CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

219304Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
General ARIA Sufficiency Memorandum

Date	2/11/2025
Product Name	Romvimza [vimseltinib (DCC-3014)]
Application Type/Number	NDA 219304
Sponsor/Applicant	Deciphera Pharmaceuticals
Reviewer	Fang Tian, PhD, MPH, MHS Division of Epidemiology I
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General ARIA Sufficiency Memorandum

CONTENTS

ARIA Sufficiency Memorandum for a Single Outcome

1. Executive Summary

Context: Is FDA considering requiring a FDAAA PMR and/or is this a part of a NISS assessment?	**FDAAA PMR** Yes	**NISS** No
FDAAA purpose[1]	Assess signals of a serious risk	
NISS	N/A	
Medical product exposure	Romvimza [vimseltinib (DCC-3014)]	
Comparators	N/A	
Outcome and MedDRA preferred term (PT)	Serious hepatotoxicity	
Review phase	During review of an original or supplemental NDA or BLA (pre-approval)	
ARIA sufficiency determination	No	
If ARIA is insufficient, identify epidemiologic area(s) of insufficiency	☐ Study Population	
	☐ Exposure	
	☒ Outcome	
	☐ Covariates	
	☐ Analytic Tools	

2. Background Information

2.1 Medical Product

Drug Name(s)	Romvimza [vimseltinib (DCC-3014)]
Indication(s)	Treatment of patients with tenosynovial giant cell tumor (TGCT)
Route of Administration	Oral use
Dosing Regimen	30 mg orally twice weekly, with a minimum of 72 hours between doses as described in the blister package
Therapeutic Class	kinase inhibitor
Mechanism of Action	Inhibit colony-stimulating factor 1 receptor (CSF1R)
Current standard of care	Excision of tumor is the mainstay of treatment.
Alternative therapeutic options	Pexidartinib is an approved systemic therapy for patients who are not candidates for surgery.

[1] Per Section 505(o)(3)(B), please ensure that the selected purpose is consistent with the PMR/PMC Development Template. This purpose will also appear in the approval letter.

Other product information (relevant to the safety concern)	Pexidartinib is a kinase inhibitor of CSF1R and is associated with a risk of severe, potentially life-threatening, liver injury.

2.2 Characterization of the Safety Concern

Vimseltinib, pexidartinib and axatilimab are colony-stimulating factor 1 receptor (CSF1R) inhibitors. Transaminase elevations (ALT and AST) have been observed in clinical studies with vimseltinib, pexidartinib and axatilimab. The transient elevation in these enzymes has not been associated with end organ damage or hepatotoxicity. Pexidartinib, however, is associated with a clinically distinct type of hepatic adverse reaction characterized by mixed or cholestatic hepatotoxicity which is unpredictable and potentially irreversible but has not been observed with vimseltinib. The applicant considers that hepatotoxicity is specific to pexidartinib based on mechanism of action (Deciphera Pharmaceuticals, Response to FDA Information Request, 10/7/2024) and is not a CSF1R class effect; however, additional data are sought to determine whether the postulated CSF1R class effect is seen in vimseltinib.

Source(s) of safety concern (Choose all that apply):		
☐ Citizen Petition	☐ Lay Media	☐ Periodic Safety Update Report
☐ Compliance Inspection/Report	☐ Medical Literature	☐ PMR/PMC Report
☐ Congressional Inquiry	☒ NDA or sNDA/BLA or sBLA[2]	☐ Not Applicable
☐ FAERS	☐ Other Submission (IND)	☐ Other: Click to enter other source(s).
☐ Foreign Regulatory Agency	☐ Other Federal Agency	
Evidence Driving the Safety Concern[3] (Choose all that apply and describe below):		
☐ Meta-analyses	☐ Observational studies	☐ Other studies (animal, in vitro)
☐ Randomized trials	☐ Pharmacovigilance activities	☒ Expert experience/mechanism of action (class-based risk)
Cases of serious and fatal liver injury have occurred with the use of another kinase inhibitor that targets CSF1R (e.g., TURALIO). Serious and fatal liver injury have not been observed with ROMVIMZA but may be anticipated to occur.		
Signal Strength[4]	Moderate	
Level of Clinical Concern[5]	Moderate	
Risk Management Strategies:		

[2] Including animal studies, in vitro studies, imbalance RCT
[3] Describe safety concern(s), including case characteristics (e.g., is there a clinical pattern of events?), temporal distribution of outcomes (e.g., acute onset vs. variable-onset), assessment of the quality, directness, precision and causal association.
[4] This is the DEPI reviewer's subjective qualitative assessment of the "strength" of the signal, as based on the quality of the source of information about the safety concern, as well as the quantity and reliability of data to support the signal.
[5] This is the DEPI reviewer's subjective qualitative assessment of the "level of clinical concern" (e.g., seriousness of safety concern, magnitude of risk, prevalence of exposure) following discussions with the relevant team members.

Serious hepatotoxicity will be monitored through a clinical PMR for a registry study for hepatotoxicity and through routine pharmacovigilance.	
Labeling	Hepatotoxicity is listed in "WARNINGS AND PRECAUTIONS" Section.
REMS	N/A
Postmarket study or commitment	A PMR will be issued for a prospective clinical registry evaluating risk for serious hepatotoxicity.
Enhanced pharmacovigilance	N/A
Other strategies	N/A
Other Regulatory Background	N/A
Regulatory Gap	While serious hepatotoxicity was not observed within the clinical program, a concern remains due to the known hepatotoxicity observed with pexidartinib. Therefore, a PMR is needed to obtain additional safety data.

2.3 Study Purpose

FDAAA Purpose[6,7]	Assess signals of a serious risk
Regulatory Goal[8]	*Signal Refinement*

3. Study Population

The desired study population consists of adult patients with tenosynovial giant cell tumor (TGCT).

3.1 Study Population

Age group(s)	18 years and above
Sex	Both male and female
Racial group(s)	All racial groups

[6] A Serious Risk is a serious adverse drug experience whose definition also includes any failure of expected pharmacologic action, which may include reduced effectiveness.

[7] Per Section 505(o)(3)(B), please ensure that the selected purpose is consistent with the PMR/PMC Development Template. This purpose will also appear in the approval letter.

[8] **Signal Evaluation**: consists of the implementation of a full epidemiological analysis to thoroughly evaluate the causal relationship between exposure to the medical product and the health outcome of interest. **Signal Refinement**: a process by which an identified potential safety signal is further investigated to determine whether evidence exists to support a relationship between the medical product exposure and the health outcome. **Signal Identification**: the detection of new and unexpected potential medical product safety concerns and may be for a targeted or multiple safety concern(s)/health outcome(s). Definitions adapted from: Robb MA, Racoosin JA, Sherman RE, Gross TP, Ball R, Reichman ME, Midthun K, Woodcock J. The US Food and Drug Administration's Sentinel Initiative: expanding the horizons of medical product safety. Pharmacoepidemiol Drug Saf. 2012 Jan;21 (1) Suppl 1:9-11. doi: 10.1002/pds.2311. PMID: 22262587.

Clinical indication	Adult patients with symptomatic tenosynovial giant cell tumor (TGCT) for which surgical resection will potentially cause worsening functional limitation or severe morbidity
Clinical setting	All care settings
What variables are needed for inclusion and exclusion criteria that will be used to define the cohort?	Inclusion: Adults (≥18 years) diagnosed with TGCT during study period Exclusion: Known pre-existing severe liver disease (cirrhosis, hepatitis C infection).

3.2 ARIA Sufficiency for Study Population

Is ARIA sufficient to assess the intended population?	Yes
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	TGCT may be identified through ICD-10-CM diagnosis codes (C49, C41.9, D48.0, D48.1, D48.9, D21.0-D21.9, M12.2, M65.8-M65.9 or M67.9) in claims data.[9] ARIA is sufficient to identify the intended population.
If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the intended population? Check all that apply.	☐ Absence of validated code algorithm
	☐ Identification of clinical concepts with code algorithms not possible or inadequate
	☐ Inability to capture intent of treatment
	☐ Inadequate sample size
	☐ Insufficient capture of information on race
	☐ Insufficient capture of patient medical and/or family history
	☐ Insufficient clinical and laboratory cancer data that might be in a registry
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient inpatient data
	☐ Insufficient laboratory data
	☐ Insufficient observation time available
	☐ Insufficient radiology/pathology data
	☐ Insufficient representation of the population of interest
	☐ Unavailable linkage with Risk Evaluation and Mitigation Strategy (REMS) registry
	☐ Other: Click to enter other explanation.
If no, what type of data would be necessary to make the determination sufficient to assess the intended population?	☐ Laboratory and/or imaging data are needed to identify the study population
	☐ Structured electronic health records review to identify the study population
	☐ Chart review (including unstructured data) to identify the study population
	☐ Linkage to disease-based registry Click to enter registry if known.
	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the study population

[9] Dharmani, Charles, et al. "Real-world drug utilization and treatment patterns in patients with tenosynovial giant cell tumors in the USA." Future Oncology 0 (2024).

	☐ Other: Click to enter other data necessary to assess the population.

4. Exposures

4.1 Exposure(s) of Interest

Information Availability	☒ If based on labeling, rather than utilization data, check this box.
Medical product(s)	Romvimza [vimseltinib (DCC-3014)]
Dosing/Duration of Use	Recommended Dosage (per labeling): 30 mg orally twice weekly, with a minimum of 72 hours between doses as described in the blister package.
Clinical setting	It will be dispensed through an outpatient pharmacy.
How will the exposure(s) be identified in ARIA?	National Drug Codes (NDC)
Other aspects of the exposure(s) of interest	Not applicable

4.2 Comparator Exposures

Information Availability	☐ If based on labeling, rather than utilization data, check this box.
Medical product(s)	Not applicable
Dosing/Duration of Use	Not applicable
Clinical setting	Not applicable
How will the comparator(s) be identified in ARIA?	Not applicable
Other aspects of the comparator(s) of interest	Not applicable

4.3 ARIA Sufficiency for Exposure of Interest and Comparator(s)

Is ARIA sufficient to assess the exposure of interest?	Yes
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	Exposure can be identified through NDC codes. ARIA is sufficient.
Is ARIA sufficient to assess the comparator of interest?	Yes
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	A comparator is not needed for this study.
If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the intended exposure or comparator of interest?	☐ Absence of validated code list algorithm
	☐ Identification of medical products with code algorithms not possible or inadequate
	☐ Inability to capture intent of treatment
	☐ Inability to identify over-the-counter medication use
	☐ Inadequate sample size
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)

Check all the apply.	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient inpatient data
	☐ Insufficient observation time available
	☐ Unavailable linkage with Risk Evaluation and Mitigation Strategy (REMS) registry
	☐ Other: Click to enter other explanation.
If no, what type of data would be necessary to make the determination sufficient to assess the exposure/comparator of interest?	☐ Structured electronic health records review to identify the exposure/comparator
	☐ Chart review (including unstructured data) to identify the exposure/comparator
	☐ Linkage to disease-based registry Click to enter registry if known.
	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the exposure/comparator
	☐ Other: Click to enter other data necessary to assess the exposure/comparator.

5. Outcome

5.1 Outcome of Interest

List outcome as it appears in the approval letter or as stated in a NISS	Serious hepatotoxicity
Clinical case definition(s)	The case definition will be developed by the sponsor with submission of the PMR. Per the PMR language, "analyses should include evaluation of alanine aminotransferase, aspartate aminotransferase, bilirubin, symptoms suggestive of hepatotoxicity, and dose reduction and treatment discontinuation related to hepatotoxicity."
Clinical setting	This study will be conducted in the outpatient setting and through routine visits with a healthcare provider.
How will the outcome be identified in ARIA? (Include any relevant validation studies)	Serious hepatotoxicity will be evaluated using laboratory data for alanine aminotransferase, aspartate aminotransferase, and bilirubin. It will additionally be identified using symptoms suggestive of hepatotoxicity and dose reduction and treatment discontinuation related to hepatotoxicity.
Timing of outcome assessment relative to exposure (i.e., risk-window)	The outcome would be expected to occur during an episode of treatment.
Other aspects of the outcome of interest	N/A

5.2 ARIA Sufficiency for the Outcome of Interest

Is ARIA sufficient to assess the outcome of interest?	No
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	While some Sentinel data partners have access to clinical laboratory data, these laboratory data will only be captured in a small subset of patients and will not be available at the required intervals (e.g. at baseline and protocol-specified intervals during follow-up). A prospective clinical study will be needed for uniform collection of laboratory data during this study.
If ARIA is insufficient, what	☐ Absence of validated code algorithm

is the root cause(s) why ARIA cannot identify the outcome of interest? Check all that apply.	☐ Identification of clinical concepts with code algorithms not possible or inadequate
	☐ Inadequate sample size
	☐ Insufficient clinical and laboratory cancer data that might be in a registry
	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient inpatient data
	☒ Insufficient laboratory data
	☐ Insufficient observation time available
	☐ Insufficient radiology/pathology data
	☐ Limited ability to ascertain cause of death
	☐ No access to patient-reported outcomes or physician-administered assessments
	☐ Other: Click to enter other explanation.
If no, what type of data would be necessary to make the determination sufficient to assess the outcome of interest?	☒ Laboratory and/or imaging data to identify the outcome
	☐ Structured electronic health records review to identify the outcome
	☐ Chart review (including unstructured data) to identify the outcome
	☐ Linkage to disease-based registry Click to enter registry if known.
	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the outcome
	☐ Click to enter other data necessary to assess the outcome.

6. Covariates

6.1 Covariates of Interest

Covariate	Why is the covariate necessary for the study?	Conduct an a priori QBA to evaluate the potential impact of unmeasured/uncontrolled confounding on study findings (Including identification of plausible values for QBA parameters) Refer to the Draft DEPI QBA framework. (Optional)	Does the a priori QBA indicate that the missing or misclassified covariates likely change the study inference?
Covariate 1: Age	Age may affect risk for serious hepatotoxicity	N/A	Not Applicable
Covariate 2: Race	Race may affect risk for serious hepatotoxicity	N/A	Not Applicable
Covariate 3: Baseline Comorbidity	Medical comorbidities may affect risk for serious hepatotoxicity.	N/A	Not Applicable

6.2 ARIA Sufficiency for Covariates of Interest

Is ARIA sufficient to assess the covariates?	Yes
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	ARIA is sufficient to identify the covariates needed for this study.
If ARIA is insufficient, which covariates are insufficient?	N/A
If ARIA is insufficient, what is the root cause(s) why ARIA cannot identify the covariates of interest? Check all that apply.	☐ Absence of validated code list algorithm
	☐ Identification of clinical concepts with code algorithms not possible or inadequate
	☐ Inability to capture intent of treatment
	☐ Inability to identify over-the-counter medication use
	☐ Information on socioeconomic status unavailable
	☐ Insufficient capture of patient medical and/or family history
	☐ Insufficient capture of information on race
	☐ Insufficient clinical and laboratory cancer data that might be in a registry
	☐ Insufficient data for niche study needs (e.g., dental records, travel medication)
	☐ Insufficient data on behavioral and/or lifestyle risk factors
	☐ Insufficient inpatient data
	☐ Insufficient laboratory data
	☐ Insufficient observation time available
	☐ Insufficient radiology/pathology data
	☐ No access to patient-reported outcomes or physician-administered assessments
	☐ Unavailable data on environmental risk factors
	☐ Other: Click to enter other explanation.
If no, what type of data would be necessary to make the determination sufficient to assess covariates?	☐ Laboratory and/or imaging data are needed to identify covariates
	☐ Structured electronic health records review to identify covariates
	☐ Chart review (including unstructured data) to identify covariates
	☐ Linkage to disease-based registry Click to enter registry if known.
	☐ Linkage to NDI is needed for data on cause of death
	☐ Primary data collection to identify the covariates
	☐ Other: Click to enter other data necessary to assess covariates.

7. Analytic Tools

7.1 Analytic Tools

Type of Analysis Desired Check all that apply.	☒ Descriptive: unadjusted incidence rates (L1)
	☐ Inferential: self-controlled risk interval (L2)
	☐ Inferential: propensity score-based method (i.e., matching, stratification

	or inverse probability of treatment weighting) (L2)
	☐ Interrupted time series (L2)
	☐ Sequential monitoring (L3)
	☐ Signal identification using TreeScan
	☐ Other: Click to enter other analysis.

7.2 ARIA Sufficiency for Analytic Tools

Is ARIA sufficient with regards to the analytic tools available to assess the question of interest?	Yes
Provide a concise explanation for your ARIA sufficiency determination. (1-2 sentences)	ARIA is sufficient for calculation of incidence rates.
If ARIA is insufficient, why are the analytic tools a major limiting factor?	☐ Insufficient capabilities in ARIA analytic tool to perform required safety issue analysis
	☐ Other: Click to enter other explanation.
If no, what analytic capabilities would be necessary to make the determination sufficient to answer the question of interest?	☐ Protocol-based assessment with customized programming
	☐ Other: Click to enter other analytic tool(s).

8. Additional Information:

8.1 Other information relevant to the ARIA sufficiency determination

N/A

8.2 Sponsor Postmarketing Requirement (PMR)

If ARIA is deemed insufficient, complete the table below:

Will a sponsor PMR be required?	Yes
If yes, how is FDA ensuring that identified reasons for ARIA insufficiency and the data or information needed to make the determination sufficient are being addressed within the PMR?	☒ PMR language in the approval letter
	☒ PMR study protocol negotiation process with sponsors
	☐ Other: Click or tap here to enter text.
If yes, provide the proposed PMR language	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.

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

/s/

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2024226
NDA#/Referenced IND for NDA:	NDA 219304/IND 131218
Applicant:	Deciphera Pharmaceuticals, LLC
Established Name/Trade Name:	vimseltinib
Indication:	treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) ☒Rare Disease/Orphan Designation ☐Pediatrics
PDUFA Goal Date:	2/17/2025
Review Division:	Division of Oncology 3
Clinical Reviewer:	Jennifer Stundon
Clinical Team Leader (TL)	Leslie Doros
Regulatory Project Manager:	Haroon Vohra
COA Reviewer:	Julia Ju, PharmD, Ph.D.
COA Deputy Director:	Selena Daniels, PharmD, Ph.D.
COA Division Director:	David Reasner, Ph.D.
Instruments reviewed:	1. Goniometry for active ROM ☒ Performance outcome (PerfO)
	2. Worst Stiffness Numeric Rating Scale (NRS) ☒ Patient-reported outcome (PRO)
	3. Brief Pain Inventory Worst Pain NRS ☒ Patient-reported outcome (PRO)
	4. Patient-Reported Outcomes Measurement Information System (PROMISPhysical Function upper and lower extremityitems ☒ Patient-reported outcome (PRO)

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1. EXECUTIVE SUMMARY

In this submission, the Applicant is seeking approval of vimseltinib for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT). The specific clinical outcome assessment (COA)-related labeling claims are for improvement in range of motion (ROM), worst pain, worst stiffness, physical function, and overall health based on data from one ongoing randomized, double-blind, placebo-controlled phase 3 clinical trial (Study DCC-3014-03-001; referred to as MOTION). The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related tothe concept(s) of interest.

The secondary efficacy COA endpoints (multiplicity controlled) (b) (4) are:

- Change from baseline in active range of motion (ROM) of the affected joint, relative to a reference standard, at Week 25, as measured by goniometry
- Change from baseline in the Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function score[1] 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) 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

The data from Study DCC-3014-03-001 demonstrated that vimseltinib had statistically significant improvement in the selected secondary efficacy COA endpoints compared with placebo.

From a COA perspective, the 15-item PROMIS® Physical Function measure adequately supports labeling claims. The BPI Worst Pain NRS and ROM data generated from a goniometer could potentially support a labeling claim, if supported by the clinical trial study design and statistical

[1] Based on 15 items that measure upper and lower extremity function. Refer to Section 5.5 for more details regarding this instrument.

analysis. The Worst Stiffness NRS and EQ-VAS and its corresponding endpoints (b) (4)

- The scoring algorithm used to define the baseline Worst Stiffness NRS 14-day average score is inadequate.
- The EQ-VAS is part of 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 (b) (4)

2 REVIEW CONCLUSIONS

The Applicant submitted an evidence dossier[2] for the ROM assessment (measured by a goniometer), 15-item PROMIS® Physical Function measure, Worst Stiffness NRS, BPI Worst Pain NRS. The ROM assessment and 15-item PROMIS® Physical Function measures were reviewed for content validity and other measurement properties, as well as score interpretability (i.e., interpretation of meaningful score change). The BPI Worst Pain NRS and EQ-VAS-based endpoints were not the focus of this review at the request of the Division. Further, the Worst Stiffness NRS was not reviewed due to lack of agreement on the scoring algorithm.

