6	4.81×10^{-4}
Baseline age	LH per year				-0.00500	1.32×10^2	0.449
Sex: Male	LH ^a				-0.421	45.0	0.0263
Race: Non-White	LH ^a				-0.00287	1.06×10^4	0.992
Tumor type: MST	LH ^a				-0.820	49.2	0.0420

RSEs are reported on the LH scale.

^a Compared to the associated reference levels: Sex: Female; Race: White or missing; Tumor type: TGCT.

Abbreviations: C_{max,ss}=maximum concentration during a dosing interval at steady state; LH=log hazard; MST=malignant solid tumor; RSE=relative standard error; TGCT=tenosynovial giant cell tumor.

Table 62 Parameter estimates for AST elevation base and covariate models

Parameter	Unit	Covariate Model			Final Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
C _{max,ss}	LH per ng/mL	0.838	17.2	5.98×10^{-9}	0.816	17.4	9.3×10^{-9}
Intercept _{placebo}	LH ^a	11.8	22.6	9.8×10^{-6}	11.4	23.1	1.5×10^{-5}
Baseline age	LH per year	0.00800	60.8	0.100			
Sex: Male	LH ^a	0.499	28.6	4.71×10^{-4}	0.533	26.5	1.63×10^{-4}
Race: Non-White	LH ^a	-0.284	82.9	0.228			
Tumor type: MST	LH ^a	0.515	39.7	0.0117	0.587	32.6	0.00219

RSEs are reported on the LH scale.

^a Compared to the associated reference levels: vimseltinib treatment; Sex: Female; Race: White or missing; Tumor type: TGCT.

Abbreviations: C_{max,ss}=maximum concentration during a dosing interval at steady state; LH=log hazard; MST=malignant solid tumor; RSE=relative standard error; TGCT=tenosynovial giant cell tumor.

Table 63 Parameter estimates for ALT elevation base, final and covariate models

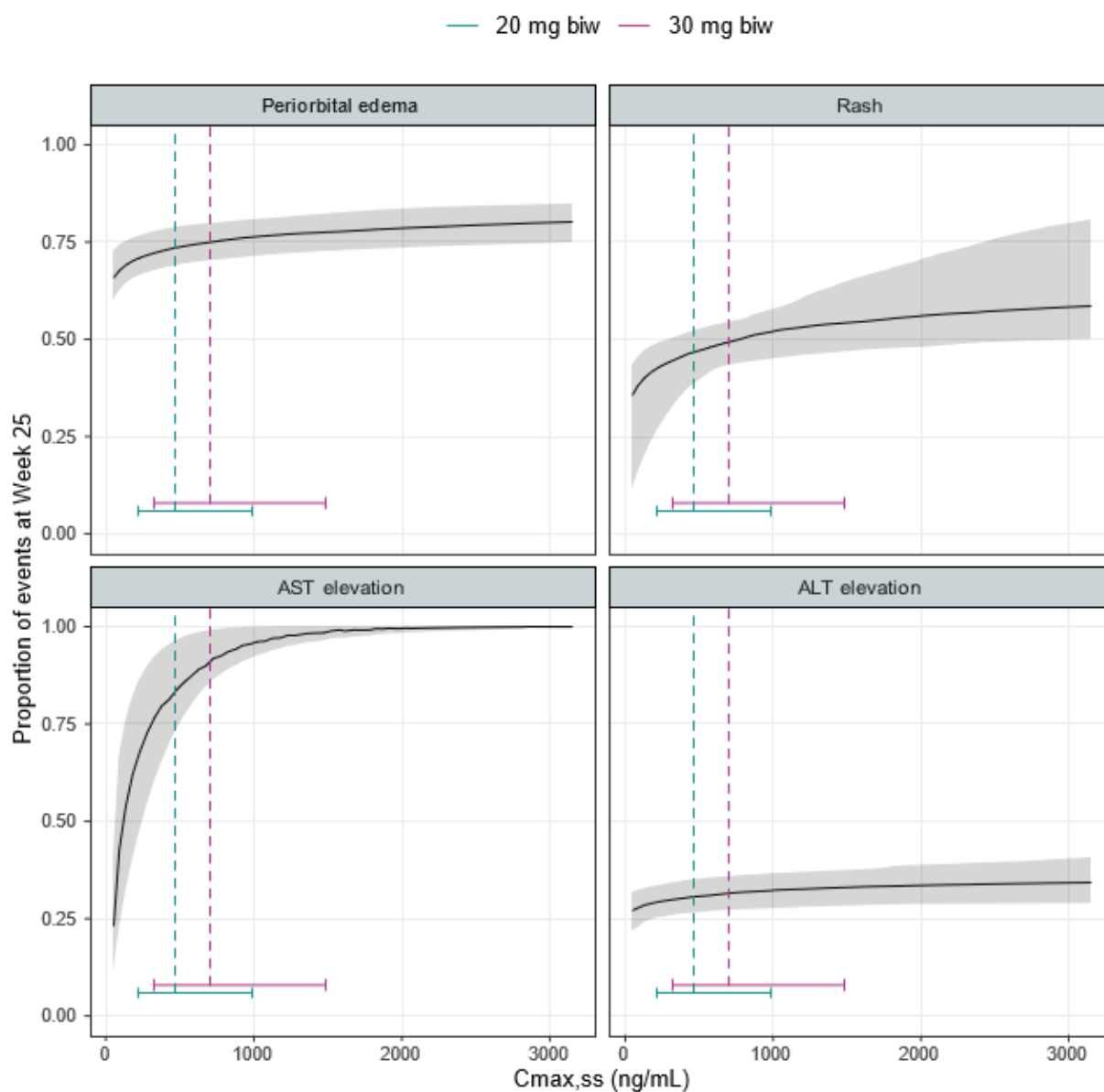
Parameter	Unit	Base and Final Model			Covariate Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
C _{max,ss}	LH per ng/mL	0.0625	45.5	0.0281	0.0620	46.9	0.0331
Baseline age	LH per year				0.00926	85.5	0.242
Sex: Male	LH ^a				0.488	43.7	0.0221
Race: Non-White	LH ^a				0.0151	2.49×10^3	0.968
Tumor type: MST	LH ^a				-0.155	2.36×10^2	0.672

RSEs are reported on the LH scale.

^a Compared to the associated reference levels: Sex: Female; Race: White or missing; Tumor type: TGCT.

