

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219304Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 131218

MEETING MINUTES

Deciphera Pharmaceuticals, LLC
Attention: Marc Mazzuca, Ph.D.
Associate Director, Regulatory Affairs
200 Smith Street
Waltham, MA 02451

Dear Dr. Mazzuca:¹

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (DCC-3014).

We also refer to the meeting between representatives of your firm and the FDA on January 16, 2024. The purpose of the meeting was to discuss the planned submission of a New Drug Application (NDA) for vimseltinib seeking full approval for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT).

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 240-402-4471.

Sincerely,

{See appended electronic signature page}

Haroon Vohra, Pharm.D.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 16, 2024 at 12:00 PM EST to 1:00 PM EST
Meeting Location: Videoconference

Application Number: IND 131218
Product Name: Vimseltinib (DCC-3014)
Indication: For the treatment of patients with symptomatic tenosynovial giant cell tumor (TGCT)

Sponsor Name: Deciphera Pharmaceuticals, LLC
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Haroon Vohra, Pharm.D.

FDA ATTENDEES

Steven Lemery	Director, Division of Oncology 3 (DO3)
Paul G. Kluetz	Deputy Director of the Oncology Center of Excellence (OCE)
Jennifer Stundon	Clinical Reviewer, DO3
Jason Moore	Clinical Pharmacology Team Leader, DCPII
Justin Collazo	Clinical Pharmacology Reviewer, DCPI
Chi Song	Biometrics Team Leader, DBV
Sirisha Mushti	Biometrics Reviewer, DBV
Matthew Thompson	Nonclinical Team Leader, OOD/DHOT
Steven Zumbrun	Nonclinical Reviewer, OOD/DHOT
Vishal Bhatnagar	Associate Director for Patient Outcomes, OCE
Wang Xing	Project Quality Team Leader, OPQ
Rajiv Agarwal	Product Quality Reviewer, OPQ
Haroon Vohra	Senior Regulatory Project Manager, DRO-OD for DO3
Norma Griffin	Chief, Regulatory Project Manager, DRO-OD for DO3

SPONSOR ATTENDEES

Ludmila Anderson	Medical Director, Pharmacovigilance
Kevin Brodbeck	Senior Vice President, Chief Technical Officer
John Bullock	Vice President, Analytical Development & Quality Control

Ann Gelormini	Vice President, Chemical Development & Manufacturing
Ehab Hamed	Senior Director, Drug Product MS&T
Brooke Harrow	Senior Director, Health Economics and Outcomes Research
Priya Jain	Vice President, Pharmacovigilance
Elena Kostik	Director, Process Chemistry, Drug Substance MS&T
Dragutin Knezic	Director, Drug Product Dev and Manufacturing, Drug Product MS&T
Rebecca Lieberman	Manager, Regulatory Affairs
Qiang Lu	Executive Director, Clinical Pharmacology
Bahar Matin	Director, Clinical Pharmacology
Marc Mazzuca	Associate Director, Regulatory Affairs
Jama Pitman	Senior Vice President, Regulatory Affairs, Quality and Portfolio Management
Rodrigo Ruiz Soto	Senior Vice President, Clinical Development
Amanda Saunders	Senior Medical Director, Clinical Development
Maitreyi Sharma	Vice President, Late Clinical Development
Matthew Sherman	Executive Vice President and Chief Medical Officer
Bryan Smith	Vice President, Biological Sciences
Christopher Tait	Associate Director, Biostatistics
Daniel Tanner	Senior Director, Non-Clinical R&D, Toxicology, ADME/D
Heather Tokatlyan	Vice President, Regulatory Affairs
Jacqueline Walsh	Director, Regulatory CMC
Tao Wang	Executive Director, Head of Biometrics

BACKGROUND

Regulatory

Deciphera Pharmaceuticals, LLC (Deciphera) submitted IND 131218 on October 14, 2016, to support the initial development of vimseltinib for the treatment of advanced malignancies (study DCC-3014-01-001). The Study May Proceed letter was issued on November 10, 2016.

On March 3, 2020, FDA issued Written Responses to the Type C guidance meeting to address Deciphera's questions regarding development of vimseltinib for the proposed indication of "patients with tenosynovial giant cell tumor (TGCT)." A summary of key advice provided in this letter is provided below.

- FDA recommended that Deciphera design a randomized study that includes an internal control to ensure a reliable assessment of clinical benefit and reliable interpretation of important clinical outcome assessment (COA) measures. FDA

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agreed that a crossover design may be acceptable for patients randomized to the placebo arm.

- While FDA acknowledged that overall response rate (ORR) is an acceptable primary endpoint, for ORR results to be considered clinically meaningful, FDA cautioned that the effect on ORR should reliably correlate with a detectable effect on tumor-related functional impairments or an improvement in tumor-related symptoms, and their effects should be durable.

On July 22, 2020, FDA and Deciphera held a teleconference dedicated to COA and patient reported outcome (PRO) measures, schedule and methods of assessment, and risk mitigation strategy for missing data for the planned registration study. Deciphera described their plans to obtain COA and PRO measures for stiffness, pain, and range of motion (ROM), and remove questions regarding swelling and joint instability.

On August 14, 2020, FDA issued Written Responses regarding key design elements of Deciphera's proposed registrational trial, DCC-3014-03-001, entitled "A Multicenter Phase 3, Randomized, Placebo-controlled, Double-blind Study of DOC-3014 to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor." FDA provided the following guidance regarding the development program:

- FDA advised that the recommended phase 2 dose (RP2D) should be selected with adequate justification based on an optimal biological dose approach and supported by nonclinical, pharmacokinetic, pharmacodynamic, response and safety data.
- The plan to enroll US patients in the proposed placebo-controlled trial is reasonable, provided that the informed consent document clearly states that pexidartinib is an FDA-approved drug for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

On January 12, 2021, an End-of-Phase 2 (EOP2) meeting was held to obtain feedback on the proposed design, statistical considerations, dosing plan, and safety database for the pivotal study DCC-3014-03-001. FDA agreed with the primary endpoint of ORR at Week 25 and key secondary endpoints (including assessments of PRO measures which would support the clinical relevance of ORR). FDA stated that there was insufficient safety information to determine if the vimseltinib 30 mg twice weekly dosage was more tolerable than the 10 mg once daily dosage regimen.

Deciphera submitted the pivotal registrational trial DCC-3014-03-001 on February 16, 2021.

Deciphera submitted an initial Pediatric Study Plan (iPSP) on March 12, 2021, requesting a full drug-specific waiver in all pediatric subsets (0 to < ^{(b) (4)} years). FDA issued an Agreed iPSP Agreement letter on July 26, 2021.

On March 8, 2023, Deciphera requested a Type C meeting to discuss and obtain feedback on the proposed plan for determining clinically meaningful thresholds for selected COA measures and on procedural and administrative NDA-related topics to support a planned marketing application for the indication of patients with symptomatic TGCT. Specific advice was provided for analysis plans for COA data. FDA stated that additional guidance on the data cutoffs for efficacy and safety, and follow-up times would be provided at the time of the pre-NDA meeting.

On November 17, 2023, Deciphera requested a Type B meeting to discuss the top-line results from study DCC-3014-03-001 to form the basis for a marketing application for the treatment of adult patients with symptomatic TGCT.

Nonclinical

Vimseltinib (DCC-3014) is an oral small molecule inhibitor of colony stimulating factor 1 receptor (CSF1R) kinase. The proposed nonclinical package includes pharmacology, pharmacokinetics, repeat-dose toxicology studies, reproductive toxicity studies, genetic toxicology and phototoxicity studies, a 26-week GLP carcinogenicity study in mice, and an ongoing 2-year GLP carcinogenicity study in rats.

Clinical

The clinical development program for vimseltinib for patients with TGCT includes two ongoing clinical trials: DCC-3014-03-001 and DCC-3014-01-001. Status summaries of these two studies are provided below.