Reviewer's comment(s): *This reviewer notes that a pain NRS, such as the BPI Worst Pain NRS, and proposed responder threshold has been previously accepted in this Division and other review divisions.*

Review Summary

- Goniometry and the 15-item PROMIS® Physical Function measure assesses relevant and important aspects of TGCT (i.e., active ROM and physical function, respectively).
- A definitive conclusion cannot be made whether the 15-item PROMIS® Physical Function measure is well-understood and interpreted appropriately due to the limited approach used to evaluate participant comprehension (see Key Issues Identified section).
- There is insufficient evidence to support the other measurement properties of the goniometer used in Study DCC-3014-03-001.
- There is insufficient evidence to support what constitutes a meaningful change in the ROM assessment.
- The rationale for the calculation of the BPI Worst Pain NRS 14-day average score for analysis of the secondary endpoint is unclear.
- There is insufficient evidence to support the calculation of the Worst Stiffness NRS 14-day average score for analysis of the secondary endpoint.
- We are 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, based on empirical cumulative distribution function (eCDF) curves by treatment arm, the change from baseline in the 15-item Physical Fuction 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® Physical Function score could be between 3 and 7-points.

[2] The applicant submitted additional evidence dossiers for other COAs, which are not the focus of this COA review.

Key Issues Identified

Issue # 1: Content Validity

1. There is insufficient evidence to support whether the 15-item PROMIS® Physical Function measure is well-understood and interpreted appropriately by the target population. Participants in the embedded exit interviews were not directly asked if they understood the instrument (instructions, items, response options) but asked to rephrase the item using their own words.
    a. The Applicant did not query about understanding and appropriateness of response options for the items in the 15-item PROMIS® Physical Function measure, but rather each set of response options for the upper and lower extremity items was debriefed only once (i.e., queried participants only on two response scales) as it related to differentiating between the response options.

2. The study population for Study DCC-3014-03-001 primarily presented with tumors in their lower limbs. There were only nine participants (n= 9/123) who presented with tumors in their upper limbs. The skewed sample could have affected the results. See Issue # 3 (bullet 6).

Issue #2: Other Measurement Properties

3. Lack of quantitative evidence to support the other measurement properties of the goniometer used in Study DCC-3014-03-001.

4. Potential inadequate scoring algorithm used for the BPI Worst Pain endpoint. There is a lack of sufficient evidence to adequately support the scoring algorithm for the BPI Worst Pain endpoint score.

    Reviewer's comment(s): *The Applicant calculated a 14-day average score over a 14-day period (Weeks 2 and 3) for patients with at least 4 of 14 days to complete diary (daily) data. An information request was submitted to the Applicant on January 28, 2025. Regarding the justification of the 14-day average score, the Applicant conducted sensitivity analyses for the ranked secondary efficacy BPI Worst Pain endpoint using a weekly average score (based on Week 3). The results from these sensitivity analyses were similar to the results with the use of a 14-day average score. There was concern regarding data missingness within the 14-day timeframe of the 14-day average score. However, the Applicant provided frequency distributions of participants with data within the 14-day period which demonstrated that the majority of the participants (n>89/123,72.4 %) had at least 8 days of results in the 14-day period. For more details regarding the Applicant's justification of the scoring algorithm, refer to the Applicant's response to FDA Information Request dated November 25, 2024 (SDN: 24, eCTD: 0024).*

5. Lack of evidence and rationale to support the calculation of the baselineWorst Stiffness NRS 14-day average score.

Reviewer's comment(s): *In the IND stage, the Applicant indicated that baseline is not defined as Cycle 1 Day 1 (C1D1), but rather as an average of the responses to the PRO assessments during the 14 days of consecutive PRO data collected during the 42-day screening period prior to C1. 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 in Study DCC-3014-03-001. The Worst Stiffness NRS 14-day average score was measured over any 14 consecutive day period during screening.*

Issue# 3: Data Interpretability

6. It is unknown what constitutes a meaningful score change in the active ROM assessment due to the limitations of the ROM-specific anchor scales.
    a. It is unclear whether the definition of ROM and the example of movements (e.g., pivot) in the PGIS-ROM and PGIC-ROM items are well-understood across patients of all educational levels.
    b. The concept measured in the PGIC-Overall Symptoms item is not aligned with the concept of the ROM assessment.
    c. The correlations between change in ROM from baseline to Week 25 and the anchor scales (PGIS-ROM, PGIC-ROM, and PGIC-overall symptoms) were low.
    d. There are a good amount of missing data in the anchor scales at Week 25.

7. Although the efficacy analysis for the 15-item PROMIS® Physical Function -based endpoint showed statistically significant results, minimal magnitude of changes was observed at the item-level in select items of the 15-item PROMIS® Physical Function score using both T-scores and raw scores. Further, there are only select items (i.e., lower limb extremity items) within the instrument that contribute more to the change observed in the total score based upon review of item-level analyses. However, it is noted that the items that are overly influencing the total score are generally specific to lower limb functioning which is consistent to the tumor location in patients at baseline.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend the following:

- Sponsors should provide evidence to support that respondents understand each of the components comprising the measure (e.g., their understanding and interpretation of instructions, items, and response options in a PRO measure).
- Sponsors should provide a sufficient rationale and corresponding information on how the instrument's scores will be analyzed as part of an endpoint, including adequate justification for the scoring algorithm of the endpoint score. Sponsors should also conduct a missing data simulation study during IND to support their proposed scoring algorithm, where applicable.
- If using anchor-based methods, sponsors should use appropriate anchor scales (ideally agreed to by the Agency).
- When using qualitative methods to inform meaningful change thresholds, sponsors should carefully structure meaningful change exercises in qualitative interviews to explore both improvement and worsening. Additionally, leading questions should be avoided to the extent possible. Neutral questions should be used to query participants on

their perception of meaningful change. If sponsors are interested in eliciting input related to different degrees of changes that are meaningful to patients, these questions should be added as probes after a neutral question on meaningful change.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
There have been several communications regarding the Applicant's COA measurement strategy during the IND stage (IND 131218), which included the following:

- Type C Meeting Minutes dated May 16, 2023
    - Questioned the clarity of the ROM definition and the example of movements (e.g., pivot) provided in the anchor scales corresponding to the ROM assessment.
    - Requested clarification regarding the score and the assessment period within the screening period that were used to determine eligibility criteria for the pain and stiffness severity levels.
    - Requested a detailed scoring algorithm and methods to handle missing data for the ROM assessment and 15-item PROMIS® Physical Function endpoint scores.
    - Requested empirical cumulative distribution function (eCDF) plots for change from baseline at Week 25 in the endpoint scores by treatment arm.

- Type B End-of-Phase 2 Meeting Minutes dated January 29, 2021
    - Requested evidence of content relevancy of the 15-item PROMIS® Physical Function measure.
    - Advised that a current state (non-comparative) global impression rating scale should be administered in the pivotal study to help interpret the COA-based endpoints.

- Type C Meeting Minutes dated July 30, 2020
    - Requested supportive evidence for the use of goniometry, along with a ROM assessment form.
    - Noted that the limitations of the Worst Stiffness NRS should be considered when interpreting treatment efficacy.
    - Requested evidence and justification that a 30% threshold or greater increase in narcotic analgesic use represents a meaningful within-patient score change in the BPI Worst Pain NRS.

Previous COA Reviews:
- C2021240_IND 131218_Patel dated September 27, 2021 (DARRTS Reference ID: 4862076)
- C2020519 _IND 131218_ Patel dated December 22, 2020 (DARRTS Reference ID: 4720827)
- C2020220 _IND 131218_ Fieo dated September 2, 2020 (DARRTS Reference ID: 4663642)

Disease Background:
Tenosynovial giant cell tumor (TGCT) is a rare tumor arising from the synovium of joints, bursae, and tendon sheaths caused by dysregulation of the CSF1 gene, which results in overproduction of CSF1 and recruitment of CSF1 receptor (CSF1R)-dependent inflammatory cells into the affected joint. The lesion can either present as a single nodule (localized form) or as multiple nodules (diffuse-type) along a synovial layer or tendon sheath. Patients with TGCT, both diffuse and localized, frequently report pain, swelling, stiffness, reduced range of motion (ROM), and joint instability.

Investigational Product:
Vimseltinib is an oral, small molecule, selective tyrosine kinase inhibitor that targets colony-stimulating factor 1 receptor (CSF1R).

Materials reviewed:
- Protocol DCC-3014-03-001 (SDN: 2, eCTD: 002, Date: June 17, 2024)
- Clinical Study Report DCC-3014-03-001 (SDN: 2, eCTD: 002, Date: June 17, 2024)
- DCC-3014-03-001 (MOTION) Clinical Outcome Assessment Evidence Dossier (SDN: 2, eCTD: 002, Date: June 17, 2024)
- Applicant Response to Information Request (IR) dated November 16, 2024. (SDN: 24, eCTD: 0024, Date: November 25, 2024)

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Study DCC-3014-03-001 are adults (≥18 years) with histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumor of the tendon sheath [GCT-TS]). Eligible participants should have:

- TGCT in a single joint and must have TGCT in joints where ROM can be assessed;
- Disease for which surgical resection will potentially cause worsening functional limitation or severe morbidity as judged by surgical consultation or a multidisciplinary tumor board; and
- Symptomatic disease with at least moderate pain or at least moderate stiffness (defined as a score of 4 or more, with 10 describing the worst condition) within the screening period and documented in the medical record.

A complete list of the inclusion and exclusion criteria is summarized in Sections 8.1 of the clinical study protocol for Study DCC-3014-03-001.

Reviewer's comment(s):
The mean (standard deviation [SD]) 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 (SD) baseline BMI was 27.37 (5.974) kg/m2. The majority of participants were non-

U.S. (89.4%) and presented with tumor(s) in the lower limb (88.6%) as recorded per interactive response technology.

5.2 Clinical Trial Design

Study DCC-3014-03-001 is a multicenter, randomized, placebo-controlled, phase 3 study of vimseltinib to evaluate the efficacy and safety in patients with TGCT. The study was comprised of two parts:

- Part 1: Double blinded treatment period (completed) [3]
- Part 2: Open label period (ongoing)

The study consists of a:

- Screening period (42-days prior to the first dose of study drug);
- Double-blind treatment period (24 weeks; Part 1);
- Open-label period (24 weeks; Part 2);
- Extension of Treatment period;
- End-of-Treatment (EOT) Visit (within 7 days after the decision to stop study drug);
- Safety Follow-up Visit (30 days (±5 days) after the last dose of study drug); and a
- Disease Followup period (up to 2 years after the last dose of study drug or until initiation of new TGCT treatment or surgery, whichever occurred first).

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. Randomization was stratified for tumor location (lower limb/all other) and region (U.S./non-U.S.).

Refer to the clinical study protocol((DCC-3014-03-001, Amendment 3) for more details on the clinical trial design.

Reviewer's comment(s):
A total of 123 participants were randomized in a 2:1 ratio to receive either vimseltinib at a dose of 30 mg twice weekly (biw) (n=83) or placebo (n=40) for 24 weeks during the Part 1 double-blind treatment period. Among those, 74 (89.2%) in the treatment arm and 34 (87.2%) in the placebo arm completed treatment during Part 1. Characteristics were similar between treatment arms.

5.3 Endpoint Position, Definition, and Assessment Schedule

The placement of the COAs in the endpoint hierarchy, including the endpoint definition is summarized below.

Primary efficacy endpoint

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

[3] Participants could cross over to open-label vimseltinib in the event of disease progression (confirmed by IRR) earlier than 24 weeks, and all participants could choose to remain on study to receive open-label vimseltinib in Part 2.

Secondary efficacy COA endpoint(s) (multiplicity controlled)

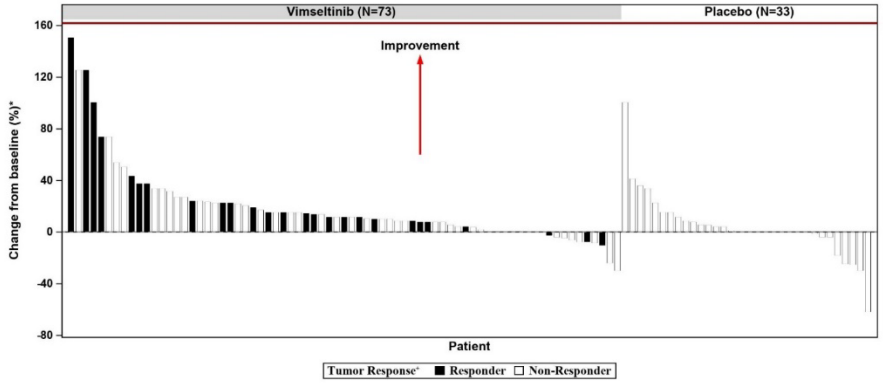
- Change from baseline in active ROM of the affected joint, relative to a reference standard, at Week 25
- Change from baseline in the 15-item PROMIS® Physical Function score at Week 25
- Change from baseline in the Worst Stiffness NRS score at Week 25
- Change from baseline in EQ-VAS at Week 25
- Response 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

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant has proposed the following specific targeted COA-related labeling claims (in *blue italicized text*):

(b) (4)

Figure 1: Change from Baseline in Active Range of Motion at Week 25 for MOTION



** Percent normal reference range for the affected joint.*

+ Response by RECIST v1.1.

(b) (4)

Reviewer's comment(s):

This reviewer notes that (b) (4) *proposed in the label are not included in this review. Refer to the draft label for* (b) (4).

The data from Study DCC-3014-03-001 demonstrated that vimseltinib had statistically significant improvement in the selected secondary efficacy COA endpoints compared with placebo.

From a COA perspective, the 15-item PROMIS® Physical Function measure and its corresponding endpoint adequately support labeling claims. Refer to Sections 5.5.4. 5.5.5, and 5.5.6 of this review regarding the evidence to support the fitness-for-purpose of this measure.

The BPI Worst Pain NRS and ROM assessment data generated from a goniometer could potentially support a labeling claim, if supported by the clinical trial study design and statistical analysis. While the BPI Worst Pain NRS was not the focus of this review, this reviewer notes that a pain NRS, such as the BPI Worst Pain NRS, and proposed responder threshold has been previously accepted in this Division and other review divisions. However, the rationale for the calculation of the BPI Worst Pain NRS 14-day average score for analysis of the secondary endpoint is unclear. This reviewer recommends that the Applicant provide the following:

- *A rationale for the number of days needed to derive the bi-weekly Brief Pain Inventory-Short Form (BPI-SF) Item 3 (Worst Pain) score. (i.e., completion of the BPI-SF Item 3 for at least 4 of the 14 days).*

- *Frequency distribution of participants who missed one to four (and one to seven) consecutive and/or non-consecutive days in MOTION, if available. In addition, conduct sensitivity analyses using the weekly BPI-SF Item 3 (Worst Pain) (requiring at least 4 out of 7 days).*

This reviewer defers to the Clinical and Biostatistics whether the results on ROM could be included in labeling due to the uncertainty associated with the reliability of this assessment and the limitations of anchor scales used in the anchor-based analysis to establish threshold of clinical meaningful change in ROM scores.

The (b) (4) *do not adequately support labeling claims due to the following reasons:*

(b) (4)

Based on this reviewer's assessment and in discussion with the review team, the following modifications were made to the label:

- *All efficacy results were presented in one table including the COA data. A footnote was added to the 15-item PROMIS Physical Function measure to describe the scoring direction and notate the items that contributed more to the observed change.*
- (b) (4) *have been deleted as the table is adequate to describe the efficacy results.*
- (b) (4) *were removed from labeling due to the reasons described above.*

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

5.5.1.1 Range of Motion (ROM) assessment

Active[4] and passive[5] ROM was assessed using a goniometer. ROM is designed to measure movement of joints in unit of degrees.

There were two forms used to collect ROM data: one form for screening through the end of Part 1 visit, which collected both affected and non-affected joint data, and one from end of Part 1 visit though 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, and EOT.

Reviewer's comment(s): *Trained site personnel (physiotherapist or orthopedic surgeon) who were blinded to the study treatment performed the ROM assessments. In the protocol, it was unclear whether the same assessor evaluated the same patients over time, As such, this reviewer submitted an information request on November 16, 2024 to requesting the Applicant to provide training materials, if any, that were used for assessment of ROM and to clarify whether the same investigator rated the same patient throughout the trial. Descriptives (e.g., frequency count and percentage, study visit) were also requested for the patients who did not have the same investigator for the assessment of ROM. In response to the IR, the Applicant stated that "While consistency was strongly encouraged, the MOTION protocol did not mandate that the same investigator conduct all assessments for a given participant. As such, it cannot be confirmed if all participants were assessed by the same investigator throughout the study." The number of assessments for each participants conducted by different assessors were not provided.*

5.5.1.2 15-item Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function measure

PROMIS® Physical Function 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 Study DCC-3014-03-001, 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 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

[4] Active is defined as measuring a motion produced by the participant's voluntary, unassisted muscle contraction,
[5] Passive is defined as measuring a motion produced by the application of external force by an examiner during assessments.

("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.

Reviewer's comment(s): *The mobile application was accessed from the patients' own device or a provisioned device.*

5.5.2 Conceptual Framework(s)

The conceptual frameworks for the ROM assessment and 15-item PROMIS® Physical Function measure are shown in the subsequent sections.

5.5.2.1 ROM Assessment

The conceptual framework for the ROM assessment is shown in Figure 1.

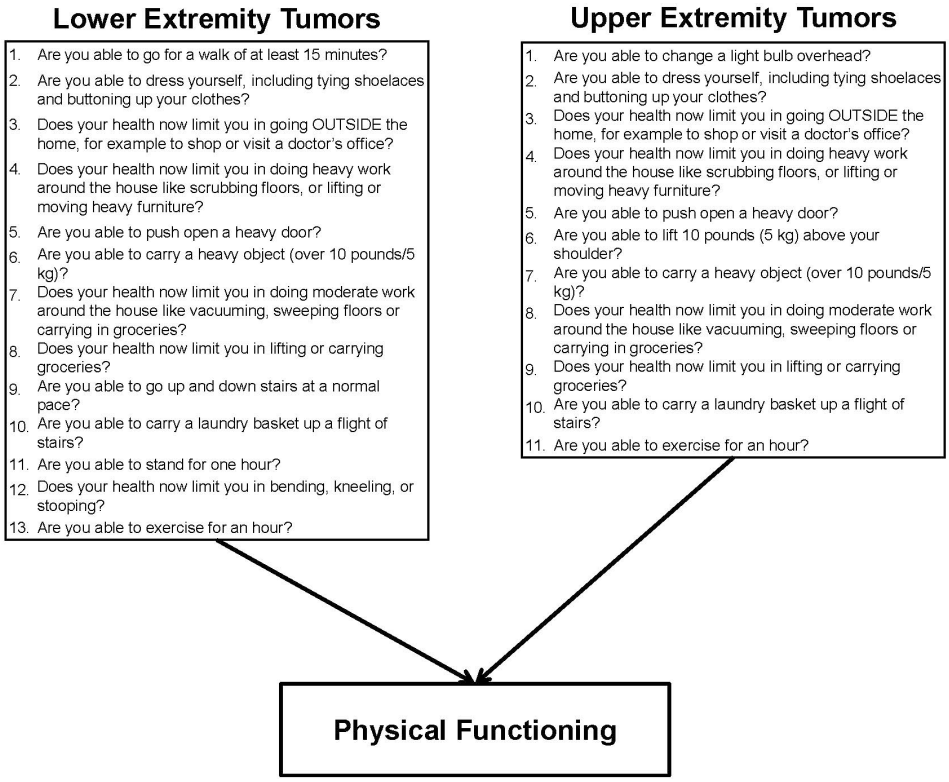
Figure 1. Conceptual framework of ROM

Source: Figure 5 in Applicant's COA Evidence Dossier

5.5.2.2 PROMIS® Physical Function

The conceptual framework for the 15-ite, PROMIS® Physical Function is shown in Figure 2.