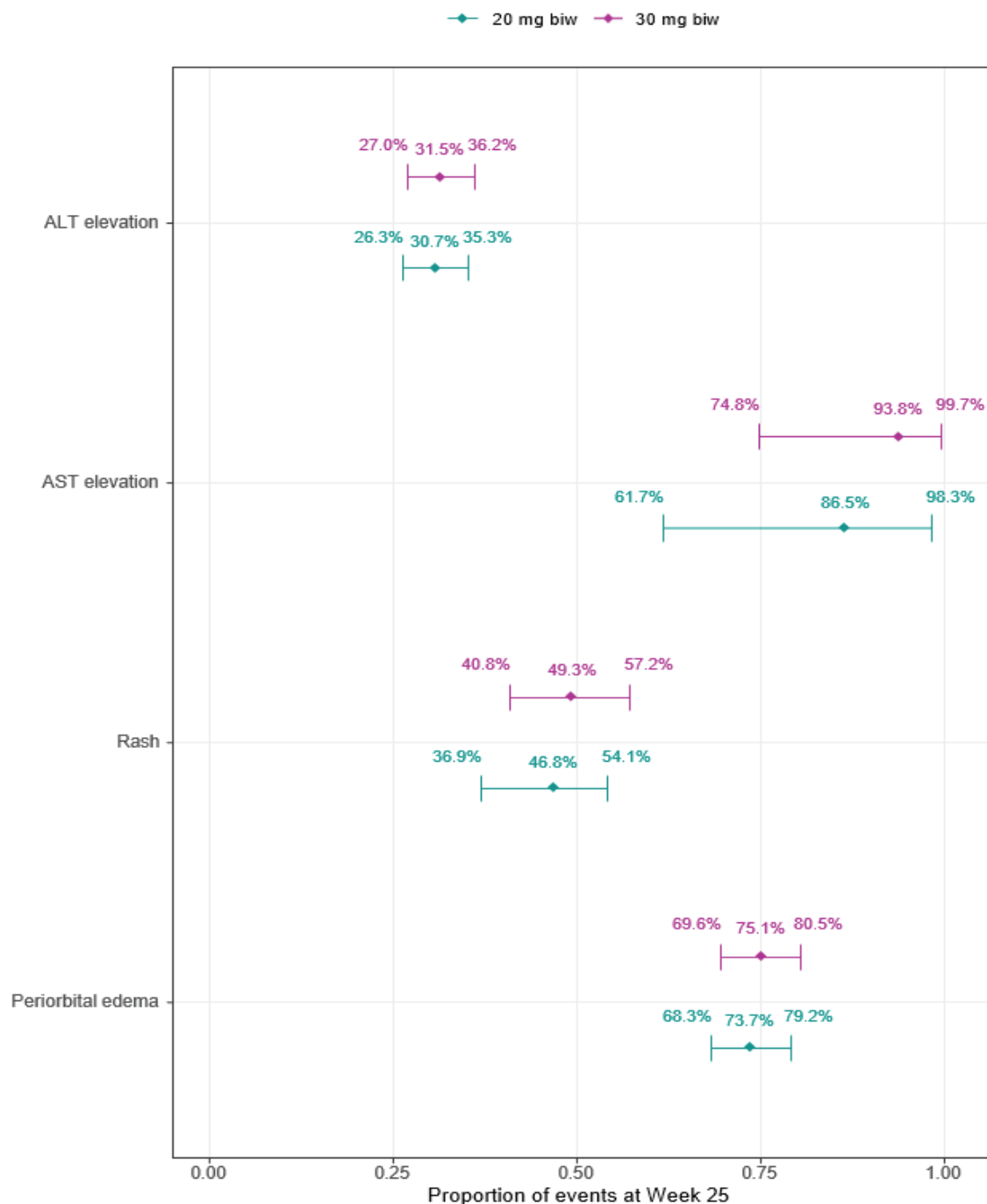
Abbreviations: C_{max,ss}=maximum concentration during a dosing interval at steady state; LH=log hazard; MST=malignant solid tumor; RSE=relative standard error; TGCT=tenosynovial giant cell tumor.

Figure 27 Predicted proportion of periorbital edema, rash, AST elevation, and ALT elevation events at Week 25 versus $C_{\max,ss}$ bins.



Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; biw=twice weekly; CI=confidence interval; $C_{\max,ss}$ =maximum concentration during a dosing interval at steady state. The solid line represents the median of the predicted proportion and the shaded area corresponds to the 90% CI. The colored error bars show the 5th to 95th percentiles of $C_{\max,ss}$ for each treatment group, and the vertical dotted lines correspond to the geometric mean of $C_{\max,ss}$ in each group.

Figure 28 Predicted proportion of periorbital edema, rash, AST elevation, and ALT elevation events at Week 25, following 20 and 30 mg BIW dosing.



Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; biw=twice weekly; CI=confidence interval. Data are colored by dose. Closed dots represent the median of the predicted proportions and the error bars correspond to the 90% CI. The numbers in text indicate the median and 90% CI.

The FDA's Assessment:

FDA agrees with the E-R analysis conducted by Applicant.

19.4.2.5. ER Review Issues

E-R relationship for CPK elevation

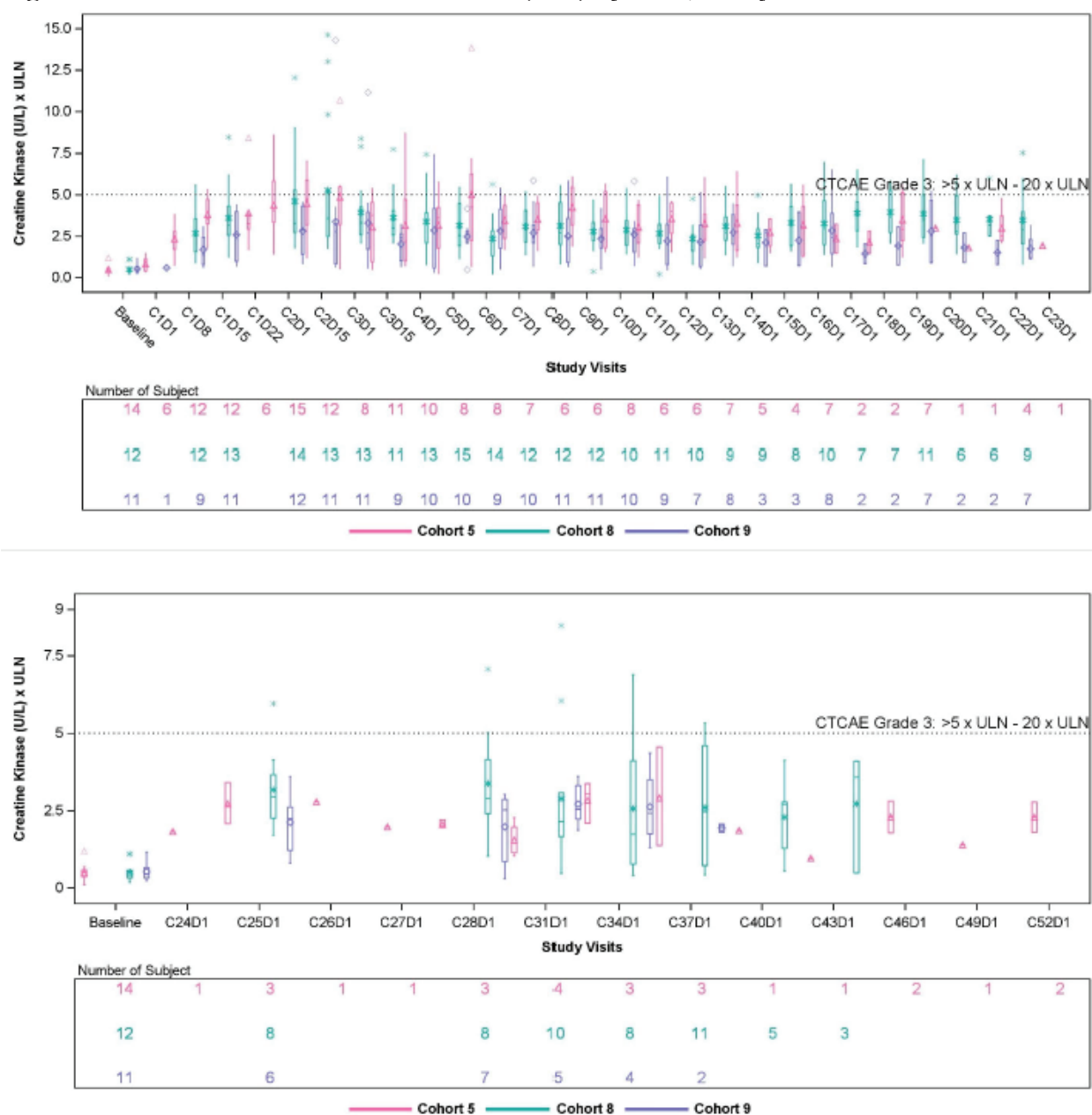
For CPK elevation that's drug-related, the incidence is 24% of any Grade and 10% of Grade ≥ 3 that led to dose reduction in 8.5% of TGCT patients in MOTION study. The E-R analysis was therefore requested by the reviewer and the results were submitted as a response to Information Request.