Pivotal Trial

DCC-3014-03-001 is a multicenter, randomized (2:1), placebo-controlled, double-blind trial of vimseltinib in 123 patients (83 in the vimseltinib arm and 40 in the placebo arm) ≥18 years of age with measurable TGCT not amenable to surgery. Patients were ineligible if they received prior CSF1/CSR1R therapy, except for imatinib and nilotinib. The primary endpoint was ORR at Week 25 as assessed by independent radiology review (IRR) according to RECIST v1.1. The key secondary endpoints, all evaluated at week 25, were ORR per TVS, change from baseline in active range of motion (ROM) of the affected joint, relative to a reference standard, change from baseline in the PROMIS-PF score, Worst Stiffness NRS score, and EQVAS, and response of at least a 30% improvement in the mean BPI Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use. Endpoints were tested hierarchically.

Patients receive vimseltinib 30 mg twice weekly or placebo for 24 weeks. Randomization was stratified by tumor location (lower limb/all other) and region (U.S./non-U.S.). Patients are treated until disease progression or unacceptable toxicity.

Efficacy Results

All randomized patients (N=123) have reached Week 25 of the study. A total of 83 patients have been treated with vimseltinib for ≥ 6 months; 58% of responders had a median follow-up of < 6 months. The median follow-up for responders is 5.6 months.

As of the data cutoff of August 22, 2023, the ORR at Week 25 was 40% (N= 83) for vimseltinib, with 5% of patients having a complete response (CR) and 35% having a partial response (PR), and 0% (N= 40) responders for placebo. Secondary endpoints included ORR per TVS, changes from baseline in measures of joint stiffness, range of motion and pain, duration of response, and incidence and severity of treatment-emergent adverse events (TEAEs).

Table 1: Primary Endpoints and Key Secondary Endpoints, Study DCC-3014-03-001

Efficacy Parameter	Vimseltinib N=83	Placebo N=40
Primary Endpoint		
ORR at Week 25, n (%)	33 (40)	0 (0)
(95% CI)	(29%, 51%)	(0%, 9%)
Complete Response, n (%)	4 (5)	0 (0)
Partial Response, n (%)	29 (35)	0 (0)
p-value	<0.0001	
Duration of Response (months)	0.03+, 11.7+	N/A
Key Secondary Endpoints		
ORR per TVS, n (%)	56 (67)	0 (0)
(95% CI)	(56%, 77%)	(0%, 9%)
p-value	<0.0001	
Mean change from baseline in active range of motion (baseline mean)	18.4 (63)	3.8 (63)
(95% CI)	(5.6, 312)	(-10.5, 18.0)
Number of patients with data at baseline and Week 25	73	33

Source: FDA Generated Table based on meeting package

Safety Results

As of the data cutoff of August 22, 2023, a total of 83 patients received at least one dose vimseltinib. All (100%) patients experienced a TEAE with the most common being periorbital edema (45%), fatigue (33%) facial edema (31%), pruritis (29%), headache (28%), nausea (25%), and AST increased (23%). Grade ≥ 3 TEAEs were reported by 31 (37%) patients in the vimseltinib arm and 4 (10%) patients in the placebo arm. Grade ≥ 3 TEAEs experienced by at least one patient in the vimseltinib arm were blood creatinine phosphokinase increased (10%), hypertension (4.8%), periorbital edema (3.6%), and

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pruritis (2.4%). There were no Grade ≥ 3 liver function abnormalities that occurred in >1 patient. Serious AEs (SAEs) occurred in 6 patients (7%), with one patient each experiencing cellulitis, subcutaneous abscess, papillary thyroid cancer, plasma cell myeloma, uveitis and fall. Five (6%) patients receiving vimseltinib had a TEAE that lead to treatment discontinuation, with one patient discontinuing treatment for each of the following: periorbital edema, plasma cell myeloma, peripheral sensory neuropathy, rash and hypertension. Per the briefing package, no drug-induced liver injury was reported.

Supportive Trial

DCC-3014-01-001 is a multi-center, open-label, first-in-human study evaluating the safety, efficacy, pharmacokinetics, and pharmacodynamics of vimseltinib in patients with TGCT and advanced tumors. The recommended Phase 2 dose (RP2D) was identified as 30 mg twice weekly. The expansion phase consisted of two cohorts (Cohort A and Cohort B). Enrollment in Cohort A included patients with TGCT who were not amenable to surgery and who had not received prior CSF1 or CSF1R therapy and Cohort B included patients with TGCT who had received prior CSF1 or CSF1R therapy and were not amenable to surgery. A total of 45 patients with TGCT have been enrolled in Cohort A. As of the data cutoff of June 27, 2023, the ORR at week 25 in Cohort A was 38% (95% CI: 24, 54) with all patients who responded having a PR. A total of 72% of patients had a DOR ≥ 6 months.

The planned NDA submission will include the data from pivotal study DCC-3014-03-001 and supportive study DCC-3014-01-001. Deciphera is planning to submit an NDA in the first half of 2024. Deciphera plans to submit updated efficacy and safety data with a data cutoff of February 2024.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Nonclinical

1. **The Sponsor believes that the scope and content of the current nonclinical package adequately supports a vimseltinib NDA submission for TGCT. Does the Agency agree?**

FDA Response: The nonclinical package appears sufficient to support an NDA submission. A final determination of the adequacy of the nonclinical data will be a review issue.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges FDA's feedback. No further discussion is needed.

2. **The Sponsor is currently conducting a 2-year rat carcinogenicity study and the Sponsor plans to submit the final study report as a future supplement to the NDA. Does the Agency agree with this proposal?**

FDA Response: The proposed plan appears reasonable, where the submission of the 2-year rat carcinogenicity study report would be a postmarketing requirement (PMR).

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges FDA's feedback. No further discussion is needed.

Clinical

3. **Does the Agency agree that the data planned for submission with the initial NDA from both the Phase 3 registration Study, DCC-3014-03-001 (MOTION) together with the data from the supportive Phase 1/2 Study, DCC-3014-01-001 are adequate to substantiate efficacy and support the submission of the NDA for full approval?**

FDA Response: The efficacy data included in the original (and complete) NDA should include a minimum of 6 months of follow-up from the date of the initial confirmed response for all responders. FDA understands Deciphera will submit updated efficacy data based on a data cutoff of February 2024 which will provide additional durability and follow-up data (initial data cutoff August 22, 2023). FDA recommends that the (top-line) efficacy data based on the February 2024 data cutoff, be submitted for FDA review prior to the submission of the original NDA. Determination of the adequacy of the data submitted based on the two data cutoff dates to support an approval in the proposed indication will depend on a favorable risk:benefit profile assessed during the review of all the clinical data in the original NDA submission.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges the Agency's feedback. The planned data cutoff of February 2024 will allow for the responders at Week 25 (DCC-3014-03-001 primary analysis) to have had the chance to have a minimum of 6 months of follow-up. The Sponsor will provide the Agency updated ORR and duration of response for responders at Week 25 for both RECIST v1.1 and TVS from the planned February 2024 datacut prior to submission of the original NDA summarized in slides in the form of email communication. Data from the other secondary endpoints were reported at Week 25 and are locked so will not change and thus will not be provided as part of this update.

Discussion During Meeting: Deciphera proposed an updated data-cut off of February 2024 for efficacy endpoints including ORR. FDA stated that the Agency would generally use the protocol pre-specified cut-off (i.e., August cut-off) for the primary analysis for describing ORR and the p value in labeling. FDA stated that the Agency would likely use the updated cut-off (February 2024) of the responding patients (from the August cut-off) for describing DOR in labeling.

FDA agreed that Deciphera could submit the updated ORR/DOR results as an information request (requesting FDA comments) in an IND amendment prior to submission of the NDA.

4. **Does the Agency agree that the data planned for submission with the initial NDA from MOTION together with the data from Study DCC-3014-01-001 are sufficient to assess the safety of vimseltinib and that the planned safety analyses are adequate to support the NDA submission?**

FDA Response: The planned clinical safety database may be considered adequate to support an NDA filing in a rare patient population provided that no unusual toxicities are identified. In the meeting package it states that Pool 1 will include patients with TGCT at the proposed dose level of 30 mg twice weekly. Clarify that this will include only patients from Study DCC-3014-03-001. Deciphera may conduct another safety pool of all patients with TGCT that received 30 mg twice weekly.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges the Agency's feedback. The Sponsor wishes to clarify that patients from Study DCC-3014-03-001 (MOTION) are a subset of Pool 1. Pool 1 will include a stand-alone column for MOTION. Reference is made to the Type C meeting (REF ID: 5178090) where agreement was reached with the Agency on the pooling strategy.