Figure 2. Conceptual framework of 15-item PROMIS® Physical Function



Source: Figure 9 in Applicant's COA Evidence Dossier

5.5.3 Scoring Algorithm

5.5.3.1 ROM Assessment

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)[6]. 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 was 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.

5.5.3.2 15-item PROMIS® Physical Function Measure

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

6 Gerhardt, J. J., L. Cocchiarella, R. D. Lea and American Medical Association (2002). The Practical Guide to Range of Motion Assessment, American Medical Association.

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.

Reviewer's comment(s): *Based on the Applicant's response to the IR submitted onNovember 25, 2024, "The analysis rule in Version 2.0 of the SAP specified that if a participant answered at least half of the questions for their tumor location, then the T-score was to be generated based on the API scoring manual and those questions with missing responses are ignored for scoring. The Sponsor would like to clarify that even though this rule was detailed, there was no missing items for any participant with a scored value. We do not have the detailed scoring algorithm since we used the scoring service described above and in the SAP."*

5.5.4 Content Validity

5.5.4.1 ROM Assessment

The Applicant completed the following activities to evaluate the content validity of the ROM assessment:

- Patient input (exit interviews embedded in Study DCC-3014-03-001)

A summary of the results of patient interviews is described below. Refer to the Applicant's COA evidence dossier (SDN: 2, received date: June 17, 2024) for full details regarding the methodology and results.

5.5.4.1.1 Patient input

Exit interviews

The Applicant conducted an embedded exit interview study with 96 patients[7] as a part of Study DCC-3014-03-001 to cognitively debrief the 15-item PROMIS® Physical Function measure, Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), and Worst Stiffness NRS to evaluate the relevance and comprehension of each

7 A total of 96 patients were interviewed for this study, however, one interview was excluded due to an audio recording malfunction, and another interview was excluded because a patient had not experienced stiffness and thus did not contribute meaningful data on the topic of stiffness. Thus, the results presented on stiffness are based on a sample size of 26 (n=26/94, 27.7%). The results for the other measures were based on more than 30 patients. See Sections 5.5.4.4 and 5.5.6 of this review.

measure, as well as patient understanding of the response scales for each measure.[8] Within these interviews, there were questions related to the patients' experience of TGCT. Interviews were conducted within 28 days prior to the end of Part 1 visit (week 25) and prior to unblinding. Participants were interviewed one-on-one for approximately 60 minutes via telephone.

The results of the exit interviews as it relates to ROM is summarized below:

- Of the 123 patients enrolled in MOTION, 96 patients were recruited across 27 sites and completed an exit interview.
- The interview sample constitutes approximately 78% of the full clinical trial sample.
- The 27 sites were from diverse geographic locations encompassing 12 countries and nine different languages: Australia (English), Canada (English), Hong Kong (Chinese), France (French), Germany (German), Italy (Italian), the Netherlands (Dutch), Norway (Norwegian), Poland (Polish), Spain (Spanish), the United Kingdom (English), and the US (English).
- Impaired ROM was reported by a majority of patients (n=51/94, 54.3%), with a small subset of patients (n=13/94, 13.8%) reporting that ROM was one of their most bothersome symptoms.
- Patients described their limited ROM as impacting their ability to bend and straighten their joints, sit for longer periods of time, complete daily activities (such as driving a car), and perform physical activity and exercise.
- Patients mentioned that by seeing improvements in their ROM, they experienced less pain and swelling, and were able to participate in activities they were previously unable to do.

Reviewer's comment(s):
This reviewer concludes that the ROM assessment may be be measuring an important aspect of TGCT (i.e., ROM). Based on the qualitative data, the majority of participants in the exit interviews did experience impaired ROM. However, a small proportion of participants indicated that it was the most bothersome symptom. It is unclear if the site personnel (physiotherapist or orthopedic surgeon) fully understood the ROM assessment forms; The Applicant stated that they provided training to site personnel (physiotherapist or orthopedic surgeon). However, the Applicant did not provide training materials for review and comments despite that the Agency requested the training materials in the IR dated November 16, 2024.
This reviewer notes that the pivotal study was a multinational trial. The Applicant states in the clinical protocol (Section 11.9.15.8. End of Part 1 Interview) that "The participant interview will be conducted in the countries where an interviewer is available to conduct in local language." In Section 4.4.1 in the Exit Interview Report, the Applicant states the following "For the non-English interviews, the discussion guides were translated by a native-language translator. The translation was then reviewed and proofread by another bilingual speaker to check the accuracy and appropriateness of the translation and to ensure cultural sensitivity. The PROMIS-PF, PGIS, PGIC, and Worst Stiffness NRS measures were forward and back-translated according to

[8] As part of the pre-specified study design which was intended to help manage the patient burden of the interviews, each patient was asked to debrief on only one measure (PROMIS-PF, PGIS/PGIC, or Stiffness). A third of the interviewees (n=33/94, 35.1%) debriefed on the PGIS/PGIC, and another third (n=33/94, 35.1%) debriefed on PROMIS-PF (including six on the Upper Extremity questionnaire and 27 on the Lower Extremity questionnaire). A total of 30 patients completed interviews on the Stiffness NRS.

regulatory guidance for COA measures.8,9 The COA measures used for the exit interview study were taken directly from, and therefore matched exactly, the final clinical trial study materials."

This reviewer defers to Clinical whether the type of goniometer used to assess ROM is acceptable.

5.5.4.2 15-item PROMIS® Physical Function Measure

The Applicant completed the following instrument development activities to evaluate the content validity of the 15-item PROMIS® Physical Function measure:

- Literatue review
- Patient input (embedded in Study DCC-3014-03-001)

A summary of the results for each activity and instrument is described below. Refer to the Applicant's PRO evidence dossier (SDN: 2, received date: June 17, 2024) for full details regarding the methodology and results of each activity.

5.5.4.2.1 Literature Review

The Applicant conducted a literature review to identify relevant published, peer-reviewed research on the content validity of the PROMIS® Physical Function item bank in the TGCT population.

The key findings are summarized below:

- Gelhorn et al. (2016)[9] conducted a qualitative study in 22 TGCT patients to identify the key symptoms and impacts of the disease. Per the authors, patients consistently reported that their symptoms impacted their physical functioning. A total of 54 PROMIS® Physical Function items were endorsed as relevant by ≥20% of the sample. The authors selected a total of 15 items as part of the final TGCT-specific PROMIS-PF measure (13 items for lower extremity tumors; 11 items for upper extremity tumors – including nine items that were overlapping across the two versions)

  Reviewer's comment(s): *This publication was previously review in the IND stage. The COA reviewer provided the following comment to the Applicant:*
  "There is concern regarding content relevancy of some of the items in the 15-item PROMIS PF measure. For example, there are items that may not be applicable to some patients (e.g., "Are you able to carry a laundry basket up a flight of stairs" may not apply to patients who do not have stairs in their homes). There are also items that may not be encountered frequently (e.g., "Are you able to change a light bulb overhead" may not be a frequent activity). Gelhorn et al. (2016) also highlights some relevancy issues for select items (i.e., "able to dress oneself" and "health limits going outside of home"). As such, we recommend you consider utilizing your planned exit interviews to confirm the content relevancy of the 15-items PROMIS PF measure for your target population."

9 Gelhorn, H. L., X. Ye, R. M. Speck, et al. (2019). "The measurement of physical functioning among patients with Tenosynovial Giant Cell Tumor (TGCT) using the Patient-Reported Outcomes Measurement Information System (PROMIS)." J Patient Rep Outcomes 3(1): 6.

- Bernthal et al. (2021) [10] explored the management of TGCT in tertiary sarcoma centers via the TGCT Observational Platform Project registry. Based on the PROMIS® Physical Function data collected, the authors observed that scores were lower among patients with TGCT indicated for surgery and systemic therapy (39.54 and 39.98, respectively) compared to PROMIS® Physical Function scores of patients indicated for wait-and-see approaches. Descriptively, PROMIS® Physical Function scores were favorable in patients who remained on systemic treatment compared to patients who switched to a different treatment strategy at 1 year.

  Reviewer's comment(s): *This literature does not include data to support the content validity of the PROMIS® Physical Function measure.*

- Palmerini et al. (2023) [11] conducted a prospective study among 176 patients with TGCT (mean age: 43.5 years) capturing PRO assessments with the PROMIS® Physical Function measure at baseline, 1-year, and 2-year follow-ups in the Tenosynovial giant cell tumor Observational Platform Project (TOPP) registry. The PROMIS® Physical Function measure included two scales for patients with lower extremity tumors with 13 items assessing lower limb function and patients with upper extremity tumors with 11 items assessing upper limb function (scale 0–100). No changes over the 2-year observation period were seen in PROMIS® Physical Function scores.

  Reviewer's comment(s): *This literature does not include data to support the content validity of the PROMIS® Physical Function measure.*

- Mastboom et al. (2018) [12] conducted a cross-sectional survey study at Leiden University Medical Center, Leiden, The Netherlands using the largest known online TGCT community on Facebook, PVNS is Pants!!, to gather participants for the Web-based questionnaire. The PROMIS® Physical Function measure include short forms of physical functioning for lower and upper extremity. Three hundred thirty-seven questionnaires, originating from 30 countries, were completed. Median age at diagnosis was 33 (interquartile range [IQR]=25-42) years, majority was female (79.8% [269/337]), diffuse TGCT (70.3% [237/337]), and affected lower extremities (knee 70.9% [239/337] and hip 9.5% [32/337]). Compared with general US population, all patients had impaired PROMIS® Physical Function T scores (44.5 and 41.3 for localized and diffuse type, respectively) compared with the general US population (T score of 50).

  Reviewer's comment(s): *This literature does not include data to support the content validity of the PROMIS® Physical Function measure.*

10 Bernthal, N. M., G. Spierenburg, J. H. Healey, et al. (2021). "The diffuse-type tenosynovial giant cell tumor (dt-TGCT) patient journey: a prospective multicenter study." Orphanet J Rare Dis 16(1): 191.

11 Palmerini, E., J. H. Healey, N. M. Bernthal, et al. (2023). "Tenosynovial Giant Cell Tumor Observational Platform Project (TOPP) Registry: A 2-Year Analysis of Patient-Reported Outcomes and Treatment Strategies." Oncologist 28(6): e425-e435.

12 Mastboom MJ, Planje R, van de Sande MA. The patient perspective on the impact of tenosynovial giant cell tumors on daily living: crowdsourcing study on physical function and quality of life. Interact J Med Res. 2018;7(1):e4. doi:10.2196/ijmr.9325

- Van De Sande et al. (2021) [13] reported PRO results from the ENLIVEN trial, which showed that patients receiving pexidartinib had greater improvements in PROMIS® Physical Function than patients receiving placebo at week 25 (mean change: 4.1 for pexidartinib vs. -0.9 for placebo, P=0.002).

  Reviewer's comment(s): *The PROMIS® Physical Function assessment results are not interpretable because of the high extent of missing data for the PRO instruments.*

5.5.4.2.2 Clinician input

The Applicant conducted interviews with clinical experts (n= 4) to obtain input on relevant symptoms and impacts, the design of the research, and potentially relevant PRO measures for the TGCT population.

Reviewer's comment(s): *The Applicant did not provide a summary of the findings from these interviews in the COA evidence dossier. However, the Applicant stated the following about these clinicians:*
"They were co-authors on the manuscripts related to the development and validation of PROs in this population (Gelhorn 2016, Gelhorn 2019) and have published on the results of clinical trials and other studies in TGCT that subsequently used these measures (Van De Sande 2021, Tap 2022, Healey 2023). Another clinical expert, Dr. Nicholas Bernthal, participated in the prior research evaluating the psychometric properties of the PROMIS-PF TGCT-specific measure (Speck 2020)."

5.5.4.2.3 Patient input

Exit interviews

Refer to Section 5.5.4.1 regarding the design of the embedded exit interview study.
The results of the exit interviews as it relates to the 15-item PROMIS® Physical Function measure is summarized below:

- One- third (n=33/94, 35.1%) of the participants in the exit interview study were debriefed on the 15-item PROMIS® Physical Function measure (including six on the Upper Extremity scale and 27 on the Lower Extremity scale).
- Over half of the participants reported issues with tumor-related physical function (n=55/94, 58.5%).
- The most frequently reported impacts due to TGCT were impacts on physical function (n=63/94, 67.0%). Overall, 86 patients (91.5%) reported issues with physical function either as a symptom or impact of their TGCT.
- The most relevant physicl function activities were the ability to go up and down stairs at a normal pace (n=27/27, 100%), the ability to exercise for 1 hour (n=26/27, 96%), and the ability to bend, kneel, and stoop (n=25/26, 96%; items 7, 2, and 13, respectively). The least relevant item was the ability to push open a heavy door (n=12/27, 44%).
- The majority of participants who were asked (n=17/21, 81%) were able to identify differences between all response options related to level of difficulty ("without any

13 Van De Sande, M., W. D. Tap, H. L. Gelhorn, et al. (2021). "Pexidartinib improves physical functioning and stiffness in patients with tenosynovial giant cell tumor: results from the ENLIVEN randomized clinical trial." Acta Orthop 92(4): 493-499.

ifficulty," "with a little difficulty," "with some difficulty," "with much difficulty," and "unable to do") for the lower extremity items.

- Most participants who were asked (n=19/25, 76%) about the response scale related to health limitations ("not at all," "very little," "somewhat," "quite a lot," and "cannot do") were able to differentiate between all response options for the lower extremity items.
- Some patients reported that they felt the upper extremity items (i.e., Items 2, 3, 6 and 9) were too vague and that more details were needed for clear comprehension.
- All participants who were asked about relevancy of the upper extremity items found
- item 3 ("Are you able to carry a heavy object (over 10 pounds/5 kg)?"), item 6 ("Are you able to lift 10 pounds (5 kg) above your shoulder?"), and item 10 ("Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?") to be relevant.
- Out of the upper extremity items, Item 11 ("Does your health now limit you in going OUTSIDE the home, for example, to shop or visit a doctor's office?") was found not relevant by three of the five participants (60%). Two participants did not have difficulties going outside, while another patient found this item to be more relevant to tumors in the llower extremities.
- The majority of participants (n= 3/5, 60%) were able to distinguish between all response options related to difficulty for Items 1 through 7 used a five-point response scale as the following: "without any difficulty," "with a little difficulty," "with some difficulty," "with much difficulty," and "unable to do"). Two participants found minimal or no difference between "with a little difficulty" and "with some difficulty."
- The majority of participants (n=3/5, 60%) were able to differentiate between the response options related to health limitations ("not at all," "very little," "somewhat," "quite a lot," and "cannot do") for Items 8 through 11.

Reviewer's comment(s):
This reviewer concludes that the items within the 15-item PROMIS® Physical Function measure are generally revelant to the target population based on the tumor location. However, it is unknown whether this instrument (instructions, items, response options) is well-understood by the target population as participants were not directly asked if they understood the instrument. Rather, partticipants were asked to rephrase the item in their own words. If participants were able to rephrase the item, the Applicant categorized them as demonstrating comprehension. This reviewer does not completely agree with this indirect approach to evaluate participant comprehension as it provides limited information.

The Applicant also did not query about understanding and appropriateness of response options for all PROMIS® Physical Function items, but rather each set of response options for the upper and lower extremity items was debriefed only once (i.e., queried participants only on two response scales) as it related to differentiating between the response options. The Applicant chose this approach to ensure feasibility and to reduce patient burden. This reviewer does not completely agree with this surrogate approach to evaluate comprehension and relevancy of the instruments' response options, as it provides limited information. It is unclear as to whether the response options are optimal and/or appropriate for all measurement concepts.

Based on the Gelhorn et al. (2016) publication, it does not look like participant comprehension of all items was fully evaluated. Per the publication, "For the 2 PROMIS-PF items that were discussed specifically during the interviews (stand for 1 hour, and do chores such as vacuuming or yard work), participants' responses indicated that the items were understood as intended, and that the response options provided were acceptable." It is also unclear what approach was used to evaluate participant comprehension for these two items.

Based on the submitted information, this reviewer cannot make a definitive conclusion whether the 15-item PROMIS® Physical Function measure is well-understood due to the limited approach used to evaluate participant comprehension. However, the approaches that were used provides some information on comprehension.

5.5.5 Other Measurement Properties

5.5.5.1 ROM Assessment

The Applicant cited literature (See Section 6.6 of the COA evidence dossier) and used data from literature to document the psychometric properties of the ROM assessment. A summary of results is provided below.

5.5.5.1.1 Reliability

A targeted review of the literature was conducted to establish the intraclass correlation coefficient (ICC) for the ROM assessment. Twelve studies in varying indications, including cerebral palsy, stroke, femoroacetabular impingement, as well as healthy subjects and patients with injuries, were reviewed to evaluate test-retest reliability for ROM measures using a goniometer. Reported ICCs across the studies ranged from 0.61 to 0.997 (See Table 1).

Table 1. Reliability Estimates Identified in the Literature

Study	ICC
Brosseau et al., 2001	ICCs ranged from 0.856 to 0.997
Glanzman et al., 2008	ICCs ranged from 0.9685 to 0.9822
Jones et al., 2014	ICCs ranged from 0.97 to 0.99
Karagiannopoulos et al., 2003	ICCs ranged from 0.86 to 0.98
Kim et al., 2018	ICCs ranged from 0.75 to 0.96; overall ICC was 0.91
Kolber et al., 2012	ICCs ranged from 0.87 to 0.92
Mitchell et al., 2014	ICCs ranged from 0.82 to 0.91
Mutlu et al., 2007	ICCs ranged from 0.61 to 0.95
Nussbaumer et al., 2010	ICCs ranged from 0.823 to 0.950
Paulis et al., 2011	ICC was 0.86
Resich et al., 2013	ICCs ranged from 0.88 to 0.94

Abbreviation: ICC = intraclass correlation coefficient

Source: Table 4 in Section 6.6.1 in the COA Evidence Dossier

5.5.5.1.2 Construct Validity

Based on the literature, ROM was lowly correlated with both the PROMIS-PF ($r=0.35$, $p < 0.001$) and Worst Stiffness NRS ($r=-0.31$, $P<0.001$) in patients with TGCT.

5.5.5.1.3 Responsiveness

For the assessment of responsiveness of ROM, the mean change from baseline to week 25 in Study PLX108-10 (ENLIVEN study) differed by treatment group, with a statistically significant improvement in patients randomized to pexidartinib compared to placebo (mean difference between groups: 8.9; $p= 0.0043$).

Reviewer's comment(s): *While literature related to the development history would be acceptable, there is insufficient detail about the methodology utilized in the cited publications as it relates to the psychometric analyses of ROM assessments and the type of goniometer used. Further, the patient population from the literature is not comparable to the target population.*

5.5.5.2 15-item PROMIS® Physical Function Measure

The Applicant provides a summary of the results from the original psychometric analyses that were conducted during the development and refinement of the15-item PROMIS® Physical Function measure, as well as results from the psychometric analyses that were conducted using data from the Study PLX108-10 (ENLIVEN study) (Speck 2020). These results are summarized in the subsequent sections.

5.5.5.2.1 Measurement Properties Assessed By Developers

5.5.5.2.1.1 Reliability

Internal Consistency Reliability

- Cella et al. (2010)[14] reported that the full PROMIS® Physical Function bank's Cronbach alpha reliability by T-scores was greater than 0.96 for scores four SDs less than the mean (poor functioning) to one SD greater than the mean.
- Hung et al. (Hung 2014)[15] assessed internal consistency reliability of the 124 physical function questions in orthopedic trauma patients. Cronbach's alpha was 0.98.
- Hung et al. (2013)[16] found internal consistency reliability to be high (person reliability =0.96) in a study of patients with any of six common foot and ankle disorders, including: ankle arthritis, ankle instability, adult acquired flatfoot deformity (pes planovalgus), hallux valgus (bunions), hallux rigidus, and hammer toe(s).