In Ph1/2 study DCC-3014-01-001 where CPK lab measurement was collected, similar elevation of CPK over time was observed in 3 cohorts of TGCT patients (cohort 5: 30 mg biw, cohort 8: 10 mg qd, cohort 9: 6 mg qd) (**Figure 29**). Notably, Cohort 5 and cohort 8 have similar exposures despite different dosing intervals. E-R analysis for maximal CPK change from baseline was evaluated using generalized linear model and non-linear models, and a continuous model with linear effect of Cav_{g,ss} was selected as the base model. The effect of Cav_{g,ss} on maximal CPK change from baseline was found statistically insignificant (p-value = 0.719) and associated with high uncertainty, suggesting a lack of E-R relationship (Table 64). In the covariate analysis, tumor type was identified as a significant covariate where patients with TGCT were more likely to have greater CPK elevation compared to patients with MST.

Pooled E-R analysis using data from both Ph1/2 and MOTION studies was conducted to further evaluate if any Grade or Grade ≥ 3 CPK first elevation by CTCAE is dependent on exposure using Cox proportional hazard model. While there was a significantly positive effect of Cav_{g,ss} for any Grade CPK first elevation (Table 65), the positive effect of Cav_{g,ss} for Grade ≥ 3 CPK first elevation was marginally non-significant (p=0.0758) (Table 66). For 20 mg biw dosage, the predicted proportion of events at week 25 was only slightly lower than 30 mg biw dosage.

Compared to the 10 mg QD dose, the 30 mg BIW dose resulted in a 14% lower Cav_{g,ss} and a 7% higher C_{max,ss}. The predicted proportion of safety events was similar between the 10 mg QD and 30 mg BIW doses. However, it remains unclear whether a sustained higher Cav_g/C_{min} of 10 mg QD could lead to additional chronic safety concerns for QD dosing regimen.

Figure 29. Box Plot of Creatine Kinase (U/L) by Visit, Study DCC-3014-01-001



Source: Figure 6 of Applicant's IR response received on 9/16/2024.

Table 64. Parameter estimates for maximal CPK change from baseline covariate model and final model

Parameter	Unit	Covariate Model			Final Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
Intercept _{peb}	U/L	9.68×10^2	17.6	8.53×10^{-8}	1.16×10^3	12.1	1.33×10^{-13}
Cavg,ss	U/L per ng/mL	0.0222	7.92×10^2	0.900	0.0627	2.77×10^2	0.719
Baseline age	U/L per year ^a	-4.36	1.4×10^2	0.478			
Sex: Male	U/L ^a	2.64×10^2	63.9	0.120			
Race: Non-White	U/L ^a	6.71×10^2	37.5	0.00861			
Tumor type: MST	U/L ^a	-6.32×10^2	32.8	0.00282	-7.15×10^2	26.4	2.36×10^{-4}

Source: Table 6 of Applicant's IR response received on 9/20/2024. Compared to the associated reference levels: Cavg,ss (ng/mL): 0; Age (year): 52.0; Sex: Female; Race: White or missing; Tumor type: TGCT. A linear effect of Cavg,ss was modeled.

Table 65. Parameter estimates for CPK first elevation of any grade based on CTCAE from covariate model and final model

Parameter	Unit	Covariate Model			Final Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
Cavg,ss	LH per ng/mL	0.677	36.9	0.00668	0.634	38.0	0.00851
Age	LH per year	0.0191	39.2	0.0107			
Sex: Male	LH ^a	0.330	66.6	0.133			
Race: Non-White	LH ^a	0.377	82.9	0.228			
Tumor type: MST	LH ^a	-1.72	28.2	3.87×10^{-4}	-1.34	34.6	0.00388

Source: Table 7 of Applicant's IR response received on 9/20/2024. Compared to the associated reference levels: Cavg,ss (ng/mL): 0; Age (year): 48.0; Sex: Female; Race: White or missing; Tumor type: TGCT. A log-linear effect of Cavg,ss was modeled. LH: log hazard scale.

Table 66. Parameter estimates for CPK first elevation of grade ≥ 3 based on CTCAE covariate model and final model

Parameter	Unit	Covariate Model			Final Model		
		Estimate	RSE (%)	P-value	Estimate	RSE (%)	P-value
Cavg,ss	LH per ng/mL	0.814	44.2	0.0235	0.587	56.3	0.0758
Age	LH per year	0.0301	35.2	0.00446	0.0281	36.6	0.00624
Sex: Male	LH ^a	0.693	42.7	0.0191			
Race: Non-White	LH ^a	0.453	97.6	0.305			
Tumor type: MST	LH ^a	-2.78	37.3	0.00733	-2.66	38.6	0.00955

Source: Table 8 of Applicant's IR response received on 9/20/2024. Compared to the associated reference levels: Cavg,ss (ng/mL): 0; Age (year): 48.0; Sex: Female; Race: White or missing; Tumor type: TGCT. A log-linear effect of Cavg,ss was modeled. LH: log hazard scale.

19.4.2.6. Reviewer's Independent Analysis

Efficacy with a high rate of dose reduction

Given AE leading to dose reduction occurred in 39% of patients early, relative to the median time to response, the impact on efficacy was evaluated. ORR by RECIST/TVS between patients with and without dose reduction at any time during treatment was compared, which showed similar % of responders (Table 67). Notably, the steady-state exposures in patients with dose reduction were higher than those without dose reduction, indicating dose modifications are needed to mitigate exposure driven toxicities. Considering these toxicities are generally reversible, the proposed dosage is considered acceptable.

Table 67. Efficacy and exposure by dose reduction in MOTION study.