- **Pool 1 (All TGCT patients at 30 mg twice weekly dose):** All TGCT patients in DCC- 3014-01-001 and MOTION who received at least one dose of vimseltinib at the recommended dose of 30 mg twice weekly will be included. Data will be summarized by Expansion cohorts (Cohort A, Cohort B), MOTION, Cohort A + MOTION and overall.
- **Pool 2 (All TGCT patients, any dose):** All TGCT patients in DCC-3014-01-001 and MOTION who received at least one dose of vimseltinib will be included. Data will be summarized by study phase (Escalation, Expansion, and MOTION) and overall.
- **Pool 3 (All patients, any dose):** All patients who received at least one dose of vimseltinib in DCC-3014-01-001 and MOTION regardless of tumor type or dose of vimseltinib will be included. Data will be summarized by tumor type (MST vs TGCT) and overall.
- **Pool 4 (All patients at 30 mg twice weekly dose):** All patients in DCC-3014-01-001 and MOTION who received at least one dose of vimseltinib at 30 mg twice weekly including those patients who received a loading dose.

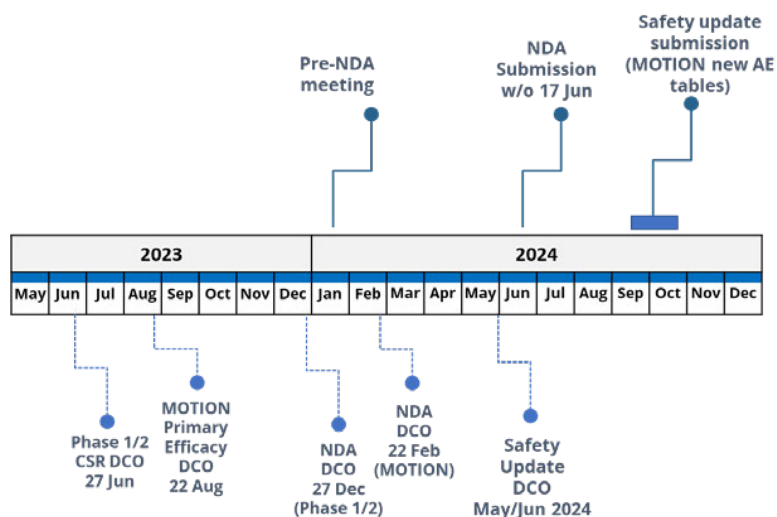
Discussion During Meeting: Deciphera stated that Study DCC-314-03-001 will be a subset of Pool 1 (all patients with TCGT who received vimseltinib 30 mg BIW); however, data from the Motion Study will also be described side-by-side with this pool. FDA agreed with this approach.

5. **The Sponsor plans to include 6 months of safety follow-up beyond the original data cuts from MOTION and DCC-3014-01-001 as part of the initial NDA submission. Does the Agency agree that no further safety update is required as part of a safety amendment during the NDA review?**

FDA Response: The safety database to be used as the primary analysis to assess for adverse events, should include a data cutoff of (approximately) no greater than 6 months prior to the date of the original NDA submission. Additionally, Deciphera will need to submit a 120-day safety update which may be used to inform labeling.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges the Agency's feedback. Safety data provided at the time of the NDA submission (June 2024) will be based on a DCC-3014-03-001 (MOTION) data cutoff of February 22, 2024, and a DCC-3014-01-001 data cutoff of December 27, 2023. At the time of these data cutoff, all patients will have had the potential to be on vimseltinib for 6 months; this includes patients originally randomized on DCC-3014-03-001 to receive placebo who crossed over to vimseltinib.

At the time of a data cutoff for an additional safety update, visit intervals will be every 3 months. Considering that the interval between the NDA data cutoffs (December 27, 2023; February 22, 2024) and the planned submission (June 2024) are within 6 months, and that all patients will have the opportunity for at least 6 months of exposure to vimseltinib, the Sponsor proposes providing updated adverse event tables from the DCC-3014-03-001 study with a data cutoff of June 2024 to include information on all new adverse events received between that data cutoff date and the February 22, 2024 data cutoff for the NDA safety update as outlined in the figure below. Deciphera will assess the updated data to inform labeling updates if required.



Discussion During Meeting: FDA stated that revised submission of safety data and the proposed plan for the 120-day safety update described in Deciphera's email response appears acceptable.

Clinical Pharmacology

6. Does the Agency agree that the clinical pharmacology data package and overall strategy are sufficient to support the filing and review of an NDA for vimseltinib for the proposed indication?

FDA Response: The proposed clinical pharmacology data package and strategy appear generally reasonable. See the Additional Comments section for further, detailed clinical pharmacology package recommendations.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges FDA's feedback. No further discussion is needed.

7. The Sponsor is conducting a clinical study in participants with mild, moderate, and severe hepatic impairment (DCC-3014-01-004). The Sponsor anticipates that data (in the form of SDTM datasets) from the mild hepatic impairment cohort will be available and submitted in the initial NDA package, and data from the moderate and severe hepatic impairment cohorts would be available for submission as a future NDA supplement. Does the Agency agree with this proposal?

FDA Response: The proposal to provide the results of Part 1 (i.e., mild hepatic impairment) of the hepatic impairment study in the initial NDA submission and submit the results of Parts 2 and 3 (i.e., moderate and severe hepatic impairment studies) as part of a future supplement(s) seems reasonable. The adequacy of

the results of the hepatic impairment evaluations to inform dosing and administration will be a review issue upon submission of the NDA and/or supplements. FDA recommends assessing the effect of hepatic impairment on PK using both Child-Pugh and NCI ODWG criteria.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges FDA's feedback. No further discussion is needed.

Chemistry Manufacturing and Controls (CMC)

8. **The Sponsor anticipates an NDA submission in June 2024. In this scenario, the Sponsor is considering** (b) (4)

[REDACTED]

FDA Response: FDA does not object to the proposal. (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges the Agency's feedback. (b) (4)

Follow-up question to the Agency: At the time of the mid-cycle meeting, would FDA be able to provide their feedback on the proposal?

Discussion During Meeting: FDA does not object to Deciphera's proposal. (b) (4)

Regulatory

9. **Does the Agency agree that the contents of the NDA as outlined in the proposed electronic Common Technical Document (eCTD) table of contents (TOC) constitute a complete application?**

FDA Response: In general, FDA does not object to the proposed content of the planned NDA submission.

To support that the patient-reported outcome (PRO) assessments are fit-for-purpose for use as secondary efficacy endpoint(s), FDA recommends that Deciphera compile all qualitative and quantitative evidence into a final evidence dossier. FDA will review the completed qualitative and quantitative data to evaluate the content validity, other measurement properties, and interpretability (i.e., clinical meaningfulness) of the instruments at the time of NDA submission. Include relevant PRO information from MOTION in section 5.3.5.1 such as full versions of the "Statistical Analysis Memo – Responder Definitions" including all figures. In the MOTION CSR, include PRO completion and compliance rate for each PRO measure.

The eCTD table of contents lists Study No. DCC-3014-04-0025 under 4.2.3.4 *Carcinogenicity*. See FDA response to Question #2 regarding the 2-year rat study.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges FDA's feedback. No further discussion is needed.

10. **Vimseltinib was granted Fast Track designation in September 2021. Does the Agency agree to accept the submission on a rolling review schedule?**

FDA Response: FDA does not object to the proposal.

Deciphera Pharmaceuticals January 12, 2024, Email Response: The Sponsor acknowledges FDA's feedback. No further discussion is needed.

Additional Comments

Clinical

11. See (boilerplate) comments below regarding submission of an assessment aid which may facilitate a more efficient review.

CMC

12. Include elemental impurities in drug product specifications per USP <232> and <233> and/or a provide risk assessment/justification per ICH Q3D.
13. Address the potential risk of formation of nitrosamine impurities. Refer to the FDA guidance "Control of Nitrosamine Impurities in Human Drugs" (<https://www.fda.gov/media/141720/download>) for more information.