[14] Cella, D., W. Riley, A. Stone, et al. (2010). "The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008." J Clin Epidemiol 63(11): 1179-1194.
[15] Hung, M., A. R. Stuart, T. F. Higgins, et al. (2014). "Computerized Adaptive Testing Using the PROMIS Physical Function Item Bank Reduces Test Burden With Less Ceiling Effects Compared With the Short Musculoskeletal Function Assessment in Orthopaedic Trauma Patients." J Orthop Trauma 28(8): 439-443.
[16] Hung, M., J. F. Baumhauer, L. D. Latt, et al. (2013). "Validation of PROMIS (R) Physical Function computerized adaptive tests for orthopaedic foot and ankle outcome research." Clin Orthop Relat Res 471(11): 3466-3474.

5.5.5.2.1.2 Construct Validity

Convergent validity

- Assessment during the initial calibration study showed construct validity through strong correlations between the 124 calibrated items and the Health Assessment Questionnaire (r=-0.80) and 36-item Short Form Health Survey (SF-36; r=-0.88) (Cella 2010).
- Hays et al. (2013)[17] evaluated the construct validity of the upper extremity and mobility domains of the PROMIS® Physical Function item bank and found that upper extremity items had strong correlations with mobility (r=0.59), global physical health (r=0.52), global mental health (r=0.32), and overall PF (r=0.64). Similarly, the mobility domain correlated with global physical health (r=0.71), global mental health (r=0.38), and overall PF (r=0.87).

Known-groups validity

Hung (2013) concluded that evidence of known-groups validity was shown through statistically significant differences in PROMIS® Physical Function scores by comorbidity status (i.e., with versus without) (t=5.10, P<0.001). Comorbidity status was defined as those who had a history of at least one ailment (hypertension, rheumatoid arthritis, osteoporosis, high blood pressure, asthma, anxiety, diabetes, breast cancer, thyroid disease, hay fever, hepatitis, gout, sleep apnea, etc.) or were willing to trade at least 1 year in current state of life for perfect foot and ankle function.

Reviewer's comment(s): *Co-morbidity status may not be an appropriate known group to differentiate clinically distinct groups. Generally, sponsors should group patients by a variable that can categorize patients by the severity of their condition (e.g., TGCT severity).*

5.5.5.2.1.3 Unidimensionality

Hung (2012)[18] evaluated the unidimensionality of the PROMIS® Physical Function items reporting a unidimensional model explaining 60.6% of the model variance across the 124 PROMIS® Physical Function items in the version 1.0 item bank.

Reviewer's comment(s): *The results presented from the cited literature is not specific to the version of the PROMIS® Physical Function used in Study DCC-3014-03-001. The patient population from the literature is also not comparable to the target population.*

5.5.5.2.2 Measurement Properties Assessed During Study PLX108-10 (ENLIVEN) (N=120)

The Applicant presents a summary of the results of the psychometric analyses conducted using data from Study PLX108-10, a multicenter, randomized, double-blind, placebo-controlled, two-part phase 3 study designed to evaluate the efficacy and safety of pexidartinib compared with placebo for the treatment of patients with pigmented villonodular synovitis (PVNS) or giant cell

[17] Hays, R. D., K. L. Spritzer, D. Amtmann, et al. (2013). "Upper-extremity and mobility subdomains from the Patient-Reported Outcomes Measurement Information System (PROMIS) adult physical functioning item bank." Arch Phys Med Rehabil 94(11): 2291-2296.
[18] Hung, M., D. O. Clegg, T. Greene, et al. (2012). "A lower extremity physical function computerized adaptive testing instrument for orthopaedic patients." Foot Ankle Int 33(4): 326-335.

tumor of the tendon (GCT-TS). In Part 1, patients were stratified by region (U.S. vs. non-U.S. sites) and extremity involvement (upper extremity vs. lower extremity involvement). Eligible participants were randomly assigned in a 1:1 ratio to the study arm and the placebo arm. Refer to the previous COA review or Clinical Review for NDA 211810 for more details regarding the study design and study population.

Reviewer's comment(s): *The populations of the two trials were similar with regard to their clinical and demographic characteristics. Age was similar across the two trials, with a mean (SD) age of 43.4 years (13.80 years) in Study DCC-3014-03-001 and 44.5 years (13.35 years) in the Study PLX108-10. Distribution of males and females across the two trials was identical, with a majority of patients (59%) being female. The relatively minor differences in race and ethnicity across the studies likely reflected the more multinational sample in Study DCC-3014-03-001 (89.4% non-US) vs. Study PLX108-10 (62.5% non-US). Similarly, for extremity involvement for tumor location, there were similar proportions of patients having upper extremity tumors (9% in Study DCC-3014-03-001; 8% in Study PLX108-10) and lower extremity tumors (91% in Study DCC-3014-03-001; 92% in Study PLX108-10).*

5.5.5.2.2.1 Reliability

Internal Consistency Reliability
The Cronbach's alphas were 0.93 and 0.91 for the lower and upper extremity items, respectively.

Reviewer's comment(s): *In general, the Cronbach's alphas were within an acceptable and reasonable range for the analysis.*

Test-retest Reliability
Test-retest reliability[19] was assessed in all participants at screening and baseline and a subset of stable participants who reported "No change" ratings on the Patient Global Rating of Concept (PGRC) – Physical Function from week 9 to week 17. The ICC was 0.80 in all participants (n= 101) at screening and baseline, and 0.88 in stable participants (n=33) from weeks 9–17.

Reviewer's comment(s): *While the ICCs were within an acceptable and reasonable range for the analysis, the results should be cautiously interpreted. Generally, analysis of test-retest reliability should be conducted on a subset of patients who report that their symptoms are stable during the study period at two specified endpoints. It is unclear how the test-retest analysis was conducted in the ENLIVEN study and whether it used two time points or a range of time points.*

5.5.5.2.2.2 Construct Validity

Convergent Validity
For assessment of convergent validity, moderate correlations were observed between the 15-item PROMIS® Physical Function measure and patient-reported assessments of TGCG symptoms, such as the BPI Worst Pain NRS (r=-0.52) and Worst Stiffness NRS (r=-0.45). Moderate to

19 Stability was defined as patients who reported "No change" on the Patient Global Rating of Concept (PGRC) – Physical Function.

strong correlations were also observed between the 15-item PROMIS® Physical Function measure and pain/discomfort, mobility, and usual activities items of the EQ-5D (r=-0.48, -0.63, and -0.67, respectively)

Reviewer's comment(s): *The 15-item PROMIS® Physical Function measure appears to have a relationship to TGCT symptoms (e.g., pain, stiffness) and other assessments with similar concepts (e.g., mobility, usual activities) as expected.*

Known-groups Validity
For assessment of known-groups validity, the 15-item PROMIS® Physical Function measure differed among patients categorized by pain and stiffness level.

Reviewer's comment(s): *It is unknown whether TGCT symptoms are appropriate known groups to differentiate clinically distinct groups. Generally, sponsors should group patients by a variable that can categorize patients by the severity of their condition (e.g., TGCT severity).*

5.5.5.2.2.3 Responsiveness

For assessment of responsiveness, PROMIS® Physical Function change scores were evaluated between baseline and week 25 among different levels of change in the PGRC-Physical Functioning measure (overall F values < 0.001). Analyses by RECIST 1.1 responder status and Tumor volume score (TVS) responder status showed trends in the expected direction, but were not statistically significant.

Reviewer's comment(s): *In general, the 15-item PROMIS Physical Function measure appears to identify differences in scores over time in individuals or groups who have changed with respect to the concept.*

5.5.5.2.2.4 Unidimensionality

Speck et al. (2020) conducted a unidimensional confirmatory factor analysis (CFA) to evaluate the unidimensionality of the PROMIS® Physical Function lower extremity item set and confirm that the 13 Physical Function candidate items comprised a single underlying factor in patients with TGCT. The model could not be estimated for the 11 PROMIS-PF upper extremity items, as there were only seven participants with upper extremity tumors with PROMIS® Physical Function data available. Model fit was assessed with comparative fit index (CFI), root mean square error
approximation (RMSEA), and standardized root mean square residuals (SRMR). A CFI > 0.95 was considered a good fit, as well as a RMSEA < 0.05 and SRMR < 0.08.

Data from 104 lower extremity and upper extremity patients were included for the model that included the nine items that overlapped across tumor location; the factor loadings ranged from 0.609 to 0.881, with the exception of item PFA16R1 ("Are you able to dress yourself, including tying shoelaces and but- toning up your clothes?"), which had a factor loading of 0.394. The authors concluded that the model showed moderate fit, with CFI and RMSEA values of 0.874 and 0.155, respectively, and an SRMR of 0.063.

Data from 97 lower extremity patients were included for the model that included the 13 PROMIS-PF lower extremity items; the factor loadings ranged from 0.626 to 0.840, with the exception of item PFA12 ("Are you able to push open a heavy door?"), which had a factor loading of 0.425. The model showed moderate fit.

Reviewer's comment(s): *Per the Applicant, "Due to the moderate model fit results reported by Speck 2020 using the PROMIS-PF data in ENLIVEN, the CFA analyses were repeated using the MOTION data to further assess the factor structure of the PROMIS-PF scales among patients with TGCT." The unidimensional model using data from 123 patients on the nine overlapping items resulted in factor loadings of 0.636 to 0.865. The model showed good fit to the data, with CFI of 0.960, RMSEA of 0.092, and a SRMR of 0.039. Data from 109 lower extremity patients were included in the model evaluating the 13 lower extremity items, with factor loadings ranging from 0.453 to 0.862. The authors concluded that the model showed good fit to the data, with a CFI of 0.959, RMSEA of 0.071, and a SRMR of 0.041.*

The results for this CFA should be cautiously interpreted as the sample size may not be sufficient to conduct a CFA.

5.5.5.2.3Measurement Properties Assessed During Study DCC-3014-03-001 (MOTION)

The Applicant did not conduct any further psychometric analyses. This section includes item-level descriptives from Study DCC-3014-03-001.

5.5.5.2.3.1 Item-level Descriptive Statistics

Tables 2 and 3 provide a summary of the median 15-item PROMIS® Physical Function scores for the lower and upper limb extremities, respectively.

Table 2. Summary of Median 15-item Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function measure scores at item-level at baseline, End-of-Treatment (EOT), and change from baseline in the Study (Lower Limb)

PROMIS® Physical Function (Lower Limb)	Placebo (N= 36)			Vimseltinib (N=77)		
	Baseline (n= 36)	End of Treatment (n=26) [n missing =10, (27.0%)]	Median Change from Baseline (mean, SD)	Baseline (n=77)	End of Treatment (n= 57) [n missing =20 (26.0%)]	Median Change from Baseline (mean,SD)
Are you able to exercise for an hour?	2.0	2.0	0 (0.2, 0.97)	3.0	4.0	1.0 (0.8, 0.95)
Are you able to push open a heavy door?	4.0	4.0	0 (-0.2, 1.13)	4.0	5.0	0 (0.2, 0.87)

Are you able to stand for one hour?	3.0	3.0	0 (0.1, 1.22)	3.0	4.0	0 (0.5, 1.07)
Are you able to carry a heavy object (over 30lb /5kg)?	4.0	4.0	0 (0.2, 1.05)	4.0	5.0	0 (0.6, 1.24)
Are you able to carry a laundry basket up a flight of stairs?	4.0	4.0	0 (0.0, 1.13)	4.0	4.0	0 (0.4, 0.93)
Are you able to dress yourself, including tying your shoelaces and buttoning your clothes?	5.0	5.0	0 (-0.3, 0.66)	5.0	5.0	0 (0.4, 0.84)
Are you able to go for a walk of at least 15 minutes?	4.0	4.0	0 (0.1, 0.89)	4.0	4.0	0 (0.6, 1.24)
Are you able to go up and down stairs at a normal pace?	3.0	3.0	0 (0.2, 0.79)	3.0	4.0	1.0 (0.8, 1.20)
Does your health now limit you in bending, kneeling, or stooping?	2.0	3.0	1.0 (0.6, 0.70)	2.0	3.0	1.0 (0.8, 1.11)
Does your health now Limit you in lifting or carrying groceries?	3.0	3.0	0 (0.0, 0.94)	3.0	4.0	1.0 (0.6, 0.96)
Does your health now limit you in doing heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	3.0	3.0	0 (0.4, 1.01)	3.0	4.0	0 (0.5, 1.14)
Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors, or carrying groceries?	3.0	3.0	0 (0.3, 0.90)	4.0	4.0	0 (0.5, 1.04)
Does your health now Limit you in going outside the home, for example to shop or visit a doctor's office?	4.0	4.0	0 (0.0, 0.85)	4.0	5.0	0 (0.4, 0.94)

Source: FDA reviewer's table

Table 3. Summary of Median Patient-Reported Outcomes Measurement Information System (PROMIS) Physical Function scores at item-level at baseline, End-of-Treatment (EOT), and change from baseline in the Study (Upper Limb)

PROMIS® Physical Function (Upper Limb)	Placebo (N= 3)			Vimseltinib (N=6)		
	Baseline (n= 3)	End of Treatment (n=26) [n missing =0, (0%)]	Median Change from Baseline (mean, SD)	Baseline (n=6)	End of Treatment (n= 57) [n missing =0 (0%)]	Median Change from Baseline (mean, SD)
Are you able to exercise for an hour?	3.0	3.0	0 (0.0, 1.00)	2.5	5.0	2.0 (1.7, 1.37)
Are you able to push open a heavy door?	2.0	3.0	0 (0.0, 1.00)	3.0	4.0	1.0 (1.0, 1.55)
Are you able to carry a heavy object (over 30lb /5kg)?	3.0	3.0	0 (0.0, 0.00)	2.5	4.0	2.0 (1.8, 1.72)
Are you able to carry a laundry basket up a flight of stairs?	3.0	3.0	0 (0.0, 0.00)	4.0	4.0	0.5 (0.8, 1.47)
Are you able to change a light bulb overhead?	3.0	3.0	0 (-0.3, 0.58)	4.0	5.0	0.5 (1.2, 1.60)
Are you able to dress yourself, including tying your shoelaces and buttoning your clothes?	3.0	4.0	0 (0.3, 0.58)	4.5	5.0	0 (1.0, 1.55)
Are you able to lift 10 pounds (5kg) above your shoulder?	2.0	3.0	0 (0.3 , 0.58)	2.0	4.0	0.5 (1.2, 1.47)
Does your health now Limit you in lifting or carrying groceries?	3.0	3.0	0 (0.0, 0.00)	3.0	4.0	0.5 (1.0, 1.26)
Does your health now limit you in doing heavy work around the house like scrubbing floors or lifting or moving heavy furniture?	2.0	3.0	0 (0.3, 0.58)	2.0	3.5	1.0 (1.2, 1.33)
Does your health now limit you in doing	3.0	3.0	0	3.0	4.0	1.5

moderate work around the house like vacuuming, sweeping floors, or carrying groceries?			(-0.3, 0.58)			(1.3, 1.21)
Does your health now Limit you in going outside the home, for example to shop or visit a doctor's office?	4.0	5.0	1.0 (0.7, 0.58)	4.0	5.0	0 (0.7, 1.03)

Source: FDA reviewer's table

Reviewer's comment(s):
Although the efficacy analysis for the 15-item PROMIS® Physical Function -based endpoint showed statistically significant results, minimal magnitude of changes was observed at the item-level in select items of the 15-item PROMIS® Physical Function score using both T-scores and raw scores. Further, there are only select items (i.e., lower limb extremity items) within the instrument that contribute more to the change observed in the total score based upon review of item-level analyses. However, it is noted that the items that are overly influencing the total score are generally specific to lower limb functioning which is consistent to the tumor location in patients at baseline.

There was no worsening observed in the PROMIS® Physical Function items at Week 25.

The sample size for the PROMIS-PF upper limb extremity items was too small to interpret the item level analysis.

5.5.6 Interpretation of Meaningful Within-Patient Score Changes

The Applicant proposed that a +10% degree change and 3-point increase in the ROM assessment 15-item PROMIS® Physical Function measure, respectively is a meaningful within-patient score change. Accordingly, the Applicant performed the following analyses to support the proposed threshold for meaningful within-patient change in these measures using data from Study DCC-3014-03-001:

- Anchor-based analyses (including anchor-based empirical cumulative distribution function [eCDF] curves)
- Distribution-based analyses
- Qualitative methods (embedded exit interviews)

5.5.6.1 Anchor-based analyses

In order to review the Applicant's anchor-based analyses, an IR was issued on November 16, 2024.

5.5.6.1.1 ROM Assessment

The Applicant used the following patient global rating scales as external anchors:

- Patient Global Impression of Severity (PGIS)-ROM item:
  The PGIS-ROM item is a single item designed to assess the severity of limitation in ROM using a 5-point VRS ranging from "None" to Very Severe". The recall period is the previous 24 hours.

- Patient Global Impression of Change (PGIC)-ROM item:
  The PGIC-ROM item is a single-item designed to assess the overall change in ROM at using a 7-point VRS ranging from "Very much better" to "Very much worse." The recall period is a comparison of current state to an earlier time period.

- Patient Global Impression of Change (PGIC)-Overall Symptoms item:
  The PGIC-Overall Symptoms item is a single-item designed to assess the overall change in symptoms at the tumor site using a 7-point VRS ranging from "Very much better" to "Very much worse." The recall period is a comparison of current state to an earlier time period.

The PGIS-ROM anchor was administered 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 PGIC-ROM and PGIC-Overall Symptoms anchors were administered at 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. See Appendix C for copies of the anchors.

Reviewer's comment(s):
The anchors corresponding to the ROM-based endpoint have limitations that impact interpretability of the results of the anchor-based analyses:

1. *It is unclear whether the definition of ROM and the example of movements (e.g., pivot) in the PGIS-ROM and PGIC-ROM items are well-understood across patients of all educational levels. The anchor scales should be plainly understood by respondents in the context of use. The general recommendation is to test draft anchor item(s) including their response categories in cognitive interviews.*
2. *The concept measured in the PGIC-Overall Symptoms item is not aligned with the concept of the ROM assessment. We generally recommend that an anchor scale measures the same concept (i.e., the aspect of the disease specified in the endpoint, as opposed to global status of the disease) of the target instrument to the extent possible to provide the most direct evidence.*
3. *The correlations between change in ROM from baseline to week 25 and the PGIS-ROM, PGIC-ROM, and PGIC-overall symptoms were low (r=-0.34, -0.39, and -0.38, respectively).*

This reviewer notes that the Applicant also utilized clinician global rating scales as external anchors. However, these items did not take into account the patient perspective. As such, this review focused on the patient global rating scales.

Table 4 describes the distributions of the PGIS-ROM at baseline and Week 25 for Study DCC-3014-03-001. Overall, three participants (n= 3/93, 3.2%) reported no limitations in ROM

("None)" with no room for improvement during the studies. For participants who endorsed other PGIS response categories at baseline, over one-third of them reported having "Moderate" limitations in ROM at Week 25. However, participants who reported "Moderate" limitations in ROM at baseline remained "moderately" limited at Week 25. For participants who reported being "severely" limited at baseline, 8.1% (n= 10) of participants improved by one category at Week 25. Similarly, participants who reported being "moderately" limited at baseline, 8.9% (n= 11) improved by one category at Week 25.

Table 4. Cross tabulation for PGIS-ROM at Baseline and Week 25, ITT Set

	PGIS (ROM) at Week 25 (N=123)					
Scale Baseline	None	Mild	Moderate	Severe	Very Severe	Missing
PGIS (ROM)						
None	3 (2.4)	0	0	0	0	0
Mild	7 (5.7)	12 (9.8)	3 (2.4)	1 (0.8)	0	2 (1.6)
Moderate	2 (1.6)	11 (8.9)	24 (19.5)	3 (2.4)	0	9 (7.3)
Severe	1 (0.8)	8 (6.5)	10 (8.1)	5 (4.1)	1 (0.8)	17 (13.8)
Very Severe	0	0	0	1 (0.8)	1 (0.8)	2 (1.6)
Missing	0	0	0	0	0	0

Source: Table 23 in 1.11.3 Response to FDA Information Request (dated November 25, 2024)

Reviewer's comment(s):
The sample size is small with a good amount of missing data (24.4%) at Week 25 for PGIS-ROM. The distributions of the PGIS-ROM score at baseline and Week 25 needs to be interpreted with caution, however, the general trend does not show much improvement in severity of limitations in ROM. Based on this data, as well as the limitations in the PGIS-ROM and PGIC-ROM items, it is difficult to interpret the results of the anchor-based analyses. As such, it iis unknown what constitutes a meaningful change in the ROM assessment.

