CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213973Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

IND 125279

MEETING MINUTES

Deciphera Pharmaceuticals, LLC
Attention: Shreya Mehta
Senior Manager, Regulatory Affairs
200 Smith Street
Waltham, MA 02451

Dear Ms. Mehta:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ripretinib (DCC-2618).

We also refer to the teleconference between representatives of your firm and the FDA on October 9, 2019. The purpose of the meeting was to discuss the planned submission of a New Drug Application (NDA) for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.

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, contact me at (240) 402 6611 or leah.her@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Senior Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 9, 2019 / 1:00 – 2:00 PM (EST)
Meeting Location:	NA; teleconference
Application Number:	IND 125279
Product Name:	ripretinib
Indication:	Treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib
Sponsor/Applicant Name:	Deciphera Pharmaceuticals, LLC
Meeting Chair:	Ashley Ward
Meeting Recorder:	Leah Her

FDA ATTENDEES

Ashley Ward	Clinical Team Leader, DOP2
Leslie Doros	Clinical Reviewer, DOP2
Leah Her	Regulatory Health Project Manager, DOP2
Whitney Helms	Nonclinical Team Leader, DHOT
Anwar Goheer	Nonclinical Reviewer, DHOT
Anamitro Banerjee	Product Quality Branch Chief, DNDPI/NDPBII
Xing Wang	Product Quality Team Leader, DNDPI/NDPBII
Tefsit Bekele	Product Quality Reviewer, DNDPI/NDPBII
Banu Zolnik	Biopharmaceutics Team Leader, ONDP/DB/BBI
Mei Ou	Biopharmaceutics Reviewer, DB/BBI
Jeanne Fourie-Zirkelbach	Clinical Pharmacology Team Leader, DCPV
Lisa Rodriguez	Statistical Team Leader, DBV
Mengdie Yuan	Statistical Reviewer, DBV
Naomi Boston	DRISK Team Leader (Acting)

SPONSOR ATTENDEES

Ehab Hamed	Senior Director, Drug Product MS&T
Jama Pitman	Vice President, Regulatory Affairs and Quality
Jing Wang	Director, Clinical Pharmacology
John Bullock	Senior Director, Analytical Development and MS&T
Julie Meade	Senior Medical Director, Clinical Development
Kathy Church	Senior Director, CMC Regulatory Affairs
Kelvin Shi	Senior Director, Biometrics

Marc Mazzuca	Senior Associate, Regulatory Affairs
Matthew Sherman	Executive Vice President and Chief Medical Officer
Mike Kaufman	Vice President, Chemical and Pharmaceutical Development
Rodrigo Ruiz Soto	Vice President, Clinical Development
Shreya Mehta	Senior Manager, Regulatory Affairs
Simin Hu	Associate Director, Biostatistics

BACKGROUND

On August 8, 2019, Deciphera submitted a meeting request to discuss the planned submission of a New Drug Application (NDA) for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. Specifically, Deciphera seeks agreement on the content and format of the planned NDA.

The meeting was granted on August 14, 2019. The meeting package was received on September 9, 2019. FDA issued Preliminary Comments on October 4, 2019. On October 7, 2019, Deciphera provided responses and a proposed revised NDA submission plan under the Real-Time Oncology Review (RTOR) pilot program, along with a request to convert the scheduled in-person meeting to a teleconference.

Key Regulatory History
The development of ripretinib initiated under this IND 125279 on August 11, 2015, with the first-in-human (FIH) clinical study, Protocol DCC-2618-01-001, entitled "A Multicenter Phase 1, Open-Label, Dose-Escalation Study of DCC-2618 to Assess Safety, Tolerability and Pharmacokinetics in Patients with Advanced Malignancies."

The information hereafter is limited to that which is applicable to the development of ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib to support the planned NDA.

<u>General</u>

- October 2, 2014: Orphan drug designation granted for ripretinib for the treatment of GIST (Designation No.: 14-4474; Office of Orphan Drug Products).

<u>Under IND 125279</u>

- March 4, 2015: Pre-IND meeting held to discuss the adequacy of the product quality information, the planned and completed nonclinical studies to support the proposed first-in-human (FIH) study, and the proposed overall development program for ripretinib in advanced solid tumors driven by c-KIT/PDGFR mutation or over-expression.