Clinical Pharmacology

14. The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format" (available at: <https://www.fda.gov/media/74346/download>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.
15. Address the following questions in the Summary of Clinical Pharmacology:
 - a. What is the basis for selecting the dosages and dosing regimen used in the trials intended to support the marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
 - b. What are the exposure-response relationships for efficacy, safety and biomarkers?
 - c. What is the effect of vimseltinib on the QT/QTc interval?
 - d. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?

- e. What are the effects of food on bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
 - f. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?
16. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
- a. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - b. Provide a final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean $\pm$ standard deviation) and median with minimum and maximum values as appropriate.
 - c. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
 - d. Submit the following for the population pharmacokinetic analysis reports:
 - Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.
 - Refer to the following pharmacometric data and models submission guidelines
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

- e. Submit the following information and data to support the population pharmacokinetic analysis:
- SAS transport files (*.xpt) for all datasets used for model development and validation.
 - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).
- f. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK, exposure-response relationships, and pharmacometric data and modeling submission guidelines.
- g. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.

Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The contents of a complete application were discussed. Deciphera Pharmaceuticals agrees to submitting a complete application at the time of the original application submission.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the

original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information⁶ and Pregnancy and Lactation Labeling Final Rule⁷ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

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Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File (except Type III) and Commercial INDs must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit [FDA.gov](https://www.fda.gov).

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification Specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see [FDA.gov](https://www.fda.gov).

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions, and the associated conformance guide, Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis

of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid (refer to <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid>)

ATTACHMENTS AND HANDOUTS

Sponsor responses to preliminary meeting comments

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

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IND 131218

MEETING MINUTES

Deciphera Pharmaceuticals, LLC
Attention: Alissa Minkoff
Associate Director, Regulatory Affairs
200 Smith Street
Waltham, MA 02451

Dear Ms. Minkoff:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DCC-3014.

We also refer to the teleconference between representatives of your firm and the FDA on January 12, 2021. The purpose of the meeting was to obtain FDA feedback on the proposed registration plans for DCC-3014 for the treatment of patients with symptomatic tenosynovial giant cell tumor (b) (4)

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-796-3074.

Sincerely,

{See appended electronic signature page}

Idara Udoh, M.S.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic
Diseases for DO2
Office of Regulatory Operations
Office of New Drugs

¹ We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database
<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End-of-Phase 2

Meeting Date and Time: January 12, 2021; 1:00 PM – 2:00 PM, EST
Meeting Location: N/A

Application Number: IND 131218
Product Name: DCC-3014
Indication: Treatment of patients with symptomatic tenosynovial giant cell tumor (TGCT) (b) (4)
Sponsor Name: Deciphera Pharmaceuticals, LLC
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

Meeting Chair: Diana Bradford
Meeting Recorder: Idara Udoh

FDA ATTENDEES

Harpreet Singh, Director, Division of Oncology 2 (DO2)
Martha Donoghue, Deputy Director, DO2
Diana Bradford, Clinical Team Leader, DO2
Sonia Singh, Clinical Reviewer, DO2
Elizabeth Duke, Clinical Reviewer, DO2
Amy Barone, Clinical Reviewer, DO2
Gautam Mehta, Clinical Reviewer, DO2
Lola Fashoyin-Aje, Deputy Director, Division of Oncology 3 (DO3)
Leslie Doros, Clinical Reviewer, DO3
Pallavi Mishra-Kalyani, Statistics Team Leader, Division of Biometrics V (DBV)
Pourab Roy, Statistics Reviewer, DBV
Jeanne Fourie Zirkelbach, Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Wentao Fu, Clinical Pharmacology Reviewer, OCP
Whitney Helms, Nonclinical Team Leader, Division of Hematology, Oncology, and Toxicology (DHOT)
Idara Udoh, Senior Regulatory Health Project Manager (RPM), Division of Regulatory Operations (DORO)
Ashley Lane, RPM, DORO
Raniya Al-Matari, RPM, DORO
Opeyemi Udoka, RPM, DORO
Emily Pak, RPM, DORO
Jacqueline Glen, RPM, DORO
Selena Daniels, Clinical Outcome Assessment (COA) Team Leader, Division of COA

Vishal Bhatnagar, Associate Director for Patient Outcomes, Oncology Center of Excellence (OCE)

SPONSOR ATTENDEES

Claus Becker, Vice President, Health Economics and Outcomes Research
Maria Estrada, Medical Director, Pharmacovigilance
Sophie Higgins, Senior Regulatory Affairs Associate, Regulatory Affairs
Bert LeBourdonnec, Vice President, Chemical, Pharmaceutical, & Preclinical Sciences
Bahar Matin, Senior Manager, Clinical Pharmacology
Alissa Minkoff, Associate Director, Regulatory Affairs
Jama Pitman, Senior Vice President, Regulatory Affairs & Quality
Rodrigo Ruiz Soto, Vice President, Clinical Development
Maitreyi Sharma, Sr. Medical Director, Clinical Development
Matt Sherman, Chief Medical Officer
Kelvin Shi, Vice President, Biostatistics and Data Management
Gege Tan, Senior Scientist, Translational Medicine
Heather Tokatlyan, Senior Director, Regulatory Affairs
Marc Vallee, Director, Biostatistics
Jing Wang, Director, Clinical Pharmacology

BACKGROUND

Meeting Purpose

On November 4, 2020, Deciphera Pharmaceuticals, LLC (Deciphera) submitted a Type B, End of Phase meeting request to obtain input on the proposed registration plans for DCC-3014. Deciphera intends to initiate a randomized trial (DCC-3014-03-001) in 2021. Specifically, Deciphera seeks agreement on the design of the planned trial, including statistical considerations, proposed dosing of the agent, adequacy of the proposed safety database, acceptability of the clinical pharmacology plan, and seeks preliminary feedback on the strategy for the initial Pediatric Study Plan (iPSP).

FDA granted the meeting as a teleconference scheduled for January 12, 2021.

Regulatory

On March 3, 2020, FDA issued Written Responses to address Deciphera's questions regarding development of DCC-3014 for the proposed indication of "patients with TGCT." A summary of key advice provided in this letter is provided below.

- FDA stated that although a single arm trial demonstrating unequivocal evidence of an important treatment effect that results in improved survival or quality of life may support a marketing application, Deciphera was advised to design a randomized study that includes an internal control in order to ensure a reliable assessment of clinical benefit and reliable interpretation of important clinical

outcome assessment (COA) measures. FDA agreed that a crossover design may be acceptable for patients randomized to the placebo arm.

- While FDA acknowledged that overall response rate (ORR) is an acceptable primary endpoint, for ORR results to be considered clinically meaningful, FDA cautioned that the effect on ORR should reliably correlate with a detectable effect on tumor-related functional impairments or an improvement in tumor related symptoms, and their effects should be durable.

On July 22, 2020, FDA and Deciphera held a teleconference dedicated to COA and patient reported outcome (PRO) measures, schedule and methods of assessment, and risk mitigation strategy for missing data for the planned registration study. Deciphera described their plans to obtain COA and PRO measures for stiffness, pain, and range of motion (ROM), and remove questions regarding swelling and joint instability.

On August 14, 2020, FDA issued Written Responses regarding the key design elements of the Deciphera's proposed Phase 3 trial, DCC-3014-03-001, entitled "A Multicenter Phase 3, Randomized, Placebo-controlled, Double-blind Study of DCC-3014 to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor." FDA provided the following guidance regarding the development program:

- It is unclear that the daily dosing regimen is optimized for efficacy and safety. FDA advised that the RP2D should be selected with adequate justification based on an optimal biological dose approach and supported nonclinical, pharmacokinetic, pharmacodynamic, response and safety data.
- The plan to enroll US patients in the proposed placebo-controlled trial is reasonable, provided that the informed consent document clearly states that pexidartinib is an FDA-approved drug indicated for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery.