In discussion with Clinical, a potential rationale for not seeing greater change in ROM is that ROM could still be restricted despite tumor shrinkage depending on the tumor location.

5.5.6.1.2 15-item PROMIS® Physical Function Measure

The Applicant used the following patient global rating scales as external anchors:

- PGIS-Physical Function item:
  The PGIS-Physical Function item is a single item designed to assess the severity of limitation in tumor-related physical functioning using a 5-point VRS ragning from"None," to "Very Severe." The recall period is the previous 24 hours.

- PGIC-Physical Function item
  The PGIC-Physical Function item is a single-item designed to assess the overall change in tumor-related physical functioning using a 7-point VRS ranging from "Very much better" to "Very much worse." The recall period is a comparison of current state to an earlier time period.

- PGIC-Overall Symptoms item:
  The PGIC-Overall Symptoms item is a single-item designed to assess the overall change in symptoms at the tumor site using a 7-point VRS ranging from "Very much better" to "Very much worse." The recall period is a comparison of current state to an earlier time period.

The PGIS-Physical Function anchor was administered 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 PGIC- Physical Function and PGIC-Overall Symptoms anchors were administered at 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. See Appendix C for copies of the anchors.

Reviewer's comment(s):
The physical function-specific PGIS and PGIC items appear reasonable. Similar to the ROM-based endpoint, the PGIC-Overall Symptoms item has limitations. Refer to Section 5.5.6.1.1 above.

In Study DCC-3014-03-001, the correlation between change in 15-item PROMIS-Physical Function score from baseline to week 25 was moderate with the PGIS-Physical Function, PGIC-Physical Function, and PGIC-overall symptoms (r=-0.43, -0.54, and -0.46, respectively).

The Applicant proposed the "Minimally improved" response category on the PGIC-Physical Function item as the target anchor change category based on the data from the embedded exit interview study. Refer to Section 5.5.6.1 for more details on the qualitative methods used for this exercise. Tables 5 and 6 shows the change in the 15-item PROMIS® Physical Function scores from Baseline to Week 25 by the PGIS-Physical Function and PGIC-Physical Function items, respectively at Week 25 in Study DCC-3014-03-001. Patients who reported a minimal improvement in the PGIC-PF item had a mean change in the 15-item PROMIS® Physical Function score of 2.6 and a median change of 2.0.

Table 5. Change form Baseline to Week 25 in 15-item Physical Function Score by PGIC-Physical Function item at Week 25

Score	Change in PGIS-PF from Baseline to Week 25							
	Any Improvement (1-, 2-, or 3-point)	3-Point Improvement	2-Point Improvement	1-Point Improvement	No Change (0-point change)	1-Point Worsening	2-Point Worsening	3-Point Worsening
Change in PROMIS-PF Score from Baseline to Week 25								
n	36	2	8	26	29	6	0	0
Mean (SD)	6.0 (5.81)	22.5 (9.19)	7.3 (2.49)	4.4 (4.14)	2.2 (4.90)	1.8 (5.31)	-	-
Median	6.0	22.5	6.5	3.5	1.0	1.0	-	-
Min-Max	-3.0 - 29.0	16.0 - 29.0	5.0 - 13.0	-3.0 - 13.0	-4.0 - 16.0	-5.0 - 8.0	-	-
95% CI	4.06 - 7.99	-60.09 - 105.09	5.17 - 9.33	2.71 - 6.06	0.38 - 4.11	-3.74 - 7.40	-	-

Abbreviations: CI = confidence interval; PF = physical functioning; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PROMIS = Patient-Reported Outcomes Measurement Information System; SD = standard deviation

Source: Table 3a.1 in the Applicant's Estimating Responder Definitions for Physical Functioning, Worst Stiffness, and Range of Motion among Patients with Tenosynovial Giant Cell Tumor (TGCT) Results Memo Version 1.0 dated 18 October 2023

Table 6. Change form Baseline to Week 25 in 15-item Physical Function Score by PGIC-Physical Function item at Week 25

Score	PGIC-PF at Week 25							
	Any Improvement	Very Much Improved	Much Improved	Minimally Improved	No change	Minimally Worse	Much Worse	Very Much Worse
Change in PROMIS-PF Score from Baseline to Week 25								
n	52	13	24	15	13	5	1	0
Mean (SD)	5.4 (5.80)	9.7 (7.17)	4.9 (4.67)	2.6 (4.05)	0.8 (3.49)	0.4 (4.22)	-1.0 ( )	-
Median	5.0	8.0	5.0	2.0	1.0	2.0	-1.0	-
Min-Max	-3.0 - 29.0	0.0 - 29.0	-3.0 - 16.0	-3.0 - 11.0	-4.0 - 7.0	-5.0 - 5.0	-1.0 - -1.0	-
95% CI	3.81 - 7.04	5.36 - 14.02	2.90 - 6.85	0.36 - 4.84	-1.34 - 2.88	-4.84 - 5.64	-	-

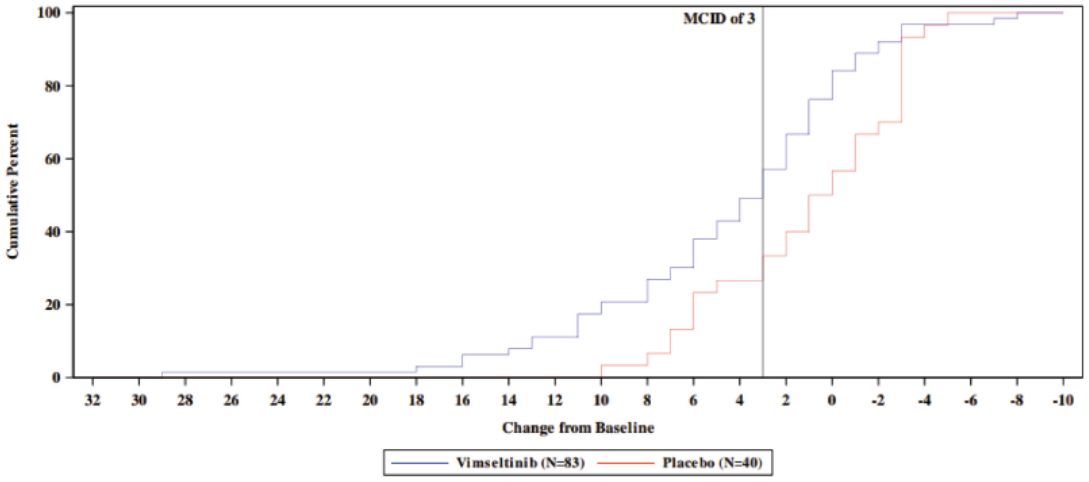
Source: Table 3a.2 in the Applicant's Estimating Responder Definitions for Physical Functioning, Worst Stiffness, and Range of Motion among Patients with Tenosynovial Giant Cell Tumor (TGCT) Results Memo Version 1.0 dated 18 October 2023

Reviewer's comment(s): *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 Section 5.5.6.1 for more details on the qualitative methods used for this exercise. To take a more conservative approach, this reviewer recommends using a 2-category change on the PGIS-Physical Function item (based on the exit interviews, refer to Section 5.5.6.1) 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-Physial 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).

We are 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 3, the change from baseline in the 15-item Physical Fuction score showed adequate separation between the vimseltinib and placebo arm across a range that likely includes a clinically meaningful change threshold. Based on the data presented in Tables 5 and 6 and Figure 3, a plausible clinical meaningful change threshold range in the 15-item PROMIS® Physical Function score could be between 3 and 7-points.

Figure 3. eCDF Plot of the Change in PROMIS-PF Score from Baseline to Week 25 by Treatment Arm



ITT = Intent-to-Treat.
Baseline is defined as the most recent non-missing measurement prior to the first administration of study drug.
Week 25 includes results within 7 days prior and up to 2 days after to End of Part 1 visit.
The data used to develop this CDF plot includes those participants with PROMIS-PF data at Baseline and Week 25. This approach differs from the responder endpoint analysis which defined those with missing data as non-responders

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

5.5.6.2 Qualitative methods

Refer to Section 5.5.4.1.2 regarding the design of the embedded exit interview study.

5.5.6.2.2 ROM Assessment

The results of the exit interviews as it relates to interpreting the ROM-based endpoint is summarized below:

- A total of 33 participants were debriefed on the PGIS-ROM item.
- Approximately three-fourths of the participants were asked to describe what ROM means to them. All of the participants asked (n=21/21, 100%) interpreted the item as intended.
- The majority of participants (n=28/33, 85%) found it easy to select a response for thie PGIS-ROM item.
- Almost all participants (n=32/33, 97%) were able to identify differences between the PGIS-ROM response options ("None," "Mild," "Moderate," "Severe," and "Very Severe).
- The majority of participants (n=32/33, 97%) understood the PGIC-ROM item as intended.
- Nearly all participants (n=30/33, 91%) reported that it was easy to provide a response to the PGIC-ROM item. Three participants (n=3/33, 9%) remarked that: recalling the change did require significant recollection; was subject to day-to-day variability for a

patient who may not have experienced any noticeable change; or was hard to grasp the context in which the question is being asked.

- The majority of participants (n=25/33, 76%) reported change in their ROM since the start of the clinical trial. Of these, 19 participants (n=19/25, 76%) found the change to be meaningful or worthwhile.
- Twenty-six of the participants were asked to identify the smallest change on the PGIC-ROM improvement scale that is meaningful. The majority of these participants (n=19/26, 73%) expressed that "minimally improved" would be worth taking the treatment as that improvement would be evident in one of their symptoms that they would find relief from. Six participants (6/26, 23%) expressed that "much improved" and one patient (n=1/26, 4%) expressed that "very much improved" would be the smallest change on the scale to make participation in the study worthwhile.

Reviewer's comment(s): *This reviewer notes that DCOA previously commented on the design of the exit interview study; however, the comments were never conveyed to the Applicant. Some of the comments were related to the structure of the meaningful change exercises. For example,*

- *Explore changes in general to include improvement and worsening*
- *Ask participants how their affected joint and its function changed and by how much. Refer to Comment 3 regarding ROM terminology.*
- *Explore participants' thoughts on what they believe constitutes a meaningful change (improvement or deterioration) in terms of PGIS/PGIC category changes (e.g., 1-category change, 2-category change, etc.).*
- *Focus on what constitutes a meaningful change from the patient perspective, rather than the smallest level of change.*

One of the limitations identified for the ROM-specific anchor scales was the ROM definition. While the Applicant reports that most participants understood the items, there is no information on the demographic characteristics to see if educational level impacted comprehension. Additionally, participants were not directly queried on whether they understood the anchors. Rather, partticipants were asked to rephrase the item in their own words. This reviewer does not completely agree with this indirect approach to evaluate participant comprehension as it provides limited information.

The qualitative results are difficult to interpret as participants were queried on the smallest level of change. Further, the primary anchor (i.e., PGIS-ROM) was not used in the meaningful change exercises.

5.5.6.2.3 15-item PROMIS® Physical Function measure

The results of the exit interviews as it relates to interpreting the 15-item PROMIS® Physical Function -based endpoint is summarized below:

- A total of 33 participants were debriefed on the 15-item PROMIS® Physical Function measure (including six participants on the Upper Extremity questionnaire and 27 participants on the Lower Extremity questionnaire).

- All patients who were asked (n=32/32, 100%) were able to identify differences between the response options "None," "Mild," "Moderate," "Severe," and "Very Severe" in the PGIS-Physical Function item.
- The majority of participants (n=29/30, 96.7%) clearly understood the PGIC-Physical Function as intended. One participant (n=1/30, 3.3%) noted that some of the listed activities were not applicable.
- Most participants (n=28/30, 93.3%) reported that it was easy to select a response on the item. Two participants (n=2/30, 6.7%) expressed that their symptoms were quite variable, making it hard to choose a response.
- The majority of participants (n=25/33, 76%) reported a change in their tumor-related physical functioning since the start of the clinical trial. Over half of these participants (n=14/25, 56%) noted that the change was meaningful or worthwhile.
- Twenty-one participants were asked what changes in tumor-related physical functioning would be perceived to be meaningful. The majority of the participants (n=14/21, 67%) reported that achieving a a response of "Minimally improved" would be meaningful, while five participants (n=5/21, 24%) reported achieving a response of"Much improved" would be meaningful.
- Most participants experienced improvements during Study DCC-3014-03-001, and most of those who experienced improvements considered them to be meaningful. Among whose who experienced improvement, a similar number of participants indicated a 1-category improvement (ranged from 3 to 7 participants for each item) or a 2-category improvement (ranged from 2 to 7 participants for each item) to be a meaningful change.
    - Participants who did not experience a meaningful improvement were asked to report how much improvement on the scale would they consider meaningful. Among those who were asked, a similar number of participants indicated a 1-category improvement would be worthwhile (ranged from 1 to 7 patients for each item) and a 2-category improvement (ranged from 0 to 5 for each item) would be worthwhile.

Reviewer's comment(s): *The qualitative results are difficult to interpret as participants were queried on the smallest level of change. Further, the primary anchor (i.e., PGIS-Physical Function) was not used in the meaningful change exercises.*

This reviewer notes that DCOA previously commented on the design of the exit interview study; however, the comments were never conveyed to the Applicant. Some of the comments were related to the structure of the meaningful change exercises. For example,

- *Explore changes in general to include improvement and worsening*
- *Explore participants' thoughts on what they believe constitutes a meaningful change (improvement or deterioration) in terms of PGIS/PGIC category changes (e.g., 1-category change, 2-category change, etc.).*
- *Focus on what constitutes a meaningful change from the patient perspective, rather than the smallest level of change.*

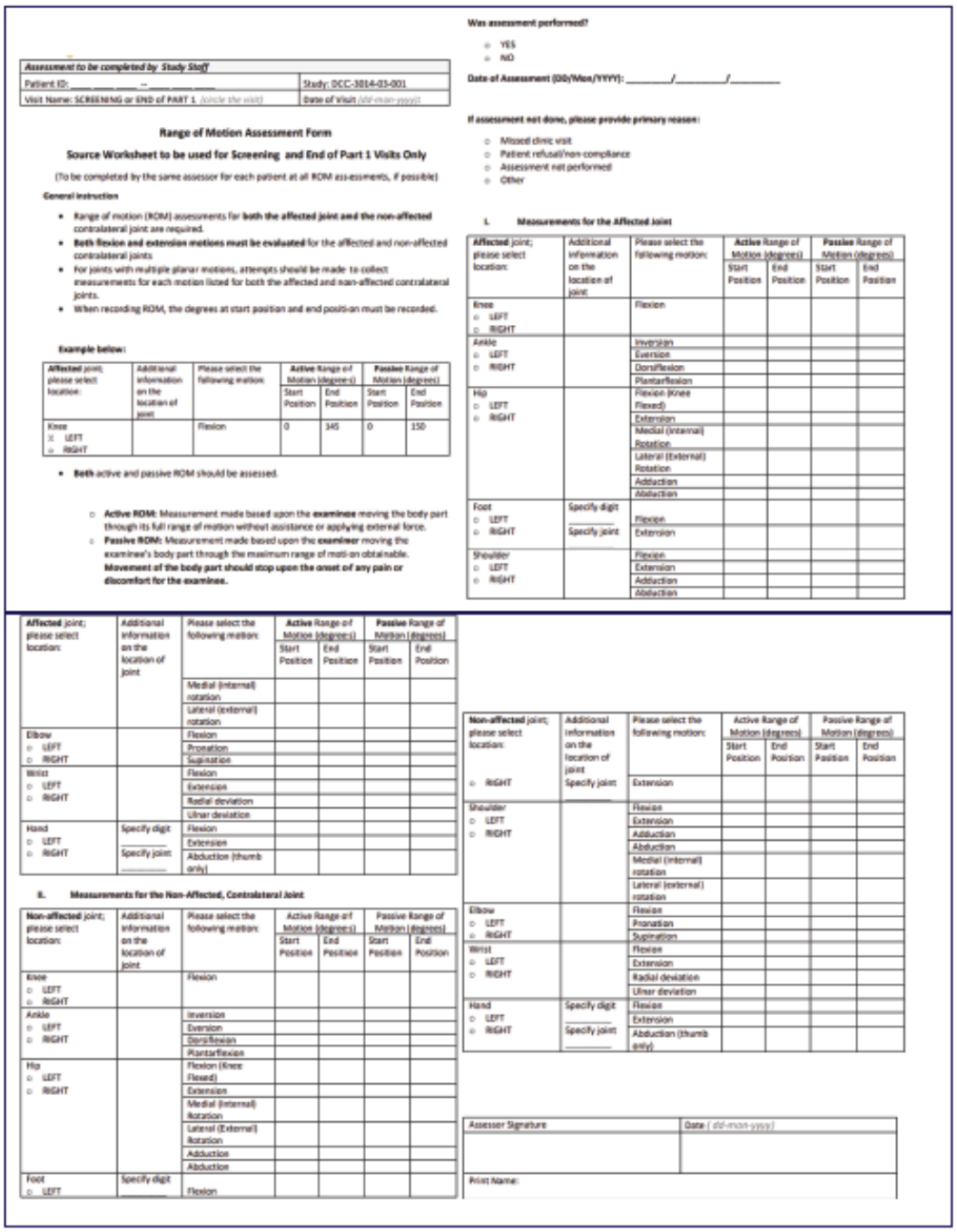
6 APPENDICES

Appendix A. Range of Motion (ROM) Assessment
Appendix B. 15-item PROMIS® Physical Function Measure
Appendix C. Copies of anchors
- Appendix C1. Patient Global Impression of Severity (PGIS) - ROM
- Appendix C2. Patient Global Impression of Change (PGIC) - ROM
- Appendix C3. Patient Global Impression of Change (PGIS) – Overall Symptoms
- Appendix C4. Patient Global Impression of Severity (PGIS) – Physical Function
- Appendix C5. Patient Global Impression of Change (PGIC) – Physical Function

Appendix D. Key findings from the Exit Interviews

Appendix A: Range of Motion assessment forms

Figure 3. Range of Motion Assessment Form: Screening and End of Part 1 Visit (Affected and Non-Affected Joint)



Assessment to be completed by: Study Staff

Patient ID: ____ ____ ____ -- ____ ____ ____ | Study: OCC-3814-03-001

Visit Name: SCREENING or END of PART 1 *(circle the visit)* | Date of Visit *(dd-mon-yyyy)*:

Range of Motion Assessment Form

Source Worksheet to be used for Screening and End of Part 1 Visits Only

(To be completed by the same assessor for each patient at all ROM assessments, if possible)

General instruction

- Range of motion (ROM) assessments for **both the affected joint and the non-affected** contralateral joint are required.
- **Both flexion and extension motions must be evaluated** for the affected and non-affected contralateral joints
- For joints with multiple planar motions, attempts should be made to collect measurements for each motion listed for both the affected and non-affected contralateral joints.
- When recording ROM, the degrees at start position and end position must be recorded.

Example below:

Affected joint; please select location:	Additional information on the location of joint	Please select the following motion:	**Active** Range of Motion (degree-s)		**Passive** Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
Knee X LEFT o RIGHT		Flexion	0	145	0	150

- **Both** active and passive ROM should be assessed.

- **Active ROM:** Measurement made based upon the **examinee** moving the body part through its full range of motion without assistance or applying external force.
- **Passive ROM:** Measurement made based upon the **examiner** moving the examinee's body part through the maximum range of motion obtainable. **Movement of the body part should stop upon the onset of any pain or discomfort for the examinee.**

Was assessment performed?