	No dose reduction (n=41)	Dose reduction* (n=42)
ORR by RECIST1.1	47%	51%
ORR by TVS	61%	74%
C _{max,ss}	735 (45%)	886 (26%)
C _{min,ss}	392 (65%)	506 (27%)
C _{avg,ss}	536 (52%)	665 (25%)
C _{avg} till the last dose by DCO	484 (54%)	469 (33%)

Source: Reviewer's analysis. *Dose reduction includes those due to TEAE and other reasons. Exposure summary: geomean (CV%). DCO: data cutoff date 8/22/2023.

19.4.2.7. Overall benefit-risk evaluation based on E-R analyses

The Applicant's Position:

An exposure efficacy analysis based on data from participants with TGCT who were randomized to receive 30 mg twice weekly dosing regimen in MOTION did not show association between vimseltinib exposure and ORR per RECIST v1.1 or TVS. A flat exposure-efficacy relationship was identified across the exposure range for the evaluated dosing regimen. The exposure-efficacy model could not predict ORR per RECIST v1.1 or TVS outside of the 30 mg twice weekly dosing regimen, as a substantial part of the simulated exposure distribution would be outside of the evaluated exposure range.

An exposure safety analysis including data from participants with TGCT who were randomized to receive 30 mg twice weekly dosing regimen in MOTION showed a positive and mostly shallow relationship between vimseltinib exposure and safety (periorbital edema, rash, ALT, and AST). Predictions from exposure-safety models showed that lower vimseltinib exposure may decrease the probability of safety events in some participants. For periorbital edema, rash, and ALT elevation, the difference in the median predicted proportions of these safety events at Week 25 was marginal at <5% following 20 mg twice weekly, compared to 30 mg twice weekly. For AST

elevation, the difference was 7.3%. However, the predictions are associated with large statistical uncertainty.

Overall, the exposure response analysis supports vimseltinib 30 mg twice weekly as the optimal dosing regimen in patients with TGCT.

The FDA's Assessment:
FDA generally agrees that Applicant's position.

19.4.3. PBPK Analysis

19.4.3.1. Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate the drug-drug interaction (DDI) potentials of vimseltinib:

- as an inducer of CYP2B6
- as an inhibitor of P-gp, BCRP, OATP1B1/3 and OCT2

The Division of Pharmacometrics has reviewed the PBPK report ((b) (4)-report, seq 002), the response to FDA's information requests submitted on September 10th (seq 0010, clin-response-ir13-20240910), and the modeling supporting files to conclude the following:

- Vimseltinib was predicted to increase dabigatran AUC and C_{max} up to 3.0-fold when simultaneously administered and considering the uncertainty on the in vitro generated IC₅₀ value of P-gp. The inhibitory effects of vimseltinib may be mitigated by administering dabigatran 4 hours after vimseltinib dosing. (b) (4)
- Vimseltinib was predicted to increase rosuvastatin AUC and C_{max} up to 2.6- and 6.3-fold, respectively when simultaneously administered and considering the uncertainty on the in vitro generated IC₅₀ value of BCRP. (b) (4)
- The PBPK analysis of CYP2B6 interaction was not evaluated because (b) (4)
- The PBPK analysis of (b) (4)

19.4.3.2. Background

Vimseltinib, also known as DCC-3014 and DP-6865, is a kinase inhibitor of the colony-stimulating factor 1 receptor (CSF1R) kinase currently being developed for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT). The available dose strengths are 14, 20 and 30 mg capsules. The recommended dosing regimen is 30 mg administered orally twice weekly at least three days apart. The tablets should be swallowed as a whole and can be taken with or without food.

Following oral administration of single doses of vimseltinib 6 to 50 mg in healthy subjects, vimseltinib C_{max} and AUC_{0-24h} were increased dose proportionally (DCC-3014-01-002). In patients with TGCT (Cohort 5 of Study DCC-3014-01-001), exposure on Cycle 2 Day 1 following twice weekly 30 mg doses was approximately 3.6-fold higher than exposure following a single 30 mg dose (Cycle 1 Day 1) (). Steady state was reached following approximately 5 weeks of 30 mg vimseltinib twice weekly administration (DCC-3014-01-001). Following administration of a single 30 mg vimseltinib with a standardized FDA high-fat meal in healthy subjects, the C_{max} of vimseltinib decreased approximately 30%, compared to the fasted state, and T_{max} was delayed by 5 hours. Its AUC_{0-inf} was comparable under the fasted and fed conditions (DCC-3014-01-002).

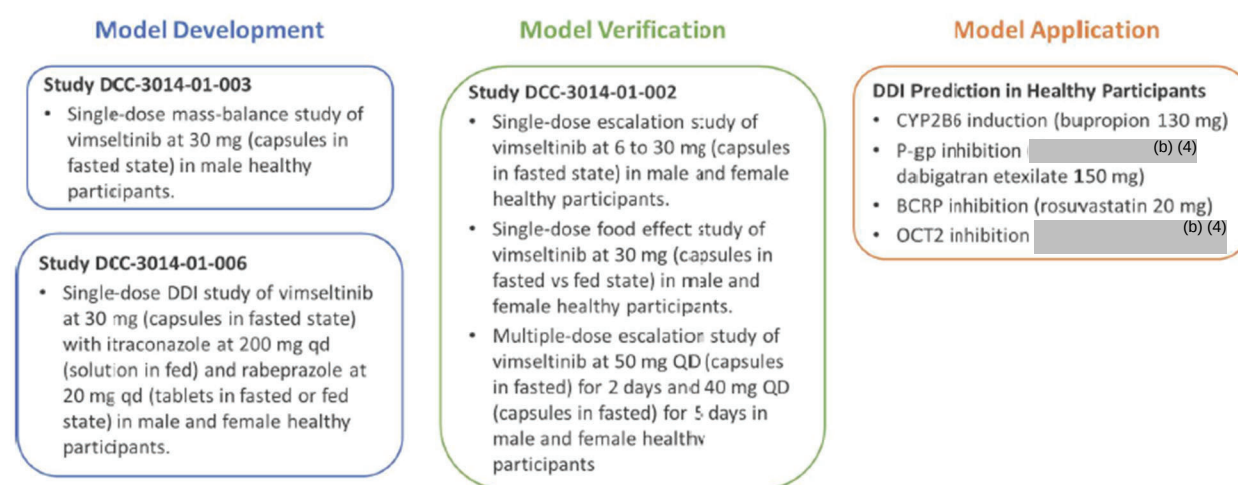
Vimseltinib has high permeability and pH-dependent solubility. It is well-absorbed and is extensively metabolized primarily via oxidation, N-demethylation, and N-dealkylation (DCC-3014-03-0023). The enzymes involved in the metabolism of vimseltinib were not identified when parent disappearance was monitored for the reaction phenotyping studies conducted using human liver microsomes and recombinant CYP enzymes due to low turnover of vimseltinib (DCC-3014-03-0007). In the human ADME study, approximately 37.5% and 42.9% of radioactivity were recovered in the urine (5.1% unchanged parent) and the feces (9.1% unchanged parent), respectively (DCC-3014-01-003).