Nonclinical

DCC-3014 is a small molecule inhibitor of colony stimulating factor 1 receptor (CSF1R) kinase. Tenosynovial giant cell tumor (TGCT) is a rare tumor of the synovial layer in joints, bursae, or tendon sheaths. Tumor growth in TGCT appears to be driven by a mutation which induces overexpression of colony stimulating factor-1 (CSF-1) on the tumor cells triggering migration of nonneoplastic monocytes and macrophages expressing the CSF-1 receptor (CSF1R) to the tumor site. The bulk of the tumor mass appears to consist of non-neoplastic inflammatory cells. To support the clinical development of DCC-3014 in the treatment of patients with symptomatic TGCT, Deciphera completed GLP-compliant 4- and 13-week toxicity studies in rats and dogs; a 26-week toxicity study in rats, a 39-week toxicity study in dogs, a 6-month carcinogenicity study in Ras-transgenic mice, and a rat fertility study are in progress. In

addition, Deciphera completed genotoxicity studies and states that DCC-3014 was teratogenic at high doses in rats.

Clinical Pharmacology

DCC-3014 exposure appears approximately dose proportional over the dose range tested in Study DCC-3014-01-001. The last pharmacokinetic (PK) sampling time point after DCC-3014 administration was 8 hours. An accurate estimation of elimination half-life was not possible due to the short PK sampling time period. There were no significant differences in the reported DCC-3014 PK parameters at steady state (Cycle 2 day 1) for 10 mg QD dosage and 30 mg twice weekly dosage.

Geometric mean (CV%) values of DCC-3014 C_{max}, C_{8hr}, and AUC_{0-8hr} for 10 mg QD and 30 mg twice weekly cohorts at Cycle 2 Day 1 were summarized as below.

- Cohort 1 (10 mg QD dose without loading dose; N=5): C_{max} 767 (12) ng/mL; C_{8hr} 447 (65) ng/mL; AUC_{0-8hr} 4510 (16) ng•hr/mL
- Cohort 8 (3-day 30 mg QD loading doses followed by 10 mg QD dose; N=7): C_{max} 753 (28) ng/mL; C_{8hr} 507 (33) ng/mL; AUC_{0-8hr} NA
- Cohort 5 (5-day 30 mg QD loading doses followed by 30 mg twice weekly; N=6): C_{max} 822 (58) ng/mL; C_{8hr} 440 (70) ng/mL; AUC_{0-8hr} 4750 (53) ng•hr/mL

Clinical

The planned Phase 3 study DCC-3014-01-001 is a multicenter, double-blind, randomized, placebo-controlled trial of DCC-3014 in adult patients with histologically confirmed and symptomatic TGCT for whom surgical resection may potentially worsen functional limitation or severe morbidity. Deciphera has provided a draft study protocol in the briefing package.

The primary efficacy outcome measure will be objective response rate (ORR) at Week 25 according to RECIST v1.1 as determined by blinded independent review. Secondary efficacy outcome measures will also be evaluated at Week 25 and will include ORR per tumor volume score (TVS); duration of response (DOR); change from baseline in active ROM of the affected joint; and PRO measures evaluating TGCT-specific symptoms (stiffness, pain) and physical function impacts.

Study participants will be required to demonstrate at least moderate pain or stiffness (defined as a score of 4 or more, with 10 describing the worst condition, on appropriate instruments) prior to the first dose and must provide at least four baseline assessments in select PRO measures during the 42-day screening period. Approximately 120 patients at an estimated 40 centers in up to 20 countries will be randomized in a 2:1 ratio to receive either DCC-3014 at the dose of 30 mg twice weekly (n=80) or placebo (n=40) for 24 weeks. Deciphera anticipates having ten clinical sites in the US that will enroll an estimated 30 patients (25% of the total study population). Randomization will be stratified by tumor location (lower limb/all other) and region (U.S./non-U.S.).

Patients will receive double-blinded treatment in 28-day cycles for a period of 24 weeks (Part 1) with the option to then crossover, if assigned to placebo, and receive open-label DCC-3014 until Week 49 (Part 2). Patients randomized to placebo in Part 1 with centrally confirmed disease progression prior to Week 25 are eligible for early crossover. Patients randomized to DCC-3014 in Part 1 will continue to receive DCC-3014 in Part 2. After Week 49, patients will continue treatment in an extension period until radiologic confirmation of disease progression or unacceptable toxicity. Disease follow-up will be performed for up to 2 years.

Statistical Considerations

The primary endpoint is ORR, assessed by blinded independent review at Week 25, based on RECIST v1.1. Assuming an actual response rate of 35% in the experimental arm and a sample size of 120 patients, the study will have 98.1% power to detect a significantly higher response than the 5% for the control arm. The primary analysis is a two-sided Fisher's exact test.

Key secondary endpoints include ORR per TVS at Week 25, mean change from baseline in ROM at Week 25, mean change from baseline in PROMIS physical function score at Week 25, mean change from baseline in the Worst Stiffness Numeric Rating Scale score at Week 25, mean change from baseline in EQ-VAS at week 25, and proportion of responders based on BPI-30 NRS score and narcotic analgesic use at Week 25. A hierarchical method of testing is proposed to control the overall Type I error of the study at 5%. The primary endpoint will be tested first and then the secondary endpoints will be tested in the above order.

DISCUSSION

Clinical

- 1) Does the Division agree that the proposed Phase 3 study design is appropriate to support the approval of DCC-3014 for the treatment of patients with symptomatic TGCT (b) (4)?

FDA Response: We agree that the key design elements of the proposed trial appear acceptable. The ability of the proposed study to support a future marketing application will depend on whether the observed ORR and DOR are of sufficient magnitude to be considered clinically meaningful, correlate with a detectable effect on tumor-related functional impairments or an improvement in tumor related symptoms, and the overall risk-benefit assessment.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

- 2) Does the Division agree that the proposed primary and secondary efficacy endpoints of Study DCC-3014-03-001 are appropriate and capture clinically meaningful outcomes to support the proposed indication?

FDA Response: The proposed primary and secondary efficacy endpoints appear appropriate to capture clinically meaningful outcomes that may support the proposed indication. Please see Additional Comments 9 and 10 regarding the proposed clinical outcome assessments. Whether the results of secondary endpoints will be appropriate for inclusion in product labeling will be a review issue.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

- 3) Does the Division agree that a 30 percentage point improvement in ORR in patients treated with DCC-3014 compared to placebo at Week 25 is clinically meaningful and could support a registration for the intended patient population?

FDA Response: Please refer to FDA Response to Question 1 regarding the potential for this study to support registration. A 30 percentage point improvement in ORR with sufficient durability of responses in patients treated with DCC-3014 compared to placebo at Week 25 may be considered clinically meaningful if supported by evidence that DCC-3014 provides a clinically meaningful effect on how a patient feels, functions or survives.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

- 4) Does the Division agree with the planned statistical analyses and the proposed hierarchical testing strategy?

FDA Response: In general, the proposed statistical analysis plan appears acceptable. Provide additional details regarding the handling of patients who cross-over from the placebo arm to the experimental arm prior to Week 25 in the analyses of secondary endpoints measured at week 25. We recommend the inclusion of an exploratory endpoint measuring ORR per RECIST v1.1 as assessed by independent radiologic review at the end of Part 2 of the study in

the population of patients who received DCC-3014 in Part 1 or in Part 2 of the study.

Deciphera Email Response Received January 11, 2021: It is expected that the number of patients who meet the criteria to be eligible to cross over from the placebo arm to the experimental arm prior to Week 25 will be low. We will provide in our Statistical Analysis Plan (SAP) a detailed description of the analyses and how data from such patients will be used. For response-type endpoints, these patients will be assigned as non-responders. For endpoints analyzed using MMRM, the general intent is for data from assessments performed after the time of cross-over in Period 1 not to be included in the planned primary MMRM analyses and be treated as missing. Sensitivity analyses will be conducted using multiple-imputation approaches based on different missing data mechanisms including missing not at random (MNAR). Details regarding the sensitivity analyses will be included in the SAP.

We agree with the recommendation for inclusion of an exploratory endpoint for ORR per RECIST v1.1 as assessed by independent radiologic review at the end of Part 2 of the study in the population of patients who received DCC-3014 in Part 1 or in Part 2 of the study. Although such an endpoint is not specified in the protocol, the imaging data is being collected for these time points and an analysis based on this will be described in the SAP.

Discussion During Meeting: No discussion occurred.

- 5) Does the Division agree that the anticipated safety database is acceptable to reasonably assess the safety profile of DCC-3014?