• August 11, 2015:	Original IND with Protocol DCC-2618-01-001 received on July 17, 2015, allowed to proceed.
• May 26, 2017:	End-of-Phase 1 / Pre-Phase 3 meeting held to discuss the adequacy of the nonclinical and clinical pharmacology plans, and design of the proposed pivotal study, Protocol DCC-2618-03-001, entitled “A Randomized, Multicenter Phase 3, Double Blind Study of DCC-2618 + Best Supportive Care (BSC) vs Placebo + BSC in Patients with Advanced Gastrointestinal Stromal Tumors after Prior Treatment with Imatinib, Sunitinib and Regorafenib” to support an NDA.
• August 17, 2017:	Deciphera submitted the potential registration-enabling study, Protocol DCC-2618-03-001 (INVICTUS), entitled "A Phase 3, Interventional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with Advanced c-KIT/PDGFRA Gastrointestinal Stromal Tumors who have Received Prior Treatment with Imatinib, Sunitinib, and/or Regorafenib." On October 18, 2017, in a Partial Hold Letter (see below), FDA provided clinical and statistical comments relating to the study design. INVICTUS was revised in November 2017 (Amendment 1), in March 2018 (Amendments 2 and 3), in August 2018 (Amendment 4), and October 2018 (Amendment 5; current version).
• August 24, 2017:	Fast Track designation request denied for DCC-2618 for treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with approved therapies, due to lack of adequate information on how the development program will affect the serious aspect of the condition or address the unmet medical need.
• October 5, 2017:	Partial Clinical Hold imposed on INVICTUS to limit patient enrollment to fewer than 50 patients due to lack of completed 13-week chronic toxicology studies as previously communicated during the May 26, 2017, meeting. FDA issued the Partial Clinical Hold letter on October 18, 2017. On April 3, 2018, the Partial Clinical Hold was removed.
• January 11, 2018:	Memorandum containing QT-IRT review comments issued. FDA stated that additional information was needed to evaluate the effects of ripretinib on QTc interval (e.g., another study).
• October 23, 2018:	Preliminary Breakthrough Therapy Designation (BTDR) Advice teleconference held to discuss DCC-2618 for treatment of patients with advanced GIST who have received prior treatment

with 1) imatinib, sunitinib, and regorafenib, and 2) imatinib. FDA stated that additional information was needed to determine whether a BTDR would be appropriate.

Subsequently on August 21, 2019, Deciphera submitted a BTDR for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. The BTDR is under review and FDA intends to respond within 60 days of the August 21, 2019 receipt date.

- November 27, 2018: End-of-Phase 2 Product Quality-only meeting held to discuss product quality development program for DCC-2618 to support registration plans.
  - FDA stated that Deciphera will need to further assess any impurities that are above the ICH Q3A/B limits.
  - FDA stated that the proposed NDA may contain 9-month drug substance stability data for three registration batches followed by an update within 30 days to provide 12-month stability data. FDA did not commit review of any stability data submitted after 30 days.
  - Deciphera noted that a comparability protocol (b) (4) (b) (4) (b) (4) will be submitted with the NDA; (b) (4)
- January 28, 2019: Advice letter containing product quality-only development comments issued.
- February 13, 2019: Administrative pre-NDA guidance meeting held.
  - FDA reiterated the January 11, 2018, comment regarding the Qtc interval and provided other clinical pharmacology-related comments to support development and an NDA.
  - FDA stated that while FDA was generally in agreement with the proposed data cut-off plan, Deciphera should ensure all responding patients included in the efficacy analyses are followed for a minimum of 6 months from onset of response or until disease progression.
  - FDA stated that the original NDA will need to include exposure data for patients who received ripretinib for ≥6 months.
  - FDA stated that a Bioresearch Monitoring (BIMO) package should also be provided for Study DCC-2618-01-001.
  - FDA disagreed with Deciphera's proposal to not include an Integrated Summary of Efficacy (ISE) for Study DCC-2618-01-001.