Vimseltinib is not a competitive or time-dependent inhibitor of any of the commonly studied CYP enzymes (DCC-3014-03-0001). Vimseltinib is not an inducer of CYP1A2 and CYP3A4. Although dose-dependent induction of CYP2B6 was observed, the fold induction of CYP2B6 mRNA and activity was below 2-fold at the vimseltinib concentration that was 50 times of its unbound steady-state C_{max} (DCC-3014-03-0009). Vimseltinib is a substrate of P-gp (DCC-3014-03-0006). Vimseltinib inhibits P-gp (IC_{50} = 4.35 μ M), BCRP (IC_{50} = 0.556 μ M), OATP1B3 (IC_{50} = 10.1 μ M), OATP1B1 (IC_{50} = 9.21 μ M), MATE1 (IC_{50} = 7.58 μ M), MATE2K (IC_{50} = 23.3 μ M), OAT1 (IC_{50} = 51.5 μ M), OAT2 (IC_{50} = 23.7 μ M), and OCT2 (IC_{50} = 0.456 μ M) (DCC-3014-03-0006, DCC-3014-03-0024). The applicant conducted clinical DDI studies with itraconazole, and rabeprazole to evaluate some of the *in vitro* findings. Refer to the Clinical Pharmacology review section for detail information on vimseltinib regarding ADME properties, *in vitro* and clinical studies used in PBPK modeling.

19.4.3.3. Methods

Simulations related to evaluation of vimseltinib as an inhibitor of transporters were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 22 Certara, Sheffield, UK). Schemes of the PBPK simulation strategy are shown in Figure 30, which summarizes the studies used for vimseltinib model development and verification, and model applications in DDI predictions. The final model input parameters were summarized in Table 68. The vimseltinib PBPK model consists of an ADAM absorption model, a full PBPK model for distribution and an enzyme kinetics model for elimination. The Simcyp library files itraconazole_Fasted soln, SV-bupropion, (b) (4), SV-dabigatran, SV-rosuvastatin, and (b) (4) were used for DDI simulations without any modification.

Figure 30. Modeling and simulation strategy



DDI: drug-drug interaction; HV: healthy participants; QD: once a day

Source: Figure 2 in the PBPK report DPHA/3/B

Table 68 Final input parameters in the vimseltinib model

PARAMETER	VALUE	SOURCE	PARAMETER	VALUE	SOURCE
Phys Chem and Blood Binding			CYP3A4 CL _{int} (μL/min/pmol)	0.0067	Retrograde calculation
MW (g/mol)	431.49	Simcyp Data Checklist	HLM CL _{int} (μL/min/mg)	3.389	Retrograde calculation
Log P	3.11	Log P CE for DP-6865 12-14-2018.xlsx	CL _R (L/h)	0.00333	Report DCC-3014-01-002
Compound type	Diprotic base	Simcyp Data Checklist	Interaction		
pKa	3.56 & 4.79	Simcyp Data Checklist	CYP2B6 Ind _{max}	(b) (4)	Estimated from DCC-3014-03-0009
B:P	0.74	DCC-3014-03-0026	CYP2B6 IndC ₅₀ (μM)		Estimated from DCC-3014-03-0009
f _u	0.034	DCC-3014-03-0002	f _{u,inc}		
Main binding protein	HSA	Simcyp Data Checklist	P-gp K _u (μM)		Computed from reported IC ₅₀ from DCC-3014-03-0006
Absorption			BCRP K _u (μM)		Computed from reported IC ₅₀ from DCC-3014-03-0006
Model	ADAM		OCT2 K _u (μM)		Computed from reported IC ₅₀ from DCC-3014-03-0006
P _{app} (x10 ⁻⁶ cm/s) – Caco-2 pH 7.4/7.4	16.8	20DCPHP2			
Calibrator P _{app} (x10 ⁻⁶ cm/s)	0.389	20DCPHP2			
P _{eff} (x10 ⁻⁶ cm/s)	3.32	Simcyp prediction (Caco-2 pH 7.4/7.4; Passive & Active)			
f _{gut}	1	Assumed (default)			
Intrinsic Solubility (mg/mL)	0.0029	Estimated from <i>in vitro</i> pH-solubility data using SIVA			
SF1	45504	Estimated from <i>in vitro</i> pH-solubility data using SIVA			
CSR	50	Obtained using sensitivity analysis to match the reported fa			
PRC (1/h)	4	Default			
Particle size d50 (μm)		(b) (4)			
Distribution					
Model	Full				
V _{ss} (L/kg)	2.1	Predicted using Method 3			
K _p scalar	1.54	Adjusts predicted V _{ss} to match allometrically scaled V _{ss} from mice, rats, dogs and monkeys			
Elimination					
Model	In vivo CL				
CL/F (L/h)	0.564	Report DCC-3014-01-003			
f _{mCYP3A4}	20%	Obtained based on matching the observed itraconazole DDI effects in the clinic			

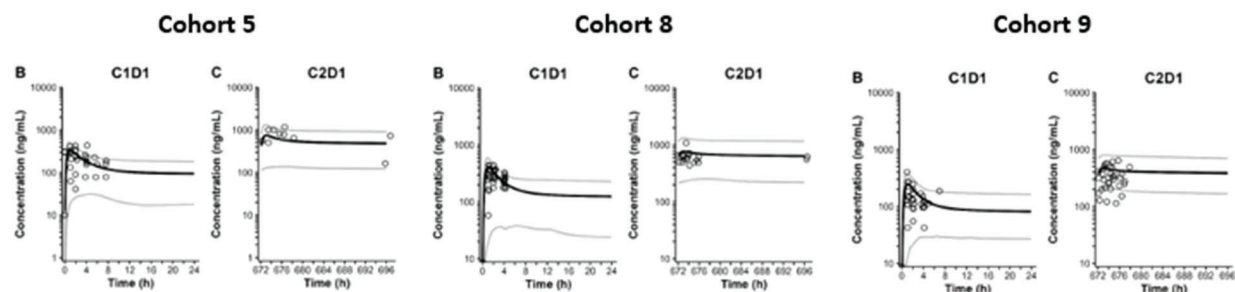
Source: Table 3 in the PBPK report DPHA/3/B

19.4.3.4. Results

1. Can the PBPK model adequately describe the PK profiles of vimseltinib?

Yes. The vimseltinib PBPK model could reasonably well describe vimseltinib PK following administration of single and multiple doses of vimseltinib in healthy subjects (Study DCC-3014-01-002) (data not shown), and in patients with TGCT (Study DCC-3014-01-001). The latter was simulated at the reviewer’s request and the results are shown in Figure 31 and Table 69.

Figure 31. Simulated and observed PK profiles following oral administration of single and multiple doses of vimseltinib in patients with TGCT



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Depicted are simulated (lines) and observed data (circles, n = 12 Clinical Study DCC-3014-01-001). The grey lines represent the 5th and 95th percentiles and the solid black line the mean data for the simulated population (n = 120). The Simcyp cancer population model was used in the simulations.