FDA Response: We acknowledge the anticipated overall safety database, including approximately 206 oncology patients and an additional 200 patients in clinical pharmacology studies. The planned clinical safety database may be considered adequate to support an NDA filing provided that no unusual toxicities are identified; however, given the expected duration of treatment in a population with a non-malignant disease, the acceptability of the size of the safety database will be determined upon review of additional data in a pre-NDA meeting package. In the pre-NDA meeting package, clearly state how many patients have received the dose intended for approval.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

- 6) Does the Division agree that DCC-3014 30 mg twice weekly is the appropriate dose for Study DCC-3014-03-001?

FDA Response: The rationale for your choice of the proposed 30 mg twice weekly dosage over the 10 mg daily dosage is not clear. Based on information reviewed in the current submission, there is no strong trend on efficacy or safety in TGCT between 30 mg BIW dose and 10 mg QD dosage. Within 30 days of this meeting, please provide a summary of integrated dose-response and exposure-response analyses for dose optimization by pooling available PK, pharmacodynamic, efficacy, and safety data to justify your dose selection. It is not clear if the current proposed exposure range is optimized for efficacy. Provide adequate justification for the proposed dosage by including consideration of in vitro receptor occupancy data and the overall shape of the exposure response relationships, and full dose range over which efficacy may be expected. As part of this justification, provide rationale for not studying higher doses or alternative dosing regimens (with additional rationale for including or not including the previously evaluated loading dose strategy) in TGCT to ensure that exposures are achieved that optimize efficacy. Alternatively, consider the need to assess more than one dosage in the proposed trial in order to ensure that the RP2D is optimized for efficacy.

Deciphera Email Response Received January 11, 2021: DCC-3014 is an orally administered, potent and highly selective switch control inhibitor of CSF1R. DCC-3014 has a greater than 100-fold selectivity for CSF1R over closely related kinases (KIT, PDGFR α , PDGFR β and FLT3), and has an even greater selectivity for CSF1R over approximately 300 other human kinases. Circulating CSF1, IL34 and non-classical monocytes (NCM) were assessed to evaluate the pharmacodynamics of DCC-3014 in the Phase 1/2 study.

CSF1R has two known ligands, CSF1 and IL34, and increases in levels of CSF1 and IL34 indicate CSF1R inhibition. The data demonstrate that the engagement of DCC-3014 to CSF1R results in an increase of circulating CSF1 and IL34 in a dose-dependent manner (Figure 1). On Cycle 2, Day 1, the steady state, mean CSF1 increase from baseline was similar across 3 dose cohorts: 27-fold with 30 mg BIW (Cohort 5; TGCT patients, n=6), 31-fold with 20 mg QD (Cohort 7; malignant solid tumor [MST] patients, n=3), and 33-fold with 10 mg QD (Cohort 8; TGCT patients, n=10). At a lower dose of 6 mg QD (Cohort 9; TGCT patients, n=4) the CSF1 increase from baseline was 5-fold. Similar results are also observed with IL34 levels.

CSF1R is primarily expressed on the surface of circulating monocytes and macrophages. The CD14dim/CD16+ NCM subset is sensitive to anti-CSF1R treatment, thus serves as a PD marker of CSF1R inhibition. DCC-3014 treatment results in the rapid and sustained reduction of CD14dim/CD16+ NCM in the peripheral blood, indicating blockade of CSF1R signaling. Patient NCM levels decreased 50–94% after 2 weeks of DCC-3014 treatment (Figure 1). Similar

trends were observed across 30 mg BIW, 20 mg QD, and 10 mg QD dose cohorts, and a comparison of pharmacodynamic data across these cohorts indicates that DCC-3014 exhibits a desirable pharmacodynamic effect at the 30mg BIW dosage selected for the planned Phase 3 study.

The increase in plasma CSF1 levels and the reduction in NCM in the peripheral blood after treatment with either DCC-3014 or pexidartinib, an approved anti-CSF1 inhibitor, are presented in

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Figure 2 and Figure 3, respectively, and similar levels of target engagement can be observed across the two agents. Taken together, the totality of the PD data based on CSF1, IL34 and NCM indicates adequate target engagement at 30 mg BIW.