- YES
- NO

Date of Assessment (DD/Mon/YYYY): _____/_____/_____

If assessment not done, please provide primary reason:

- Missed clinic visit
- Patient refusal/non-compliance
- Assessment not performed
- Other

i. Measurements for the Affected Joint

Affected joint; please select location:	Additional information on the location of joint:	Please select the following motion:	**Active** Range of Motion (degrees)		**Passive** Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
Knee o LEFT o RIGHT		Flexion				
Ankle o LEFT o RIGHT		Inversion Eversion Dorsiflexion Plantarflexion				
Hip o LEFT o RIGHT		Flexion (Knee Flexed) Extension Medial (Internal) Rotation Lateral (External) Rotation Adduction Abduction				
Foot o LEFT o RIGHT	Specify digit: _____ Specify joint: _____	Flexion Extension				
Shoulder o LEFT o RIGHT		Flexion Extension Adduction Abduction				
Elbow o LEFT o RIGHT		Flexion Pronation Supination				
Wrist o LEFT o RIGHT		Flexion Extension Radial deviation Ulnar deviation				
Hand o LEFT o RIGHT	Specify digit: _____ Specify joint: _____	Flexion Extension Abduction (thumb only)				

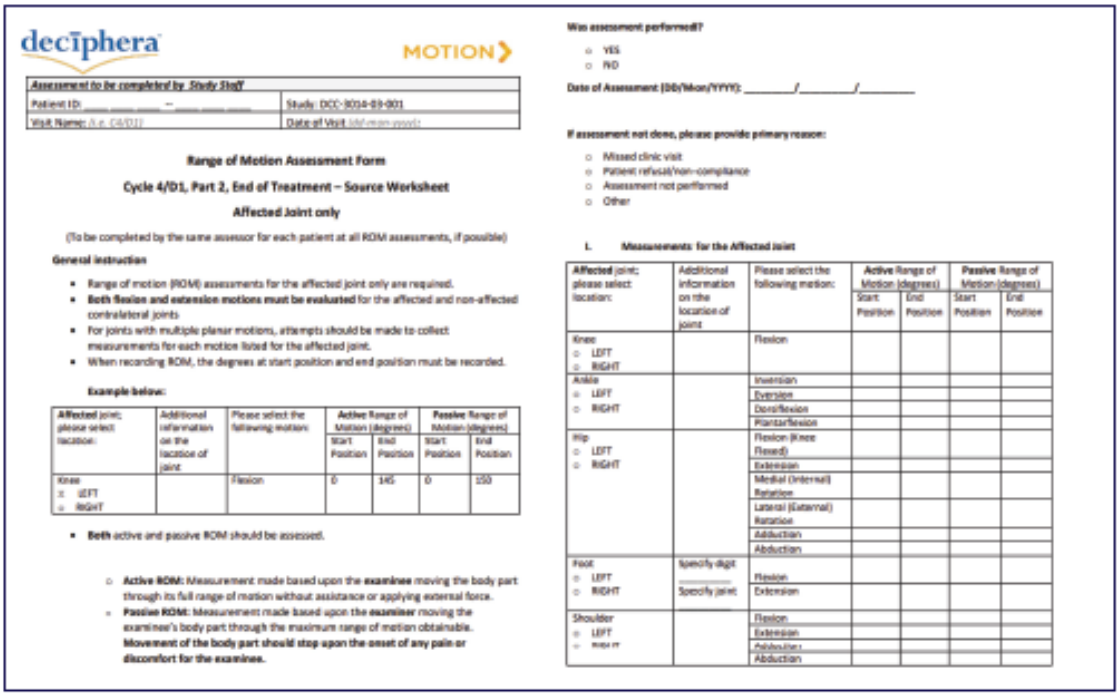
ii. Measurements for the Non-Affected, Contralateral Joint

Non-affected joint; please select location:	Additional information on the location of joint	Please select the following motion:	Active Range of Motion (degrees)		Passive Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
Knee o LEFT o RIGHT		Flexion				
Ankle o LEFT o RIGHT		Inversion Eversion Dorsiflexion Plantarflexion				
Hip o LEFT o RIGHT		Flexion (Knee Flexed) Extension Medial (Internal) Rotation Lateral (External) Rotation Adduction Abduction				
Foot o LEFT	Specify digit: _____	Flexion				

Non-affected joint; please select location:	Additional information on the location of joint	Please select the following motion:	Active Range of Motion (degrees)		Passive Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
o RIGHT	Specify joint: _____	Extension				
Shoulder o LEFT o RIGHT		Flexion Extension Adduction Abduction Medial (Internal) rotation Lateral (external) rotation				
Elbow o LEFT o RIGHT		Flexion Pronation Supination				
Wrist o LEFT o RIGHT		Flexion Extension Radial deviation Ulnar deviation				
Hand o LEFT o RIGHT	Specify digit: _____ Specify joint: _____	Flexion Extension Abduction (thumb only)				

Assessor Signature	Date *(dd-mon-yyyy)*
Print Name:	

Figure 4. Range of Motion Assessment Form: Part 2 End of Treatment (Affected Joint Only)



decīphera MOTION

Assessment to be completed by Study Staff	
Patient ID: ____ ____ ____ – ____ ____ ____	Study: DCC-8014-03-001
Visit Name: (i.e. C4/D1)	Date of Visit (dd-mon-yyyy)

Range of Motion Assessment Form

Cycle 4/D1, Part 2, End of Treatment – Source Worksheet

Affected Joint only

(To be completed by the same assessor for each patient at all ROM assessments, if possible)

General instruction

- Range of motion (ROM) assessments for the affected joint only are required.
- **Both flexion and extension motions must be evaluated** for the affected and non-affected contralateral joints
- For joints with multiple planar motions, attempts should be made to collect measurements for each motion listed for the affected joint.
- When recording ROM, the degrees at start position and end position must be recorded.

Example below:

Affected joint; please select location:	Additional information on the location of joint	Please select the following motion:	**Active** Range of Motion (degrees)		**Passive** Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
Knee x LEFT o RIGHT		Flexion	0	145	0	150

- **Both** active and passive ROM should be assessed.
  - **Active ROM:** Measurement made based upon the **examinee** moving the body part through its full range of motion without assistance or applying external force.
  - **Passive ROM:** Measurement made based upon the **examiner** moving the examinee's body part through the maximum range of motion obtainable. **Movement of the body part should stop upon the onset of any pain or discomfort for the examinee.**

Was assessment performed?

- o YES
- o NO

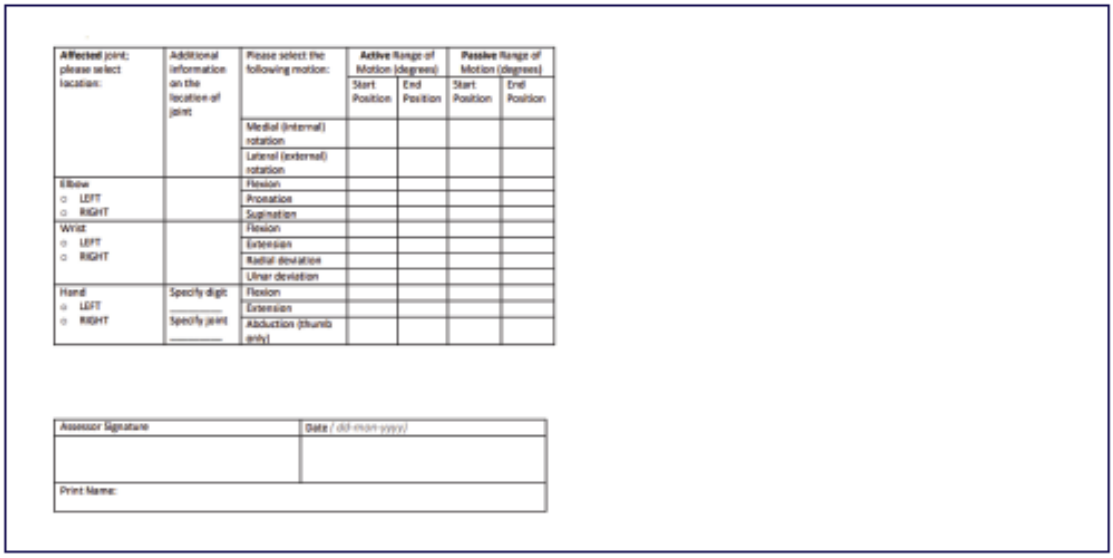
Date of Assessment (DD/Mon/YYYY): _____/_____/_____

If assessment not done, please provide primary reason:

- o Missed clinic visit
- o Patient refusal/non-compliance
- o Assessment not performed
- o Other

L. Measurements for the Affected Joint

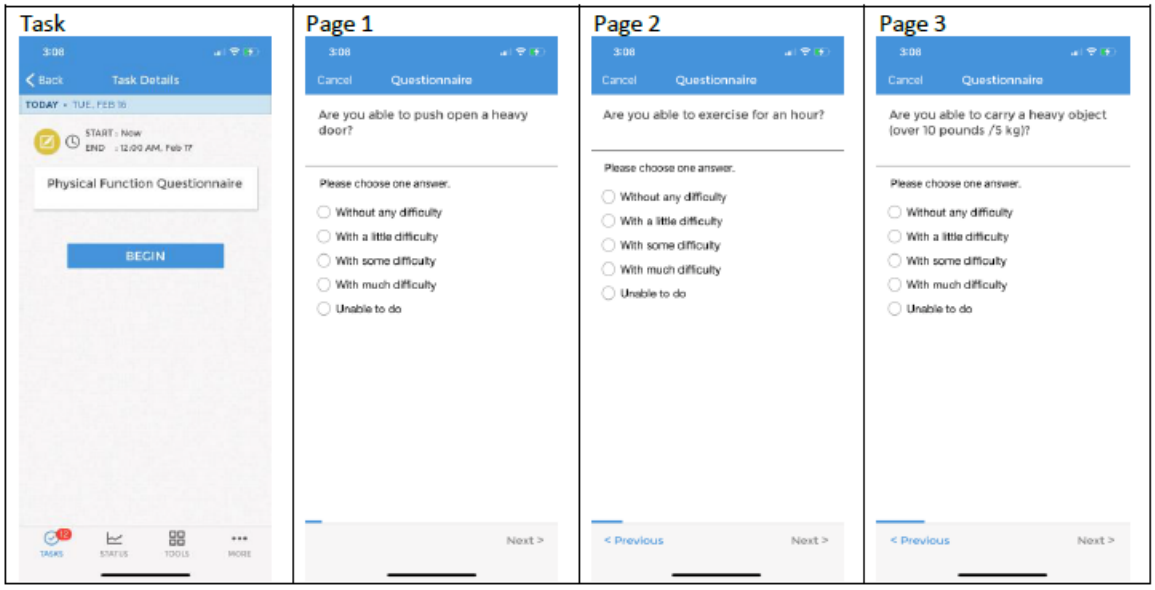
Affected joint; please select location:	Additional information on the location of joint	Please select the following motion:	**Active** Range of Motion (degrees)		**Passive** Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
Knee o LEFT o RIGHT		Flexion				
Ankle o LEFT o RIGHT		Inversion Eversion Dorsiflexion Plantarflexion				
Hip o LEFT o RIGHT		Flexion (Knee Flexed) Extension Medial (Internal) Rotation Lateral (External) Rotation Adduction Abduction				
Foot o LEFT o RIGHT	Specify digit: _____ Specify joint: _____	Flexion Extension				
Shoulder o LEFT o RIGHT		Flexion Extension Adduction Abduction				

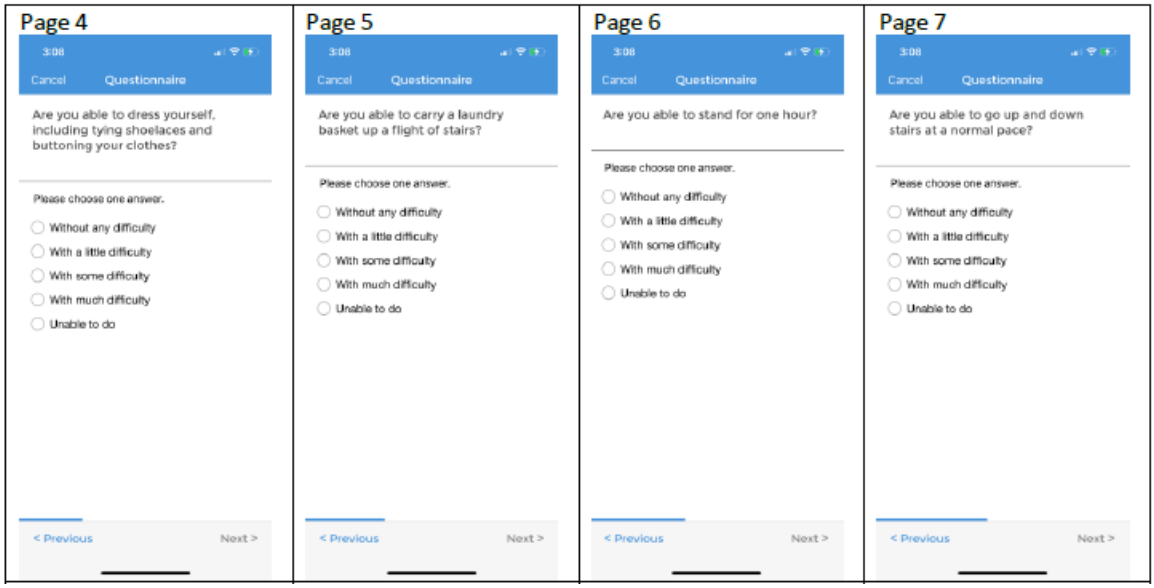


Affected joint; please select location:	Additional information on the location of joint	Please select the following motion:	**Active** Range of Motion (degrees)		**Passive** Range of Motion (degrees)	
			Start Position	End Position	Start Position	End Position
		Medial (Internal) rotation				
		Lateral (external) rotation				
Elbow o LEFT o RIGHT		Flexion Pronation Supination				
Wrist o LEFT o RIGHT		Flexion Extension Radial deviation Ulnar deviation				
Hand o LEFT o RIGHT	Specify digit: Specify joint: _____	Flexion Extension Abduction (thumb only)				

Assessor Signature	Date (dd-mon-yyyy)
Print Name:	

Appendix B. 15-item PROMIS® Physical Function Measure





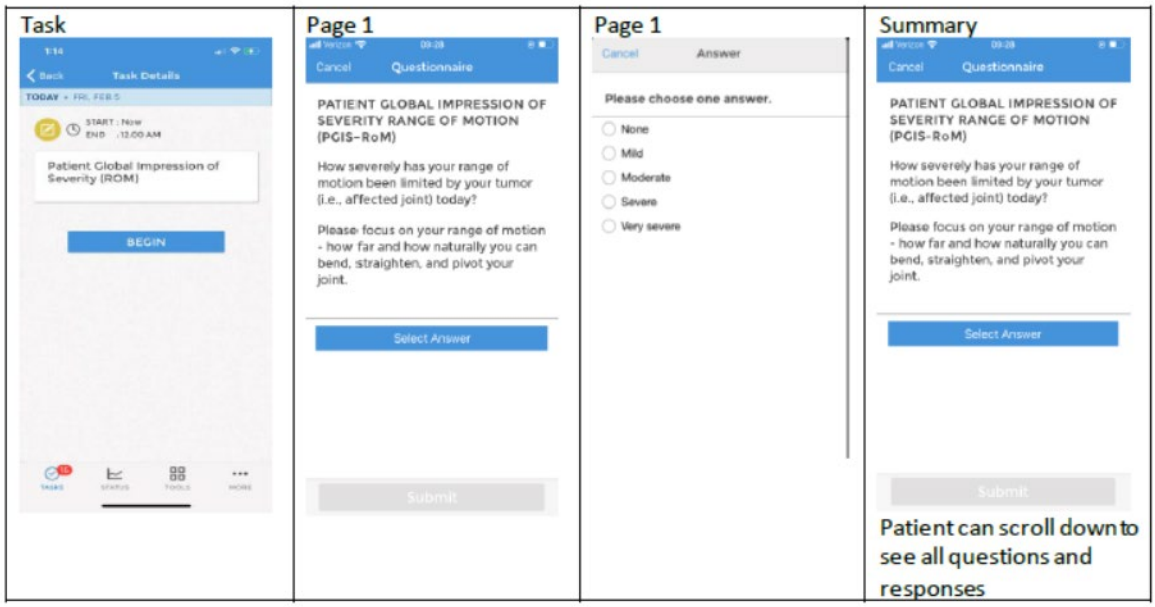

Page 8
Cancel Questionnaire
Are you able to go for a walk of at least 15 minutes?
Please choose one answer.
Without any difficulty
With a little difficulty
With some difficulty
With much difficulty
Unable to do
< Previous
Next >
Page 9
Cancel Questionnaire
Are you able to lift 10 pounds (5 kg) above your shoulder?
Please choose one answer.
Without any difficulty
With a little difficulty
With some difficulty
With much difficulty
Unable to do
< Previous
Next >
Page 10
Cancel Questionnaire
Are you able to change a light bulb overhead?
Please choose one answer.
Without any difficulty
With a little difficulty
With some difficulty
With much difficulty
Unable to do
< Previous
Next >
Page 11
Cancel Questionnaire
Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?
Please choose one answer.
Not at all
Very little
Somewhat
Quite a lot
Cannot do
< Previous
Next >
Page 12
Cancel Questionnaire
Does your health now limit you in lifting or carrying groceries?
Please choose one answer.
Not at all
Very little
Somewhat
Quite a lot
Cannot do
< Previous
Next >
Page 13
Cancel Questionnaire
Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?
Please choose one answer.
Not at all
Very little
Somewhat
Quite a lot
Cannot do
< Previous
Next >
Page 14
Cancel Questionnaire
Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?
Please choose one answer.
Not at all
Very little
Somewhat
Quite a lot
Cannot do
< Previous
Next >
Page 15
Cancel Questionnaire
Does your health now limit you in bending, kneeling, or stooping?
Please choose one answer.
Not at all
Very little
Somewhat
Quite a lot
Cannot do
< Previous
Next >

Appendix C: Copies of anchors

Appendix C1. Patient Global Impression of Severity (PGIS) - ROM

Patient Global Impression of Severity (RoM)

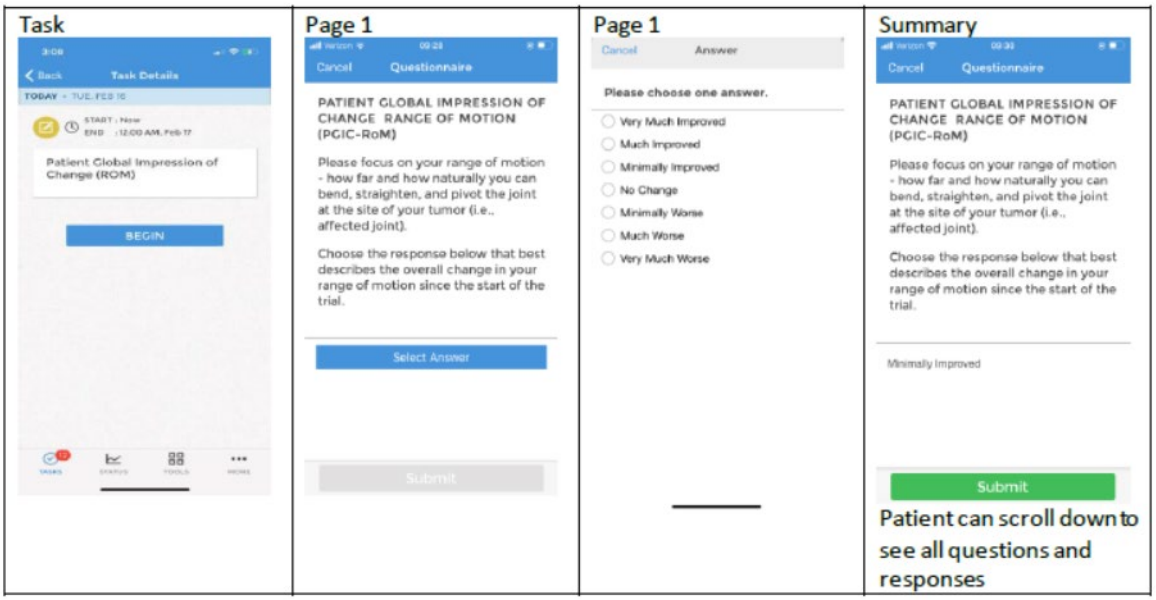
- Questionnaire for how range of motion has been limited by tumor.
- Available for completion via the task calendar per protocol



Appendix C2. Patient Global Impression of Change (PGIC) - ROM

Patient Global Impression of Change (RoM)