Source: Figures 2-4 in the clin-response-ir13-20240910 (seq 0010)

Table 69 Simulated and observed PK parameters following oral administration of single and multiple doses of vimseltinib in patients with TGCT

Patients with TGCT	Loading doses	Maintenance doses	Trials	Cycle 1 Day 1		Cycle 2 Day 1	
				AUC _{0-4h} (ng/mL*h)	C _{max} (ng/mL)	AUC _{0-4h} (ng/mL*h)	C _{max} (ng/mL)
Cohort 5	30 mg QD 5d	30 mg BIW 28d	Simulated	876	307	2457	705
			Observed	745	273	2710	838
			S/O	1.18	1.12	0.907	0.841
Cohort 8	30 mg QD 3d	10 mg QD 28d	Simulated	1016	360	2646	702
			Observed	904	320	2450	709
			S/O	1.12	1.13	1.08	0.991
Cohort 9	20 mg QD 3d	6 mg QD 28d	Simulated	606	216	1603	426
			Observed	442	163	1210	371
			S/O	1.37	1.33	1.32	1.15

QD, once daily; BIW, twice a week; S/O, simulated/observed; d, day. The Simcyp cancer population model was used in the simulations.

Source: Tables 4 -6 in the clin-response-ir13-20240910 (seq 0010)

2. Can PBPK analyses be used to estimate the effects of vimseltinib on substrates of CYP2B6 and transporters?

Induction effects of vimseltinib on the CYP2B6 substrate bupropion

At the vimseltinib concentration that was 50 times of its unbound steady-state C_{max} at the currently recommended dosing regimen, (b) (4). Therefore, vimseltinib is not considered as a clinical CYP2B6 inducer based on the ICH M12 Guideline on Drug Interaction Studies. Therefore, the PBPK analysis of induction effects of vimseltinib on the CYP2B6 substrate bupropion was not evaluated.

Effects of vimseltinib on the OATP1B and BCRP substrate rosuvastatin

The predicted effects of vimseltinib on rosuvastatin were inadequate for reasons detailed below.

(b) (4)

Source: Table 11 in clin-response-ir13-20240910

Effects of vimseltinib on the P-gp substrate dabigatran etexilate

Dabigatran etexilate is a P-gp substrate. Dabigatran is a metabolite of dabigatran etexilate and is not a P-gp substrate. The effects of P-gp inhibitors on dabigatran etexilate are assessed by changes in dabigatran plasma exposure. The ability of the PBPK models of dabigatran etexilate and dabigatran to predict P-gp interaction was assessed using clinical DDIs of dabigatran with verapamil, clarithromycin, quinidine, and ketoconazole (Dabigatran Simcyp summary report). Of note, the ketoconazole DDI data was also used in the model development. Large range of IC₅₀ values of these inhibitors are reported in the Certara DDI Database. The difference in IC₅₀ between minimum and maximum values of each inhibitor ranges from 22- to 7450-fold if all the results were considered, and 1.5- to 280-fold if only experiments conducted in the condition similar to that of vimseltinib (e.g. Caco-2 cells and (b) (4) as a probe substrate) were considered. In addition, the reviewer (b) (4)

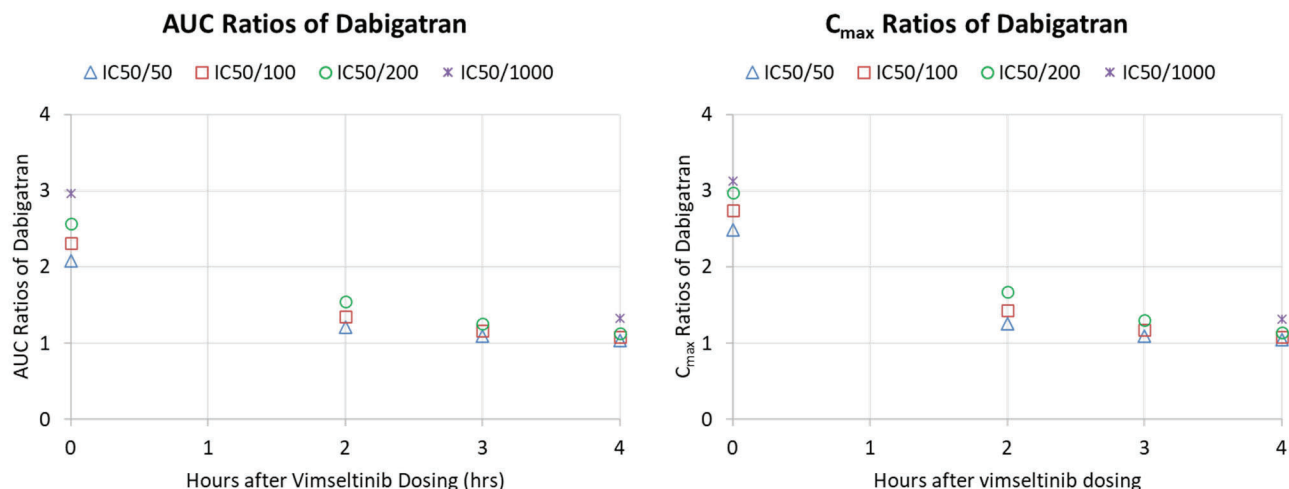
[REDACTED]

The applicant was requested to simulate the effects of vimseltinib on dabigatran exposure when the P-gp K_i was 50-, 100-, and 200-fold lower than the in vitro IC₅₀, and the dose staggering scheme under the above conditions. The results are shown in Figure 33. When vimseltinib and dabigatran etexilate were administered simultaneously and considering a P-gp K_i value 200-fold lower than the in vitro IC₅₀ value, vimseltinib was predicted to increase dabigatran AUC and C_{max} by approximately 2.6- and 3.0-fold, respectively, which were approximately 2-fold higher than that predicted using the K_i value calculated from the in vitro IC₅₀ value using the Cheng-Prusoff equation (PMID: 4202581). In addition, the reviewer also simulated the effects of vimseltinib on dabigatran exposure by reducing the P-gp IC₅₀ value by 1000-fold. Vimseltinib was predicted to increase both dabigatran AUC and C_{max} by approximately 3.0-fold. When dabigatran etexilate was administered 4 hours after vimseltinib dosing, the inhibitory effects of vimseltinib on dabigatran exposure were diminished (e.g. increases in AUC and C_{max} were approximately 1.25-fold) regardless of the K_i value used in the simulations. Therefore, despite uncertainties in the predicted interaction effect of vimseltinib, the potential risk for a clinically significant interaction between vimseltinib and the P-gp substrate dabigatran etexilate may be mitigated via dose staggering.