Figure 1 Study DCC-3014-01-001 pharmacodynamic assessment

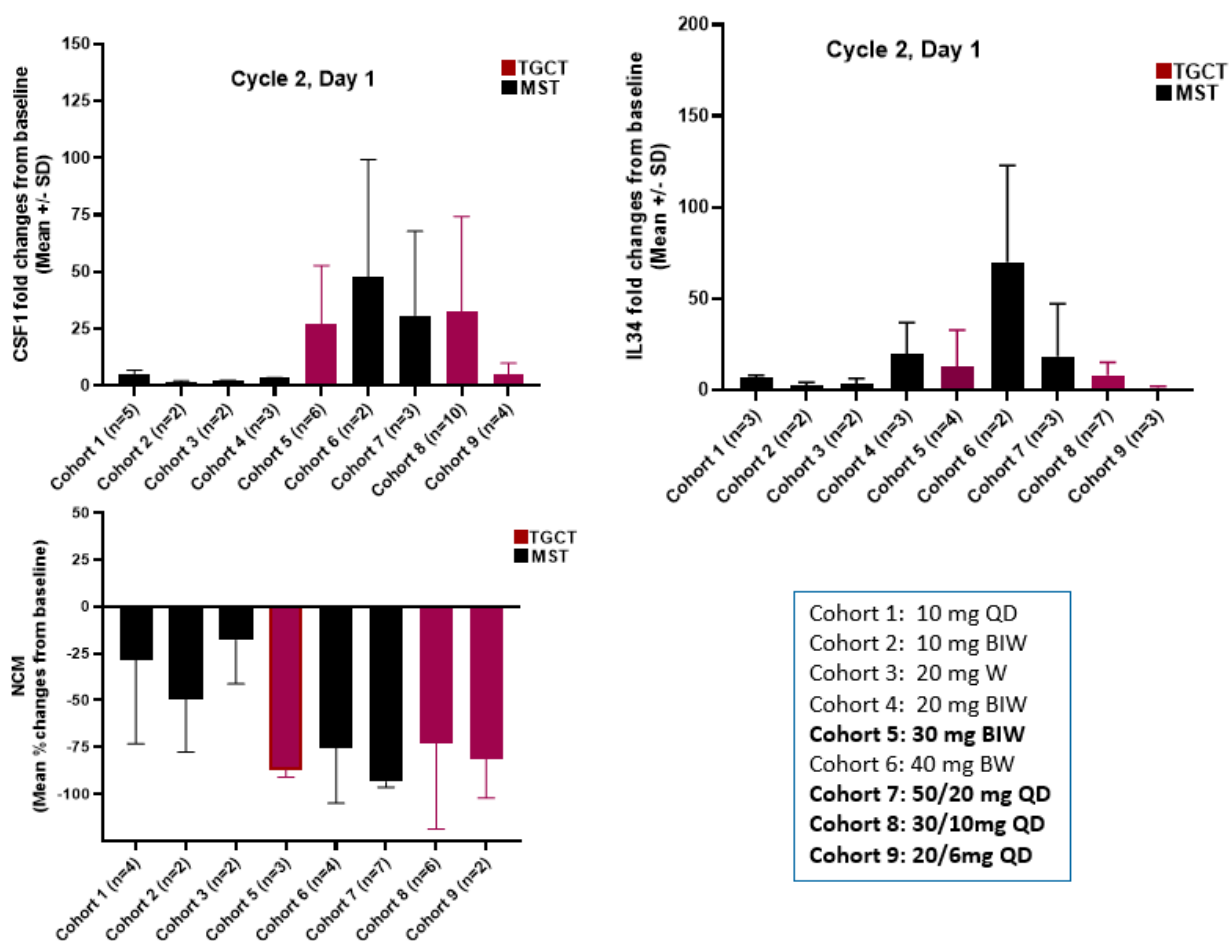


Figure 2 Anti-CSF1 inhibitors cause an increase in plasma CSF1 levels

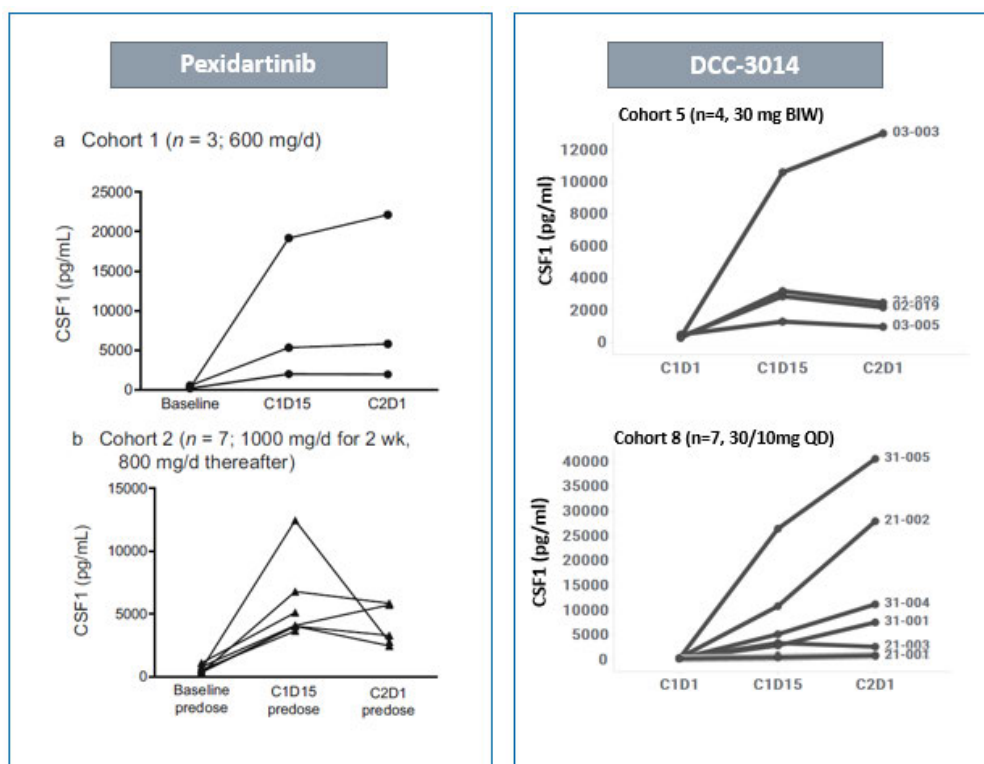
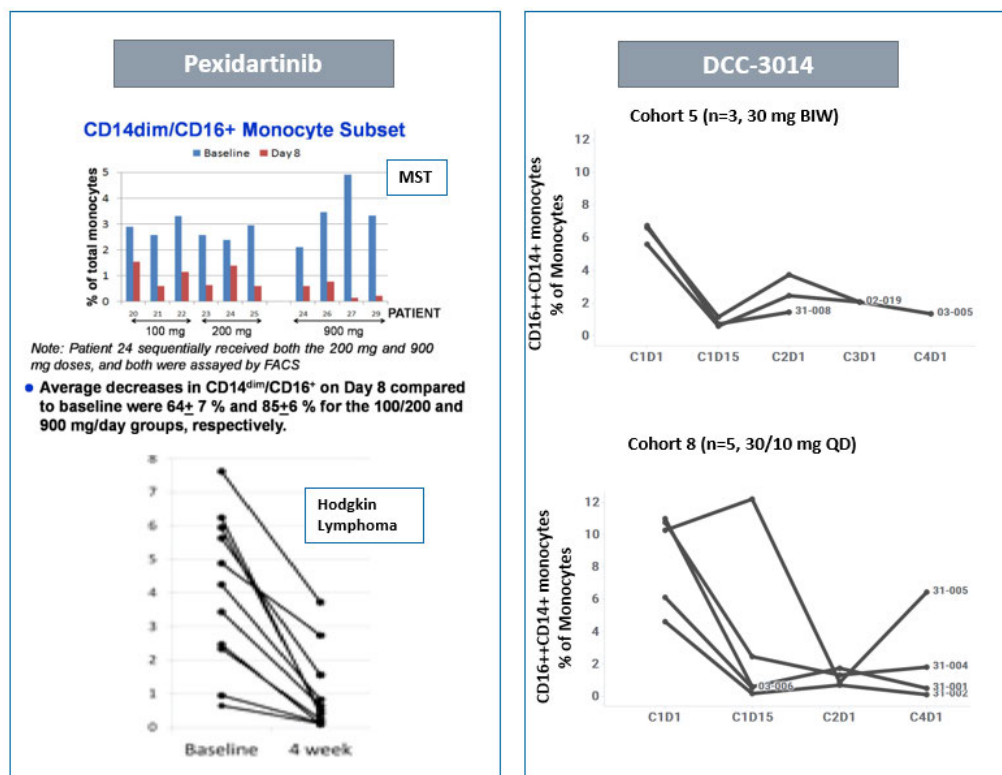


Figure 3 Anti-CSF1 inhibitors reduce non-classical monocytes in the peripheral blood



The exposure-response relationship associated with DCC-3014 treatment has not been fully characterized at this time. Preliminary analyses did not indicate an apparent relationship between DCC-3014 exposure and efficacy in patients from TGCT cohorts in the Phase 1/2 study. We plan to continue to collect data and further evaluate exposure-response related to DCC-3014 treatment.

Given the similarities across the PK, PD, efficacy, and safety data from Cohort 5 (30 mg BIW) and Cohort 8 (10 mg QD), our decision to select 30 mg BIW was based on a directionally more tolerable safety profile observed in patients dosed with 30 mg BIW compared to 10 mg QD in the Phase 1/2 study. We hypothesize that dosing less frequently throughout the week, rather than daily, may be better tolerated. As a result of several conversations with TGCT physicians, we understand there is a need to select an efficacious dose with a manageable safety profile as TGCT affects relatively young and otherwise healthy patients and DCC-3014 will be a chronic therapy for a slowly progressing and non-life-threatening condition. While we have explored higher doses in other solid tumor patients, we do not believe testing higher doses is warranted as the doses tested resulted in an ORR of over 40% across TGCT patients in Cohorts 5, 8 and 9, and the PD data (as presented above) demonstrate maximal target engagement at the doses tested. Further, we do not believe the loading dose is necessary as it

originally aimed to shorten the time to reach steady state in the dose escalation study. Considering that TGCT is a non-malignant and non-life-threatening disease and reaching steady state quickly is therefore not critical, the loading dose was removed from the dosing regimen planned for the Phase 3 study.

Given the similarities among the data from patients dosed with 30 mg BIW and 10 mg QD, and the heterogeneity of the TGCT patient population, we do not believe assessing both dosages in the planned Phase 3 trial would lead to a definitive demonstration of optimized efficacy for one dosage over the other. In selecting 30 mg BIW for the Phase 3 study, we have taken a conservative approach from a safety perspective in order to ensure an efficacious and tolerable dose that can be administered long term.

Discussion During Meeting: FDA acknowledged the additional information provided by Deciphera, but noted that the proposed patient population will be receiving DCC-3014 for prolonged periods and are relatively healthier and younger than patients with cancer, and that determining a recommended dosage based on safety data from 6 patients is not optimal. FDA stated that there is insufficient safety data in TGCT to support Deciphera's determination that the proposed 30 mg twice weekly dosage (Cohort 5, n=6) is more tolerable and optimized compared to the 10 mg QD dosage regimen (Cohort 8, n=12) and further dose finding information is needed. FDA recommended that Deciphera provide additional safety data to justify the final dosage regimen selected for Study DCC-3014-03-001, especially given that the proposed trial appears to be designed to definitively demonstrate efficacy and safety in TGCT.

Deciphera stated that the 30 mg twice weekly dosage regimen was chosen based on findings suggesting increased tolerability in this cohort (Cohort 5). For example, myalgia occurred in 17% of patients with TGTC in Cohort 8, and increased facial edema, skin disorders, and rash were observed in Cohort 8 compared to Cohort 5. FDA noted that the existing safety database for Cohort 5 is limited, and recommended that additional work be done for dose optimization. Deciphera agreed to send additional safety data to support the proposed RP2D, reflecting safety data from approximately 20 patients enrolled in the expansion cohort, prior to initiation of the phase 3 trial.