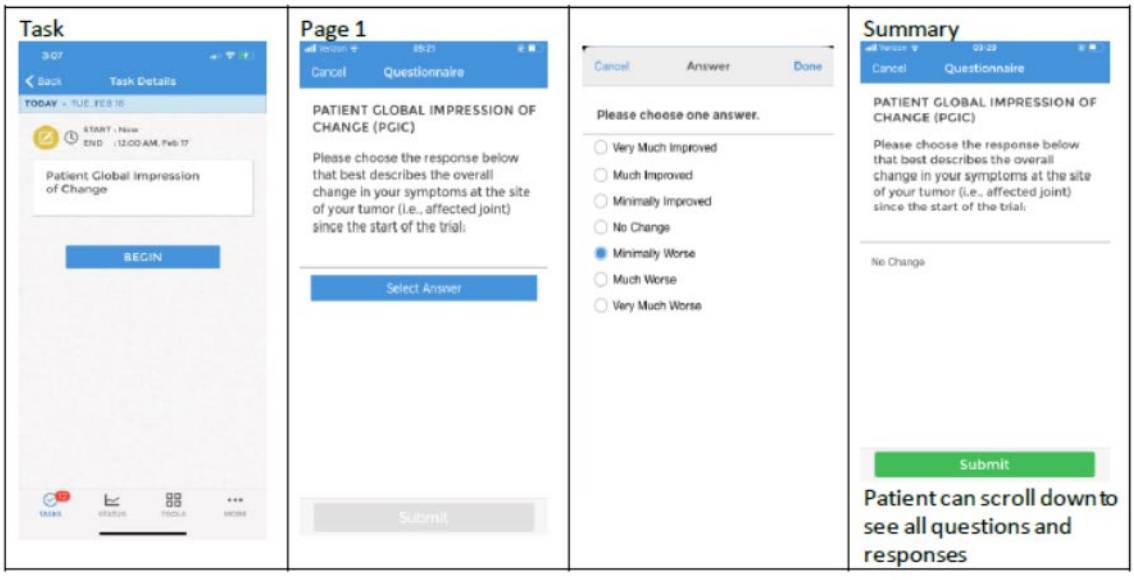
- Questionnaire about overall impression of change from patient perspective as it relates to range of motion.
- Available for completion via the task calendar per protocol



Appendix C3. Patient Global Impression of Change (PGIS) – Overall Symptoms

Patient Global Impression of Change

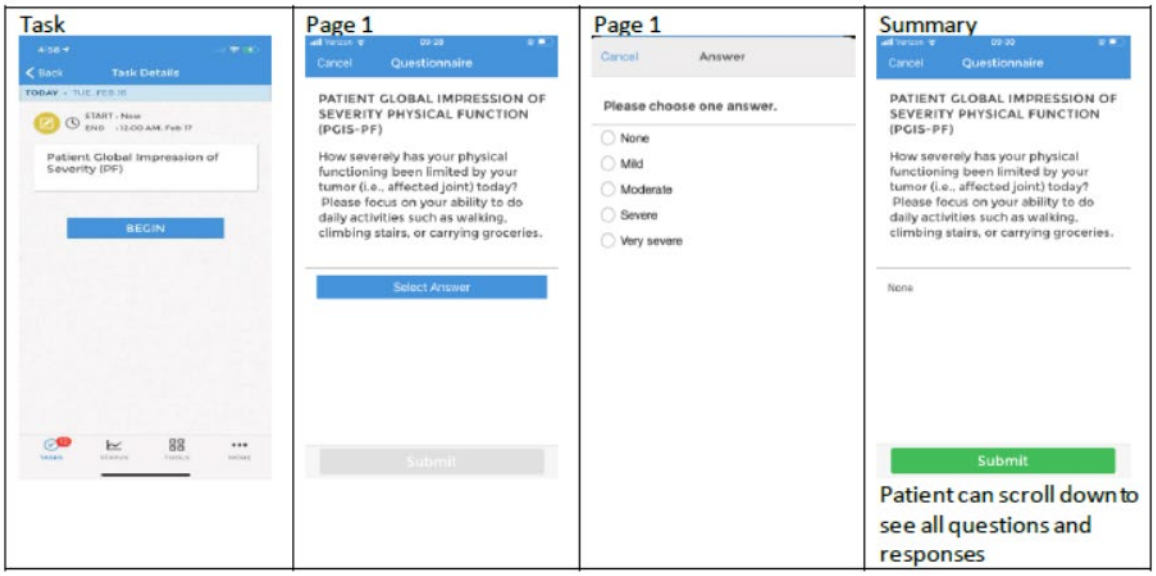
- Questionnaire about overall impression of change from patient perspective.
- Available for completion via the task calendar per protocol



Appendix C4. Patient Global Impression of Severity (PGIS) – Physical Function

Patient Global Impression of Severity (PF)

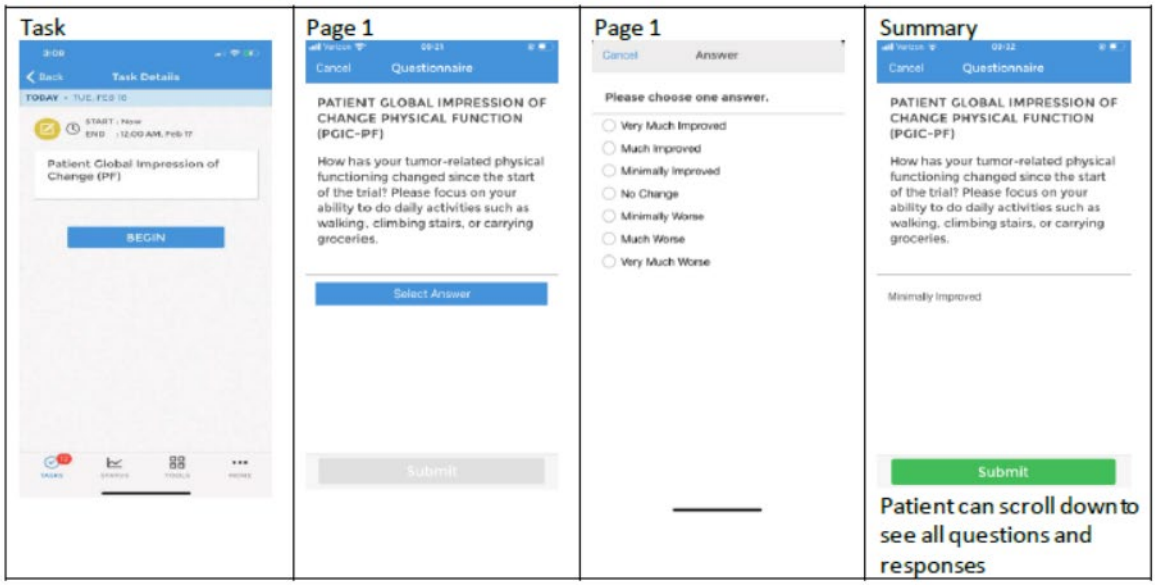
- Questionnaire for how physical function has been limited by tumor.
- Available for completion via the task calendar per protocol



Appendix C5. Patient Global Impression of Change (PGIC) – Physical Function

Patient Global Impression of Change (PF)

- Questionnaire about overall impression of change from patient perspective as it relates to physical function.
- Available for completion via the task calendar per protocol



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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	January 21, 2025
To:	Haroon Vohra, PharmD Senior Regulatory Health Project Manager **Division of Oncology III (DO3)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Laurie Buonaccorsi, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Rebecca Falter, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	ROMVIMZA (vimseltinib)
Dosage Form and Route:	capsules, for oral use
Application Type/Number:	NDA 219304
Applicant:	Deciphera Pharmaceuticals, LLC

1 INTRODUCTION

On June 17, 2024, Deciphera Pharmaceuticals, LLC submitted for the Agency's review an original New Drug Application (NDA) 219304 for ROMVIMZA (vimseltinib) capsules, for oral use. With this submission, the Applicant proposes an indication for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology III (DO3) on July 25, 2024 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ROMVIMZA (vimseltinib) capsules. On January 9, 2025, DO3 requested that the Applicant revise the PPI to a Medication Guide (MG) due to the risk of hepatotoxicity and due to special dosing instructions, which should be communicated with patients in the form of a MG. On January 15, 2025, the Applicant resubmitted the patient labeling as a MG.

2 MATERIAL REVIEWED

- Draft ROMVIMZA (vimseltinib) capsules MG received on January 14, 2025, and received by DMPP and OPDP on January 15, 2025.
- Draft ROMVIMZA (vimseltinib) capsules PI received on June 17, 2024, revised throughout the review cycle, and received by DMPP and OPDP on January 15, 2025 and January 17, 2025.
- Approved TURALIO (pexidartinib) capsules comparator labeling November 16, 2023.

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG, the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the PI
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the MGs meet the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable

3 CONCLUSIONS

The MG is acceptable with our recommended changes.

4 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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REBECCA A FALTER
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01/21/2025 01:02:24 PM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 19, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 219304
Product Name, Dosage Form, and Strength:	Romvimza (vimseltinib) Capsules, 14 mg, 20 mg, and 30 mg
Applicant Name:	Deciphera Pharmaceuticals, LLC (Deciphera)
FDA Received Date:	December 10, 2024
TTT ID #:	2024-9865-1
DMEPA 2 Safety Evaluator:	Ngoc-Linh Do, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 PURPOSE OF MEMORANDUM

Deciphera submitted revised container labels and carton labeling received on December 10, 2024 for Romvimza. The Division of Oncology 3 (DO3) requested that we review the revised container labels and carton labeling for Romvimza (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 DISCUSSION

Deciphera accepted all of our recommendations except for our recommendations B.1, C.1, and D1.[b]

We acknowledge Deciphera responses to our recommendations B.1 and D.1 that they do not consider the "Not for Sale" blister packs (2-week blister packs) as professional samples because the intent of the 2-week blister packs are for patients "who require a temporary supply of free medication because of a delayed insurance coverage decision or a lapse in insurance coverage" and that the 2-week blister packs "will not be distributed to the physician nor will company sales representatives be involved in distribution; rather, this 2-week supply will be shipped directly to the patient from the non-commercial pharmacy and will be provided free of cost."

We also acknowledge Deciphera response to (b) (4) .

We find Deciphera's responses acceptable from a medication error perspective.

3 CONCLUSION

The December 10, 2024 revised container labels and carton labeling are acceptable from a medication error perspective. We have no additional recommendations at this time.

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[a] Do, N. Label and Labeling Review for Romvimza (NDA 219304). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Oct 15. TTT ID: 2024-9865.

[b] Response to FDA's Carton and Container Comments date 05 December 2024. Waltham (MA): Deciphera Pharmaceuticals, LLC; 2024 Dec 10. Available from: \\CDSESUB1\EVSPROD\nda219304\0026\m1\us\111-info-amend\resp-carton-container-20241210.pdf.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 3, 2024

To: Haroon Vohra, PharmD, Senior Regulatory Health Project Manager, Division of Oncology 3 (DO3)

Doris Auth, PharmD, Associate Director for Labeling, DO3

From: Rebecca Falter, PharmD, BCACP, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Emily Dvorsky, PharmD, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ROMVIMZA™ (vimseltinib) capsules, for oral use

NDA: 219304

Background: In response to DO3's consult request dated July 24, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI)/Medication Guide, and carton and container labeling for the original NDA submission for ROMVIMZA™ (vimseltinib) capsules, for oral use.

PI/PPI/Medication Guide: OPDP's review of the proposed PI is based on the draft labeling accessed from SharePoint on November 22, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI/Medication Guide, and comments will be sent under separate cover.

Carton and Container Labeling: OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 17, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Rebecca Falter at (301) 837-7107 or Rebecca.Falter@fda.hhs.gov.

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REBECCA A FALTER
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Clinical Inspection Summary

Date	11/25/2024
From	Courtney McGuire, MD Michele Fedowitz, MD, Team Leader Jenn Sellers, MD, PhD, Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jennifer Stundon, MD, Medical Officer Leslie Doros, MD, Clinical Team Leader Haroon Vohra, Regulatory Project Manager Division of Oncology 3 (DO3)
NDA #	219304
Applicant	Deciphera Pharmaceuticals, LLC
Drug	Vimseltinib
NME (Yes/No)	Yes
Therapeutic Classification	CSF1R inhibitor
Proposed Indication	Treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT)
Consultation Request Date	7/17/2024
Summary Goal Date	12/1/2024
Action Goal Date	2/6/2025
PDUFA Date	2/17/2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The Applicant, Deciphera Pharmaceuticals, LLC, submitted clinical data from Study DCC-3014-03-001 (NCT05059262) to the Agency in support of a New Drug Application (NDA 219304) for vimseltinib. The proposed indication is for treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).

Dr. Gelderblom (Site 341), Dr. Blay (Site 402), and the imaging CRO ((b) (4)) were inspected.

The inspection of the imaging CRO, (b) (4) revealed no significant discrepancies, regulatory violations, or Good Clinical Practice (GCP) noncompliance. The inspection for Drs. Gelderblom and Blay did not find significant concerns regarding the study conduct, data integrity, GCP, or regulatory compliance. Based on the results of these inspections, data generated by the inspected CIs and the imaging CRO and submitted by the Applicant appear acceptable in support of the proposed indication.

II. BACKGROUND

On June 17, 2024, Deciphera Pharmaceuticals, LLC, submitted NDA 219304 seeking approval of vimseltinib (DCC-3014) for the treatment of adult patients with symptomatic TGCT, a rare proliferative non-malignant neoplasm involving the synovium and tendon sheath. Vimseltinib is an oral, small molecule, selective inhibitor of CSF1R, a tyrosine kinase receptor expressed predominantly on monocytes and macrophages.

For this NDA, the primary evidence of safety and efficacy for vimseltinib for the proposed indication and the focus of the BIMO inspections was a single phase 3 trial, Study DCC-3014-03-001 (data cutoff August 22, 2023).

Study Design

Study DCC-3014-03-001 is an ongoing, 2-part, phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate efficacy and safety of vimseltinib in patients with TGCT for whom surgical resection may have caused worsening functional limitation or severe morbidity. The study consisted of a 42-day screening period, a 24-week, double-blind treatment period (Part 1), a 24-week, single-arm, open-label period (Part 2), and an extension of treatment period.

In Part 1, following a 42-day screening period, the study randomized eligible subjects (2:1) to receive vimseltinib 30 mg twice weekly or placebo for 24 weeks with stratification by tumor location (lower limb/all other) and region (U.S./non-U.S.). At Week 25, the study assessed the primary and secondary efficacy endpoints. Subjects completing Part 1 without confirmed disease progression by blinded independent radiology review (BIRR) were eligible to receive open label vimseltinib in Part 2. In addition, placebo subjects with confirmed disease progression by BIRR before Week 25 were eligible for early entry into Part 2.

Clinical Endpoints

- Primary efficacy endpoint:
  - Object response rate (ORR) per RECIST v1.1 at Week 25 based on BIRR of magnetic resonance imaging (MRI).

- Key secondary endpoints (assessed at Week 25):
  - ORR per tumor volume score (TVS) by BIRR.
  - Change from baseline in active range of motion (ROM) of the worst affected joint.

Study Status

The study enrolled the following subjects at 30 sites across 13 countries in Asia, Europe, North America, and Australia, including 13 subjects enrolled across 7 sites in US.

Safety population: N = 122
Efficacy population: N = 123

Two foreign clinical investigators (CIs), Drs. Hans Gelderblom and Jean-Yves Blay, were selected for clinical inspections. The Contract Research Organization (CRO), (b) (4) Inc., was chosen for inspection of the conduct of the central imaging review.

III. RESULTS

1. **Dr. Hans Gelderblom (Site 341 / Study DCC-3014-03-001)**
   Leiden University Medical Center
   Albinusdreef 2
   Leiden, Zuid-Holland, Netherlands 2333ZA

Inspection Dates: October 14, 2024, to October 17, 2024

This investigator was inspected as a BIMO review-based inspection for Study DCC-3014-03-001. The last inspection in March 2019 identified an Inspectional Observation for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

As of the data cutoff (August 22, 2023), the site screened, enrolled, and randomized 14 subjects. Eight (8) subjects discontinued from study treatment, of which 4 subjects discontinued from the study and 4 remain in ongoing follow-up. Six (6) subjects actively remain in the study.

The inspection reviewed subject-related source documents for the 14 randomized subjects including but not limited to the following: informed consent forms (ICFs), laboratory sample requisition forms, laboratory results (local and central), tumor sample requisition forms, subject pre-randomization review forms, surgical assessment questionnaires, medical history, patient progress notes (inclusive of AEs, vital signs, concomitant medications, etc.), MRI transmittal forms, local MRI assessments, ROM assessments, and pharmacy accountability records. The inspection verified that corrective actions were implemented for maintaining subject source records in response to the March 2019 Inspectional Observation.

The inspection reviewed the following study-related documents: protocol and its amendments, ICFs, initial Institutional Review Board (IRB) approval, local Ethics Committee approvals, Curriculum Vita (CV), Statements of Investigator Conducting Foreign Clinical Trials forms, Clinical Trial Research Agreements, Financial Disclosure forms, Site Signature and Delegation Log, training records, laboratory accreditations, Site Visit Sign-in Log, Subject Screening and Enrollment Log, Protocol Deviation log, electronic case report forms (eCRF), investigational product (IP) dispensation and accountability records, and site monitoring records.

The inspection verified that MRI tumor assessments supporting the primary and key secondary

efficacy endpoints (i.e., ORR) were performed at protocol specified time points and submitted to the central imaging CRO. The inspection verified the ROM measurements for the worst affected joint at protocol specified timepoints supporting the key secondary efficacy endpoint.

There was no evidence of underreporting of AEs or protocol deviations. There was no evidence of unblinding in Part 1.

Based on the results of the inspection, Study DCC-3014-03-001 data generated at Dr. Gelderblom's site appear acceptable in support of the proposed indication in the NDA.

2. Dr. Jean-Yves Blay (Site 402 / Study DCC-3014-03-001)
Centre Léon Bérard 28 rue Laennec
Lyon Cedex 08, Rhone, France 69373

Inspection Dates: October 21, 2024, to October 25, 2024

This investigator was inspected as a BIMO review-based inspection for Study DCC-3014-03-001. The last inspection was in September 2014, and there were no significant findings.

As of the data cutoff (August 22, 2023), the site screened 13 subjects, and 10 subjects were enrolled and randomized.

The inspection reviewed subject-related source documents for the 10 randomized subjects including but not limited to the following: ICFs, inclusion/exclusion criteria, visit summaries and progress notes, MRI dates, AE follow-up records, summary of cycles/dosing, narcotics logs, laboratory reports, electrocardiogram analysis reports, surgical assessment questionnaires, and ROM assessments.

The inspection reviewed the following study-related documents: CV, Organization Charts, Statement of Investigator forms, Financial Disclosure forms, ethics approvals and correspondences, protocol, ICFs, site training documents, Delegation of Authority Log, laboratory accreditations, Screening and Enrollment log, eCRF, Electronic Data Capture (EDC) system, study monitoring reports, Sponsor correspondences, shipping records, and IP accountability log.

The inspection verified that MRI tumor assessments supporting the primary and key secondary efficacy endpoints (i.e., ORR) were performed at protocol specified time points (Baseline, Week 13, and Week 25) and submitted to the central imaging CRO. The inspection verified the ROM measurements supporting the key secondary efficacy endpoint.

There was no apparent evidence of underreporting of AEs or protocol deviations. The protocol-specified blinding procedures were followed.

Based on the results of the inspection, Study DCC-3014-03-001 data generated at Dr. Blay's site appear acceptable in support of the proposed indication in the NDA.

3. (b) (4) **(Study DCC-3014-03-001)**

Inspection dates: (b) (4)

(b) (4) was inspected as a BIMO review-based inspection for Study DCC-3014-03-001. There were no prior inspections for the firm.

This inspection reviewed (b) (4)'s responsibilities to perform BIRR for Study DCC-3014-03-001. Records reviewed during the inspection included standard operating procedures, firm history, firm organizational chart, quality assurance activities, training records, outsourced services, (b) (4) Deciphera Contracts, record retention, electronic system validations, blinding activities, data production / review / storage, Independent Review Charters, imaging data, adjudication procedures, and correspondences.