Of note, the Applicant (b) (4)

[REDACTED]

Figure 33 Effects of vimseltinib on dabigatran exposure following staggered dosing



Ten virtual trials of 10 patients with cancer (50% female) aged 20 to 50 years receiving 150 mg dabigatran etexilate (P-gp probe substrate) as a single dose with and without co-administration of vimseltinib (30 mg given every 84 hours for a total of 46 days) were generated. All simulations were performed under steady-state conditions for vimseltinib. Staggering simulations were performed in which the dose of dabigatran etexilate was administered 0 to 4 hours after the last dose of vimseltinib (30 mg every 84 hours for 46 days). K_i values that were 50-, 100-, 200- and 1000-fold lower than in vitro IC50 value for P-gp were applied in these simulations. The simulated geometric mean AUC_{inf} and C_{max} values and corresponding GMRs for dabigatran with and without coadministration of vimseltinib are presented.

Source: Table 10 in clin-response-ir13-20240910

Effects of vimseltinib on the OCT2 substrate (b) (4)

The PBPK analysis predicting the potential for drug interaction of vimseltinib with (b) (4) by (b) (4) OCT2 inhibition is considered inadequate.

[Redacted content]

(b) (4)

19.4.3.5. Conclusions

- PBPK analysis was considered adequate to inform the interaction potential between vimseltinib and the P-gp substrate dabigatran. Vimseltinib was predicted to increase dabigatran AUC and $C_{\max}$ 2- to 3.0-fold when administered simultaneously and considering the uncertainty on the in vitro generated IC_{50} of P-gp,. However, dabigatran AUC and $C_{\max}$ were predicted to increase up to 1.3-fold when dabigatran etexilate was administered 4 hours after vimseltinib dosing regardless of the K_i value used in the simulations. Therefore, despite uncertainties in the predicted effect, the potential risk for a clinically significant interaction between vimseltinib and the P-gp substrate dabigatran etexilate may be mitigated via dose staggering. (b) (4)
- Vimseltinib was predicted to increase rosuvastatin AUC and $C_{\max}$ up to 2.6- and 6.3-fold, respectively when simultaneously administered and considering the uncertainty on the in vitro generated IC_{50} of BCRP. (b) (4)
- The PBPK analysis of CYP2B6 interaction was not evaluated because (b) (4)
- The PBPK analysis of vimseltinib interaction with (b) (4) is considered inadequate because the (b) (4)

19.4.4. Bioanalytical Method Validation Analysis

The FDA's Assessment:

Plasma concentrations of vimseltinib were determined with method # (b) (4) 1100004 at (b) (4) for Studies MOTION, DCC-3014-01-002, DCC-3014-01-003, DCC-3014-01-004, and DCC-3014-01-006. Plasma concentrations of vimseltinib were determined with method # (b) (4) at (b) (4) for Study DCC-3014-01-001. Plasma concentrations of vimseltinib were determined with method# (b) (4) 5051604 at (b) (4) for Study DCC-3014-01-004.

Table 70: Summary of Bioanalytical Method Performance of (b) (4) 1100004

Bioanalytical method review summary	Determination of DCC-3014 and DP-7005 in Human K2-EDTA Plasma by LC-MS/MS ((b) (4) 1100004). This method underwent three amendments. • <u>Validation amendment report No.1: Partial Validation ((b) (4) 1100004 am1).</u> This amendment extended the calibration standards for DP-7005 only. • <u>Validation amendment report No.2: Additional Long-Term Stability, Cross Validation, and Interference Check ((b) (4) 1100004 am2).</u> This amendment was created to report long-term stability in human K2-EDTA plasma for DCC-3014 stored for 372 days at -70°C and stored for 525 days at -20°C. Additionally, the assay procedure underwent cross validation for laboratory relocation, meeting the established acceptance criteria. This amendment also reported the interference evaluation of the samples, for each analyte at the concentration of the LLOQ calibration standard, in the presence of itraconazole and hydroxyitraconazole, each at about 3000 ng/mL, and rabeprazole at about 1000 ng/mL. • <u>Validation amendment report No.3: Additional Matrix Effect ((b) (4) 1100004 am3).</u> For this post- validation study, additional analyses were conducted under ((b) (4) 1100004 using ((b) (4) -2638 to evaluate matrix effect using the procedure and criteria in the M10 Guidance.		
Method description	The method was validated for a range of 1-2000 ng/mL for DCC-3014 based on the analysis of 50 µL of human K2-EDTA plasma. Human plasma containing DCC-3014 and the internal standard, DCC-3014-¹³CD3, was extracted using protein precipitation and analyzed by a Sciex API 5000 LC-MS/MS equipped with an HPLC column. The peak area of the m/z 432.1→306.1 DCC- 3014 product ion was measured against the peak area of the m/z 436.1→310.1 DCC-3014-¹³CD3 internal standard product ion. The peak area of the m/z 390.1→306.2. Quantitation was performed using separate weighted 1/x² (for each analyte) linear least squares regression analyses generated from calibration standards prepared on the day of extraction.		
Materials used for calibration curve & concentration	Stock solutions of reference standards and internal standards: dimethyl sulfoxide/methanol (1:1). The solvent used to prepare intermediate solutions of reference standards from stock solutions: methanol/water (1:1). Combined working internal standard solution: methanol/water (1:1) Matrix of standard calibration curve: human K2-EDTA plasma. DCC-3014: 1, 2, 10, 50, 250, 1000, 1800, and 2000 ng/mL		
Validated assay range	DCC-3014: 1-2000 ng/mL		
Material used for QCs & concentration	Matrix of QCs: human K2-EDTA plasma DCC-3014: 1 ng/mL (LLOQ), 3 ng/mL (QC low), 1000 ng/mL (QC medium), 1600 ng/mL (QC high), 10,000 ng/mL (QC very high)		
Minimum required dilutions (MRDs)	N/A		
Source & lot of reagents (LBA)	This method did not use any critical reagents.		
Regression model & weighting	Separate weighted 1/x ² (for each analyte) linear least squares regression		
Validation parameters	Method validation summary		Acceptability
	No of standard calibrators from LLOQ to ULOQ	8	Yes

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.9% to 3.6%	Yes
	Cumulative precision (%CV) from LLOQ to ULOQ	1.9% to 5.4%	Yes
<u>QCs performance during accuracy & precision</u>	Cumulative accuracy (%bias) in 4 QCs	-2.5% to 4%	Yes
	Inter-batch %CV	2.5% to 7.3%	Yes
	Percent total error (TE)	N/A	Yes
Selectivity & matrix effect	(b) (4) 1100004: 6 individual lots of human K2-EDTA plasma were tested. Acceptance criteria were met for selectivity. For the evaluation of matrix effect, the precision met acceptance criteria overall. (b) (4) 1100004 _am3: Matrix effect was evaluated according to the M10 Guidance. 6 individual lots assessed met acceptance criteria for DCC-3014.		Yes
Interference & specificity	No significant interference was seen from the medications tested in the validation.		Yes
Hemolysis effect	(b) (4) 1100004: IS-normalized matrix factor of DCC-3014 in hemolytic samples (obtained from 1 lot): 1.09 (2 ng/mL) and 0.986 (1800 ng/mL) (b) (4) 1100004 _am3: Matrix effect for the hemolytic lot was evaluated according to the M10 Guidance. The results at low and high QC levels had a mean % bias and % CV within 15% for DCC-3014.		Yes
Lipemic effect	(b) (4) 1100004: IS-normalized matrix factor of DCC-3014 in lipemic samples (obtained from 1 lot): 0.956 (2 ng/mL) and 1.03 (1800 ng/mL) (b) (4) 1100004 _am3: Matrix effect for the hemolytic lot was evaluated according to the M10 Guidance. The results at the low QC level had a mean % bias and % CV within 15% for DCC-3014. The results at the high QC level had a mean % CV within 15% for DCC-3014. The assessment at the high QC level had a mean % bias of 17.5% for DCC-3014.		Yes
Dilution linearity & hook effect	Six replicates of the dilution QC level were diluted 10x prior to analysis. The following acceptance criterion was applied: intra-run precision and accuracy must be within 15%. The dilution integrity met the acceptance criterion. DCC-3014 concentration of 10,000 ng/mL was diluted 10-fold. %CV=1.6%; %Bias=-3.1%		Yes
Bench-top/process stability	Stable for up to 24 hours at room temperature		Yes