Deciphera also agreed to provide additional analysis on the exposure-response relationship once the additional data from the expansion cohort in the ongoing trial is available.

Deciphera requested that FDA clarify whether submission of a protocol for the randomized trial prior to availability of the additional data from the expansion cohort would be problematic. FDA stated that this would not be considered a hold issue, but strongly recommended that Deciphera seek advice from FDA regarding whether the dose optimization concerns are adequately addressed by

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Silver Spring, MD 20993

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the additional analyses and data prior to initiation of the proposed trial. Deciphera acknowledged this advice and agreed with this approach. Deciphera will reference this discussion in the cover letter with the protocol when submitted, and include an update on the timing of submission of the additional data supporting the proposed dose.

Clinical Pharmacology

- 7) Does the Division agree that the proposed clinical pharmacology plan is adequate to support a registration for the intended indication?

FDA Response: Please refer to FDA Response to Question 6. Otherwise, the proposed clinical pharmacology plan appears generally acceptable. The adequacy of the data will be determined following our review of your NDA submission.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

Regulatory

- 8) Does the Division agree with the proposal for requesting a drug-specific waiver in the initial Pediatric Study Plan?

FDA Response: The proposal to request a drug-specific waiver in the iPSP based on rarity of the intended patient population and impracticability to conduct such pediatric studies appears reasonable, but a final determination will be made based on the review of the submitted iPSP.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: During the meeting, FDA provided additional guidance with respect to Question #8. FDA encouraged Deciphera to consider enrollment of older adolescent patients in the proposed study and to address this population in the iPSP, including the potential for extrapolation of efficacy in this age group.

ADDITIONAL FDA COMMENTS

- 9) Regarding the clinical study protocol to be submitted to the IND:
- a. Ensure that case report forms specify the reason for determining that surgical resection would lead to functional impairment or excessive morbidity in patients.
 - b. The study calendar does not specify whether liver function will be evaluated as part of regular serum chemistry studies. Revise the scheduled assessments to indicate which specific liver function tests will be assessed and at what frequency.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

- 10) Regarding the EQ-5D-5L, we do not agree that it adequately measures QoL for the following reasons:
- a. The concept of interest in the EQ-5D-5L is health status and not quality of life; it does not evaluate the different aspects of life that may be affected by the condition and/or treatment.
 - b. The EQ- 5D-5L is a generic preference-based measure intended to provide a single health utility index value (i.e., utility scores) for use in economic analyses. As such, it lacks evidence of content validity for use in estimating clinical benefit for labeling claims.
 - c. The use of a visual analog scale can be problematic (e.g., issues with administration and interpretability, such as inconsistencies with the length of the VAS due to formatting issues, higher rates of missing data or incomplete data with VAS)^{2,3}.

Despite the limitations with the EQ-5D-5L, we acknowledge that it may be needed for other regulatory authorities and/or payers. As such, this does not preclude you from using this instrument.

² Dworkin RH, Turk DC, Farrar JT, et al., "Core Outcome Measures for Chronic Pain Clinical Trials: IMMPACT Recommendations." Pain, vol. 113, pp. 9-19, 2005.

³ Hawker GA, Mian S, Kendzerska T, et al., "Measures of Adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP)." Arthritis Care & Research, vol. 63, Supplement 11, pp. S240-252, 2011.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA's feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

11) We have the following comments regarding Appendix A:

a. Range of motion (ROM):

We acknowledge that your trial design does not allow you to assess intra-rater reliability (test-retest reliability) of the goniometry. Literature related to the reliability of this instrument may be acceptable; however, submit copies of publications for reviews. A standalone study is also an acceptable option.

b. PROMIS Physical Function (PROMIS PF):

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.

c. We do not agree with your plan to directly estimate responders using a patient global impression of change (PGIC) domain items rather than in-trial determination of thresholds for meaningful within-patient change using anchor-based methods, as this approach does not inform whether patients experienced meaningful changes (improvement or deterioration). Anchor-based methods are the primary methods we use to interpret meaningful within-patient score changes in COA endpoints. Anchor-based methods should be supplemented with anchor-based empirical cumulative distribution function and probability density function curves.

Further, there are limitations with the use of a PGIC scale to estimate responders (e.g., susceptibility to recall error, less reliable measure of change from baseline). At a minimum, we recommend a current state (non-comparative) global impression rating scale (such as your proposed Patient Global Impression of Severity scale), when appropriate, as an anchor scale as these scales are less likely to be subject to recall error than global

impression of change scales; it also is a more reliable measure for change from baseline data.

We continue to recommend that you plan to incorporate anchor-based methods for the proposed COAs in your protocol and analyses. Other methods may be explored to complement the anchor-based methods or when anchor-based methods are not feasible (i.e., when no adequate anchor measure(s) are available, small sample size). For example, patients can be queried via cognitive interviews, exit interviews, or surveys to help inform the improvement threshold. See Comment d about considerations for use of external anchors.

- d. External anchors should have the following properties:
 - i. Selected anchor scales should be associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of the target COA endpoint. For example, for an endpoint measuring a specific aspect of the disease, an anchor scale measuring the global status of the disease may not be helpful.
 - ii. The anchor scale should be easier to interpret than the COA endpoint itself and meaningful to patients. The anchor scale's response categories should be distinct and non-overlapping and should represent meaningful differences among adjacent response categories. For example, an anchor scale that uses a 0-10 numeric rating scale would not be easy to interpret and would not be an appropriate anchor scale in most contexts. An example of a commonly used response scale for rating severity is none, mild, moderate, or severe.
 - iii. The anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible. Additionally, the selected anchors should be assessed at comparable time points as the target COA endpoint but completed by the respondent after the target COA in the order of assessments.
 - iv. The anchor scale should be plainly understood by respondents in the context of use; you should consider testing the draft anchor item(s) including their response categories in cognitive interviews.

Submit exact copies of your anchor scales for review and concurrence prior to implementing them in your clinical trial(s). Also, provide the final qualitative report to support the comprehension of the ROM-specific anchor scales for review, including data on the frequency counts of how many participants understood the ROM and physical function terminology.

Refer to FDA Discussion Document: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making.⁴

- e. We acknowledge that you plan to conduct exit interviews to better understand the TGCT patient experience of stiffness, including potential confounders relating to other symptoms of TGCT (e.g., pain). We note that you target the “End of Part 1 Interview” to be approximately 1.5 hours. There is concern that the length of the interviews may affect data quality and increase respondent burden. As such, we recommend that you structure your interviews to elicit focused, meaningful input on the instruments you plan to use to support the key patient-reported outcome endpoints. Note that the COVID-19 pandemic has had impact on biomedical research, including qualitative research with patients. We recommend that you consider whether and how the pandemic might affect your planned research and plan accordingly (e.g., potential need for future protocol amendments). We encourage you to submit your exit study protocol, including interview guide, for review.
- f. Plan to provide the final usability study report at the time of NDA submission.

Deciphera Email Response Received January 11, 2021: Deciphera acknowledges the FDA’s feedback and confirms that further discussion is not required.

Discussion During Meeting: No discussion occurred.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with

⁴ <https://www.fda.gov/media/132505/download>

molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be “designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling” (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to [FDA.gov](https://www.fda.gov).⁵

FDARA REQUIREMENTS

Sponsors may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor’s initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency’s current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive

⁵ <https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology>

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justification for a waiver or deferral can be provided.

Meeting requests should be sent to the appropriate review division with the cover letter clearly stating “**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**” These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.⁶

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁷

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdere-data@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁸ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND)

⁶ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁷ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁸ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.⁹

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

⁹ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission “**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**” in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion

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needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources¹⁰ and the CDER/CBER Position on Use of SI Units for Lab Tests website.¹¹

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.¹²

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification for *Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.¹³

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions*, and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*, be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated

¹⁰ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

¹¹ <https://www.fda.gov/media/109533/download>

¹² <http://www.fda.gov/ectd>

¹³ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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*Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications.*¹⁴

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical

¹⁴ <https://www.fda.gov/media/85061/download>

trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR¹⁵: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid¹⁶

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

No action items.

ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting summary.

¹⁵ <https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program>

¹⁶ <https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project>

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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