The inspection verified the primary and key secondary efficacy endpoints (i.e., ORR by RECIST v1.1 and TVS, respectively) for 25 efficacy responders by comparison of tumor dimensional measurements, volume measurements, and response assessments in source records with data line listings at Baseline and Week 25. There were no discrepancies identified. Table 1 lists the subjects whose tumor measurements were verified:

Table 1. Unique Subject IDs for Verified Measurements

(b) (6)

Based on the results of the inspection, the imaging review data generated by (b) (4) (b) (4) appear acceptable in support of the proposed indication in the NDA.

{See appended electronic signature page}

Courtney McGuire, M.D.
Primary reviewer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Michele Fedowitz, M.D.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Jenn Sellers, M.D., Ph.D.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

cc:
Review Division/Deputy Division Director Acting/ Chana Weinstock
Review Division/Project Manager/ Haroon Vohra
Review Division/Clinical Team Lead/ Leslie Doros
Review Division/Clinical Reviewer/ Jennifer Stundon
OSI/Office Director/David Burrow
OSI/GCP Program Analysts/Yolanda Patague

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JENN W SELLERS
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 15, 2024
Requesting Office or Division:	Division of Oncology 3 (DO3)
Application Type and Number:	NDA 219304
Product Name, Dosage Form, and Strength:	Romvimza (vimseltinib) capsules, 14 mg, 20 mg, and 30 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Deciphera Pharmaceuticals, LLC
FDA Received Date:	June 17, 2024 and September 19, 2024
TTT ID #:	2024-9865
DMEPA 2 Safety Evaluator:	Ngoc-Linh Do, PharmD
DMEPA 2 Team Leader:	Tingting Gao, PharmD

1 INTRODUCTION

As part of the approval process for Romvimza (vimseltinib) capsules, the Division of Oncology 3 (DO3) requested that we review the proposed Romvimza Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 219304.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	**Appendix Section**
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
Information Request	D

3 DISCUSSION

The recommended dosage for Romvimza is “30 mg twice weekly, at least 3 days apart”. Deciphera proposes to use blister pack presentation (see Figure 1) to provide instructions to patients to self-administer the correct dose and at the right time.

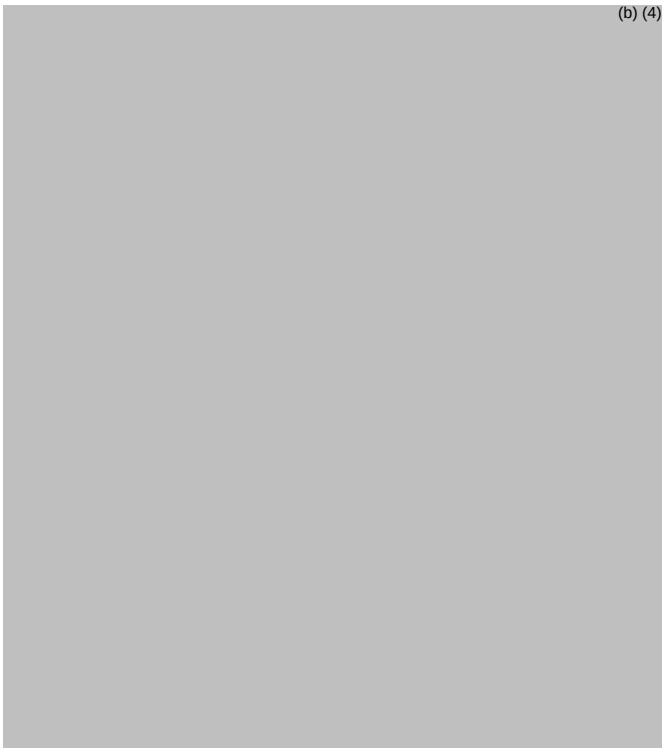

Figure 1. Inner card of the proposed blister pack with dosing instructions.

Since we are not aware of similar blister cards presented in this configuration, we sent an Information Request (IR) on September 18, 2024[a], via email, for information to support patient understanding of the proposed blister pack presentation to correctly self-administer Romvimza as recommended.

Deciphera submitted a human factors summary report[b] that summarized the findings from formative studies that evaluated the patient's ability to comprehend the instructions for opening the blister packs and to correctly comprehend the dosing instructions for the two-doses a week schedule. Based on patients' feedback, the following updates were applied to the blister pack in summary:

1. The addition of a pictural instructions next to the opening instructions for further clarity.

2. Removal of the terms "(b) (4)" in the instructions and the "(b) (4)" and "(b) (4)" in the dosing table and replaced with "take medication on the same days each week" and "DOSE 1" and "DOSE 2' respectively.

3. Redesign of the blister pack labeling and instructions to facilitate intended dosing.

Based on the feedback and risk control mitigation included in the submitted formative human factors summary report, Deciphera concluded that the proposed Romvimza blister pack presentation is appropriate to support patient understanding to take Romvimza dose twice weekly, on the same days of each week. Thus, we reviewed the submitted information from a medication error perspective and agree that the proposed blister instruction panel and blister card presentation appear reasonable. Nevertheless, we determined that the proposed blister pack container label and carton labeling for Romvimza could be further improved to ensure safe product use.

4 CONCLUSION

The proposed Romvimza Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Oncology 3 (DO3) in Section 5 and for Deciphera in Section 6.

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[a] Ford, L. NDA 219304 (Romvimza (vimseltinib)) Information Request. Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2024 Sep 18. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8076f2c5.

[b] Response to HF Information Request. Waltham (MA): Deciphera Pharmaceuticals, LLC; 2024 Sep 19. Available from: \\CDSESUB1\EVSPROD\nda219304\0013\m5\53-clin-stud-rep\535-rep-effic-safety-stud\tgct\5354-other-stud-rep\vim-dosing-comp-hf\vim-dosing-comp-hf-study-24may30.pdf.

5 RECOMMENDATIONS FOR THE DIVISION OF ONCOLOGY 3 (DO3)

A. Prescribing Information

1. Section 2 Dosage and Administration, Section 2.1 (Recommended Dosage)
    a. We recommend adding instructions about what to do if the dose is missed or vomited per *Guidance for industry: Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*.

2. Section 16 How Supplied/Storage and Handling
    a. We recommend presenting the various strengths of the blister packs in table format to improve readability. Revise the Supplied Information to read:

Table 7: Romvimza 14 mg, 20 mg, and 30 mg Capsules

Strength	Description	Package Size and Type	NDA Number
14 mg	Size 4 hard gelatin capsule with white body and orange cap with black print "DCV14", packed in oPA-film/ aluminum foil /PVC-film blisters with push-through aluminum foil lidding.	Each carton contains one child-resistant blister pack containing 8 capsules (four-week supply)	73207-302-40
20 mg	Size 2 hard gelatin capsule with white body and yellow cap with black print "DCV20", packed in oPA-film/ aluminum foil /PVC-film blisters with push-through aluminum foil lidding.	Each carton contains one child-resistant blister pack containing 8 capsules (four-week supply)	73207-303-40
30 mg	Size 1 hard gelatin capsule with white body and yellow cap with black print "DCV20", packed in oPA-film/ aluminum foil /PVC-film blisters with push-through aluminum foil lidding.	Each carton contains one child-resistant blister pack containing 8 capsules (four-week supply)	73207-304-40

    b. For clarity and to stay consistent with the package terminology used throughout the PI, we recommend revising the statement, (b) (4) to "Store capsules in their original blister packs until ready to be taken. Do not store ROMVIMZA in another container." to present the affirmative instruction first, followed by the negative statement.

B. Patient Package Insert (PPI)

(b) (4)

6 RECOMMENDATIONS FOR DECIPHERA PHARMACEUTICALS, LLC

A. General Comments (Container Labels and Carton Labeling for both the intended-to-market version and the professional sample)

1. As currently presented, the expiration date format, "DD MMM YYY", does not follow the recently revised USP General Chapter <7> guideline for the expiration date. USP Chapter <7> Labeling requires the year, to be listed first, followed by the month, and the date at the end. When all-numeric dates are used, they must be formatted using the year, the month, and, if applicable, the day, separated by hyphens or forward slashes in one of the following formats: YYYY-MM-DD or YYYY-MM. When alphanumeric dates are used, months must be displayed using at least three letters in one of the following formats: YYYY-MMM-DD or YYYY-MMM. To minimize confusion and reduce the risk for deteriorated drug medication errors, revise the expiration date format to comply with USP Chapter <7> Labeling guideline.
2. We recommend revising the strength statement (e.g., "30 mg" to state "30 mg per capsule" for the 30 mg capsule blister pack) to make it clear that the designated strength is per unit so there is no confusion as to how much product is contained in a single unit as compared to the total contents of the entire blister card. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (May 2022)*.
3. As currently presented, the strength statement is currently located on the bottom right corner of the principal display panel (PDP), which may be mistaken as the net quantity statement. We recommend moving the strength statement to the upper part of the PDP to increase the prominence of the strength information.
4. The proprietary name, Romvimza is presented (b) (4) We typically reserve highlighting a portion of the name as a strategy to mitigate name confusion. Therefore, we recommend you utilizing a single font color for the entire proprietary name to improve readability and avoid misinterpretation of

the proprietary name. Delete the statement, "(b) (4)" from the PCP as the statement is not a required information. (b) (4)

5. On the back panel, to ensure consistency with the terminology in the Prescribing Information, we recommend revising the dosage statement, "(b) (4) (b) (4)" to read:

   Recommended Dosage: See Prescribing Information.

   Additionally, move the statement above the "Do not open, break, or chew the capsules" and increase the space between the sentences to improve readability.

6. As currently presented on the back panel, the statement "(b) (4) (b) (4)" is expressed as a negative statement. Post-marketing reports have shown that negative statements (e.g., do not) may have the opposite of the intended meaning because the word "not" can be overlooked and misinterpreted as an affirmative action. We recommend revising this statement to "Swallow capsules whole. Do not open, break, or chew the capsules." to present the affirmative instruction first, followed by the negative statement.

B. General Comments (Container Labels and Carton Labeling for professional sample)

1. As currently presented on the "Not for Sale" blister packs, the statement "Not for Sale" does not clearly denoted that it is a drug sample. Not indicating that this is a sample may lead to dispensing errors. We recommend revising the statement to "Professional Sample – Not for Sale" to the principal display panel in accordance with 21 CFR 203.38(c).

C. Container Labels (Inner Card) for the intended-to-market version and the professional sample

1. As currently presented, the "Rx only" statement, NDC number or placeholder, and the expiration date placeholder are missing on the inner card. To prevent medication errors in the event that the inner card is detached from the outer sleeve, we recommend including "Rx only" statement, NDC number or placeholder, and the expiration date placeholder on the inner card.

2. For clarity and to reduce clutter, we recommend revising the following statements included on the "INSTRUCTIONS" panel to read as follows:

   a. 1 **Dose 1:** Enter the day that you first start your medication.

      Day of the week for **Dose 1:** _____

   b. 2 Match the day of **Dose 1** with Dose Box below to determine the day of the week to take **Dose 2**. (Circle one box)

c. 3 The box you circled are the days of the week you will always take **Dose 1** and **Dose 2** for each week.

d. Consider including the text "CIRCLE ONE BOX" as part of the highlighted dose boxes to increase the prominence of this important instruction. For example:

D. Container Labels (Inner Card) for the professional sample

1. As currently presented, the "Professional Sample – Not for Sale" statement is missing on the inner card. To prevent medication errors in the event that the inner card is detached from the outer sleeve, we recommend adding "Professional Sample – Not for Sale" on the inner card.

E. Container Labels (Outer Sleeve) for the intended-to-market version and the professional sample

1. For clarity, we recommend revising the net quantity statement from (b) (4) to the following "# capsules (#-week supply)" to present the total number of capsules first, followed by the week supply. See examples below:
   - For the 4-week blister pack: "8 capsules (4-week supply)"
   - For the 2-week blister pack: "4 capsules (2-week supply)"
2. For clarity as well as to be consistent with the terminology used from the PI, container labels, and carton labeling, revise the statement "(b) (4) (b) (4)" to "Store capsules in the original blister pack until ready to be taken". Do not put Romvimza in another container."
3. The linear barcode is missing on the outer sleeve label. Add the product's linear barcode on the back panel of each individual outer sleeve label in accordance with 21 CFR 201.25(c)(2). The barcode should be placed in a conspicuous location where it will not be difficult to read because of distorted text.

F. Carton Labeling for the intended-to-market version and the professional sample

1. As currently presented, the product identifier is missing a placeholder for the machine-readable, 2D data matrix barcode format. Ensure the 2D data matrix barcode is included as part of the product identifier. See Guidance for Industry:

Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (June 2021).

2. As currently presented, the net quantity statement “8 capsules” and “4 week pack” does not indicate that there is one blister pack in each carton. We recommend including a “contains” statement to indicate that there is one blister pack in each carton for clarity. For example:

    - For the 4-week blister pack: “8 capsules (4-week supply)
      Contains one blister pack”
    - For the 2-week blister pack: “4 capsules (2-week supply)
      Contains one blister pack”

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Romvimza received on June 17, 2024 from Deciphera Pharmaceuticals, LLC.

Table 2. Relevant Product Information for Romvimza

Initial Approval Date	N/A
Active Ingredient	vimseltinib
Indication	treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT)
Dosage Form	capsules
Strength	14 mg, 20 mg, and 30 mg
Route of Administration	oral
Dose and Frequency	30 mg orally taken twice weekly at least 3 days apart with or without food Dose Modifications for Adverse Reactions **Dose Reduction** / **Twice Weekly Dose** First / 20 mg Second / 14 mg ROMVIMZA should be discontinued in patients unable to tolerate a 14 mg dose.
How Supplied	ROMVIMZA 30 mg capsules packed in child-resistant, blister (b) (4). Available in a carton of 1 blister (b) (4): • 8 count blister (b) (4) ROMVIMZA 20 mg capsules packed in child-resistant, blister (b) (4). Available in a carton of 1 blister (b) (4): • 8 count blister (b) (4) ROMVIMZA 14 mg capsules packed in child-resistant, blister (b) (4). Available in a carton of 1 blister (b) (4): • 8 count blister (b) (4)

Table 2. Relevant Product Information for Romvimza	
Storage	Store at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions to 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].
Container Closure	Child resistant blister pack is comprised of an inner card containing 4 count or 8 count blisters that is inserted into the outer sleeve and heat sealed

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[c] along with postmarket medication error data, we reviewed the following Romvimza labels and labeling submitted by Deciphera Pharmaceuticals, LLC.

- Prescribing Information received on June 17, 2024, available from \\CDSESUB1\EVSPROD\nda219304\0002\m1\us\114-labeling\114a-draft-label\romvimza-uspi-label.docx
- Patient Package Insert received on June 17, 2024, available from \\CDSESUB1\EVSPROD\nda219304\0002\m1\us\114-labeling\114a-draft-label\romvimza-patient-label.docx
- Container label(s) received on June 17, 2024
- Carton labeling received on June 17, 2024
- Professional Sample Blistercards received on June 17, 2024
- Professional Sample Carton Labeling received on June 17, 2024

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

[c] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX D. INFORMATION REQUEST

To facilitate our review of the blister pack presentation, we sent an Information Request (IR)[d] on September 18, 2024 to request the following information:

> For the proposed blister card presentation, do you have any information or data to support patient's understanding or use of this presentation (e.g., understanding or use of circling the appropriate box for Dose 2 depending on the day for Dose 1)? If yes, please submit the information or data to facilitate our review.

On September 19, 2024, Deciphera Pharmaceuticals submitted the human factors summary report, "Vimseltinib Dosing Comprehension-Human Factors Summary Report", in response to our IR.

Response to Information Request, received on September 19, 2024, available from \\CDSESUB1\EVSPROD\nda219304\0013\m5\53-clin-stud-rep\535-rep-effic-safety-stud\tgct\5354-other-stud-rep\vim-dosing-comp-hf\vim-dosing-comp-hf-study-24may30.pdf.

[d] Ford, L. FDA Communication: [EXTERNAL] Information Request for NDA 219304 Romvimza (vimseltinib) - IR and Sample request. Silver Spring (MD): FDA, CDER, OSE (US); 2024 SEPT 18. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8076f2c5

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

/s/

NGOC - LINH DO
10/15/2024 05:00:11 PM

TINGTING GAO
10/15/2024 06:12:20 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY PRODUCTS

Date: October 8, 2024

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Cardiac Safety IRT, DCN

To: Haroon Vohra RPM
Division of Oncology 3

Subject: QT Consult to NDA 219304 (SDN 002)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 7/25/2024 regarding the sponsor's proposed QT related label language. We reviewed the following materials:

- Cardiac Safety Assessment Report (link)
- Previous IRT review for IND 131218 dated 02/28/2024 in DARRTS; (link)
- Labeling (link)

1 IRT response

1.1 PROPOSED LABEL

Below are proposed edits to the label submitted to SDN 2 (link). Our changes are highlighted (addition, ~~deletion~~). Our suggestions to section 12.2 could be modified when the results of the hepatic impairment study are known.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

At the maximum recommended dose of ROMVIMZA, clinically significant QTc interval prolongation was not observed. However, (b) (4)

(b) (4)

Reviewer's comment: *The sponsor's and FDA's C-QTc model including all subjects shows clinically significant QT prolongation at the maximum tested dose (i.e., 40 mg BID for 5 days). We propose to use labeling language for this product consistent with the "QTc Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry" draft guidance (link).*

2 BACKGROUND

The sponsor (Deciphera) has submitted an NDA for ROMVIMZA (vimseltinib capsules of 14, 20, and 30 mg strengths) seeking marketing approval for treatment adult patients with symptomatic tenosynovial giant cell tumor (TGCT). Vimeseltinib is a small molecule inhibitor of colony stimulating factor 1 receptor (CSF1R) kinase. The proposed therapeutic dose is 30 mg twice a week orally.

At the pre-NDA meeting on January 16, 2024, it was decided that the sponsor could submit the NDA as a rolling review. Vimseltinib was granted Fast Track designation on September 28, 2021, and in this NDA submission the sponsor is requesting a priority review.

The CS-IRT reviewed the sponsor's Cardiac Safety Assessment report previously in a review dated 02/28/2024 in DARRTS. It was determined that vimseltinib caused concentration-dependent increase in QTcF interval in the Phase 1 study in healthy adults. Although no clinically significant QT prolongation was observed at the proposed therapeutic dosing regimen (30 mg BID) and at the tentative high clinical exposure (body weight < 54 Kg), clinically significant QT prolongation was observed at the highest dose tested in the QT assessment (40 mg BID for 5 days). The highest tested dose in the QTc assessments provided a 1.8-fold tentative high clinical exposure. High clinical exposure scenario was not yet known at the time of the review, as a dedicated hepatic impairment study was still ongoing. Since further increases in exposure could occur in subjects with hepatic impairment, it was concluded that QTc prolongation cannot be excluded in patients with hepatic impairment as impact on vimseltinib was not known.

In the current NDA the sponsor has not yet completed the hepatic impairment study. The preliminary pharmacokinetic report from the study indicates that patients with mild hepatic impairment have similar Cmax and AUC as healthy matched subjects. The impact of moderate and severe hepatic impairment (Child-Pugh B and C) on vimseltinib PK has not yet been established.

As the impact of moderate and severe hepatic impairment on vimeseltinib PK was not known, it was recommended that the sponsor (b) (4)

In the proposed ROMVIMZA label the sponsor states the following:

1. Section 12.2 Pharmacodynamics/Cardiac Electrophysiology: (b) (4)
2. Section 12.3/Specific Populations/ (b) (4)

Reviewer's Comments:

- *Clinically significant QT prolongation was observed at the highest dose in QT assessment,* (b) (4)
- *The label should also state that QT effects in subjects with moderate and severe hepatic impairment have not been characterized.*
- *In general, while 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.*

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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

/s/

DEVI KOZELI on behalf of RAMAN K BAWEJA
10/10/2024 08:28:46 AM
Signing on behalf of Ray as he is OOO

ELIFORD N KITABI
10/10/2024 08:39:07 AM

CHRISTINE E GARNETT
10/10/2024 06:59:08 PM