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Freeze-Thaw stability	Stable for up to 5 freeze-thaw cycles from -20°C to ambient or -70°C to ambient	Yes
Long-term storage	Stable at -20°C for 525 days and at -70°C for 372 days	Yes
Parallelism	N/A	Yes
Carry over	The blank matrix sample following the ULOQ standard was used to assess carryover. The following acceptance criteria were applied: if a peak was noted, the peak response at the retention time of the analyte must be ≤20% of the peak response of the LLOQ standard analyzed within the same run. A peak response noted at the retention time of the IS must be ≤5% of the mean of the non-zero internal standard responses for the run. Acceptance criteria for carryover were met during method validation	Yes
Method performance in Study DCC-3014-03-001 (Report (b) (4) 5030142)		
Assay passing rate	92.1%	Yes
Standard curve performance	- Cumulative bias range: -2.2% to 2% - Cumulative precision: 2.8% to 5.8%	Yes
QC performance	- Cumulative bias range: -7.5% to -4% - Cumulative precision: 4.8% to 8.4%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 10% (151/1440) study samples. 92.1% of samples met the prespecified criteria for DCC-3014.	Yes
Study sample analysis/stability	Study samples were analyzed within the 525 days at -20°C.	
Standard calibration curve performance during accuracy and precision runs	Total 8 of standard calibrators from LLOQ to ULOQ for DCC-3014: 1, 2, 10, 50, 250, 1000, 1800, and 2000 ng/mL	
Method performance in Study DCC-3014-01-003 (Report (b) (4) 5010986)		
Assay passing rate	100%	Yes
Standard curve performance	- Cumulative bias range: -3.5% to 6% - Cumulative precision: 2.7% to 6.2%	Yes
QC performance	- Cumulative bias range: -1.9% to 4.2% - Cumulative precision: 3.5% to 10.1%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 9% (23/248) study samples. 100% of samples met the prespecified criteria for DCC-3014.	Yes
Study sample analysis/stability	Study samples were analyzed within the 525 days at -20°C.	
Standard calibration curve performance during accuracy and precision runs	Total 8 of standard calibrators from LLOQ to ULOQ for DCC-3014: 1, 2, 10, 50, 250, 1000, 1800, and 2000 ng/mL	
Method performance in Study DCC-3014-01-006 (Report (b) (4) 5035405)		
Assay passing rate	93.5%	Yes
Standard curve performance	- Cumulative bias range: -3% to 3.2% - Cumulative precision: 2.4% to 5.7%	Yes
QC performance	- Cumulative bias range: -0.6% to 2.2% - Cumulative precision: 5.8% to 10%	Yes

NDA/BLA Multi-disciplinary Review and Evaluation {NDA 219304}
ROMVIMZA (vimseltinib)

Method reproducibility	Incurred sample reanalysis was performed on 13% (260/2034) study samples. 93.5% of samples met the prespecified criteria for DCC-3014.	Yes
Study sample analysis/stability	Study samples were analyzed within the 525 days at -20°C.	
Standard calibration curve performance during accuracy and precision runs	Total 8 of standard calibrators from LLOQ to ULOQ for DCC-3014: 1, 2, 10, 50, 250, 1000, 1800, and 2000 ng/mL	
Method performance in Study DCC-3014-01-002 (Report (b) (4) 5010845_am1)		
Assay passing rate	83.1%	Yes
Standard curve performance	- Cumulative bias range: -3.5% to 2.4% - Cumulative precision: 2.5% to 5.9%	Yes
QC performance	- Cumulative bias range: -5.7% to -1% - Cumulative precision: 1.2% to 8.1%	Yes
Method reproducibility	Incurred sample reanalysis was performed on 7% (240/3634) study samples. 83.1% of samples met the prespecified criteria for DCC-3014.	Yes
Study sample analysis/stability	Study samples were analyzed within the 525 days at -20°C.	
Standard calibration curve performance during accuracy and precision runs	Total 8 of standard calibrators from LLOQ to ULOQ for DCC-3014: 1, 2, 10, 50, 250, 1000, 1800, and 2000 ng/mL	
Method performance in Study DCC-3014-01-004 (Report (b) (4) 5064385)		
Assay passing rate	N/A. <i>Since this study has been completed and a PMR on hepatic impairment has been issued, an ISR can be performed on the method performance to be used to fulfill that PMR.</i>	Yes
Standard curve performance	- Cumulative bias range: -3.5% to 3.2% - Cumulative precision: 0.3% to 7%	Yes
QC performance	- Cumulative bias range: -5.5% to 0% - Cumulative precision: 3.4% to 9%	Yes
Method reproducibility	Incurred sample reanalysis has not been conducted and will be performed in the following runs, as the Applicant claims that the study is in process. <i>Since this study has been completed and a PMR on hepatic impairment has been issued, an ISR can be performed on the method performance to be used to fulfill that PMR.</i>	Yes
Study sample analysis/stability	Study samples were analyzed within the 525 days at -20°C.	
Standard calibration curve performance during accuracy and precision runs	Total 8 of standard calibrators from LLOQ to ULOQ for DCC-3014: 1, 2, 10, 50, 250, 1000, 1800, and 2000 ng/mL	

Signatures

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Clinical Reviewer Team Leader	Leslie Doros	DO3	Sections: 1, 2 3, 4, 7, 8, 9, 10, 12, 13, 19.1, 19.1	Select one: ☒ Authored ☒ Approved
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Statistical Reviewer	Sirisha Mushti	DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	Select one: ☒ Authored ☒ Approved
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Statistical Team Leader	Chi Song	DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	Select one: ☒ Authored ☒ Approved
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Division Director (OB)	Shenghui Tang	DBV	Sections: 1, 7, 8.1, 8.3 and 8.4	Select one: ☒ Approved
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CDTL	Leslie Doros	DO3	Sections: All	Select one: ☒ Authored ☒ Approved
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Deputy Division Director (Clinical)	Chana Weinstock	DO3	Sections: All	Select one: ☒ Authored ☒ Approved
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Office Director	Paul G. Kluetz	OCE	Sections: All	Select one: ☒ Authored ☒ Approved
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02/14/2025 12:37:14 PM