	Subsequently, on March 14, 2019, FDA issued an Advice letter containing additional advice regarding the ISE in response to Deciphera's request.
• June 21, 2019:	Fast Track designation request granted for the investigation of ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib, to demonstrate clinically meaningful and statistically robust improvement in progression free survival (PFS) compared to placebo.
• August 8, 2019:	Deciphera submitted the statistical analysis plan for INVICTUS in the same submission as this current meeting request.
• September 5, 2019:	An informal teleconference held to discuss potential participation in on-going Oncology Center of Excellence (OCE) pilot programs: Project Orbis, Real-Time Oncology Review (RTOR), and the Assessment Aid (AA). On September 16, 2019, Deciphera expressed intent to participate in all three OCE pilot programs. Decision regarding participation in Project Orbis is pending at this time.
• September 10, 2019:	Deciphera submitted treatment protocol DCC-2618-99-001, entitled "Expanded Access Program For Ripretinib in Patients with Locally Advanced Unresectable or Metastatic GIST Who Have Received Treatment with Prior Therapies." The protocol is under review and FDA intends to respond within 30 days of the September 10, 2019, receipt date.

Registration Plans
Deciphera plans to submit an NDA for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib in December 2019. Deciphera plans to seek a priority review and a regular approval.

Clinical Development
The clinical studies supporting the planned NDA for ripretinib are below:

- Study DCC-2618-01-001, entitled "A Multicenter Phase 1, Open-Label Study of DCC-2618 to Assess Safety, Tolerability, Efficacy, and Pharmacokinetics in Patients with Advanced Malignancies" (Study 01-001; status – escalation: enrollment completed; expansion: GIST cohorts are completed but enrolling other cohorts; on-going)

- Study DCC-2618-03-001, entitled “A Phase 3, INterVentional, Double-Blind, Placebo-Controlled Study to Assess the Safety and Efficacy of DCC-2618 In Patients with AdvanCed Gastrointestinal Stromal TUmorS who have Received Treatment with Prior Anticancer Therapies” (INVICTUS; status – enrollment completed; ongoing)

- Study DCC-2618-01-002, entitled “A Phase 1, Randomized, Open-Label, Single-Dose, Partial Replicate, Three-Period, Crossover Study to Evaluate the Relative Bioavailability and Safety of Two Formulations of DCC-2618 in Healthy Adult Subjects” (Study 01-002; status – enrollment completed; study ongoing)

- Study DCC-2618-01-003, entitled “A 2-Part, Phase 1, Fixed-Sequence, Open-Label Study to Evaluate the Effects of CYP3A4 Inhibition and Gastric Acid Suppression on Single-Dose Pharmacokinetics of DCC-2618 in Healthy Adult Subjects” (Study 01-003; status – enrollment completed; study ongoing)

Deciphera plans to initiate a hepatic impairment study in September 2019 (Study DCC-2618-01-004). Deciphera also notes that Study 01-001 has been amended to include a renal impairment cohort to evaluate the effect of renal impairment. Deciphera states that both studies will be on-going at the time of the NDA review.

Contents of the NDA

Deciphera plans to include 12-month drug substance stability and 9-month drug product stability in the proposed NDA. Deciphera proposes to submit an update to the drug product stability during the review cycle within 90-days of the original application.

The proposed NDA is planned to be based on the safety and efficacy data primarily from INVICTUS (data cut-off: May 31, 2019) and supported by data from Study 01-001 (data cut-off: March 1, 2019). Deciphera plans to submit a full clinical study report (CSR) for INVICTUS, and Studies 01-002 and 01-003, and an interim CSR for Study 01-001.

Deciphera plans to provide a Summary of Clinical Safety (SCS) and an Integrated Summary of Safety (ISS) with narratives in Module 2, and datasets and appendices in Module 5. A similar approach is planned for the Summary of Clinical Efficacy (SCE) and Integrated Summary of Efficacy (ISE).

The ISS will include three pooled analyses as described below (however, safety data from the clinical pharmacology studies will be reported separately in individual CSRs):

- Pool 1 – Detailed analysis of safety in patients with GIST from INVICTUS who received at least one dose of ripretinib at the proposed dosing regimen (150 mg QD) (i.e., the efficacy evaluable pool)

- Pool 2 – Overview of safety in all patients from both studies (INVICTUS and Study 01-001) who received at least one dose of ripretinib at the proposed dosing regimen (150 mg QD).
- Pool 3 – Overview of safety in all patients from both studies with any type of cancer who have received at least one dose of ripretinib.

Deciphera proposes that based on the safety profile observed to-date in the clinical development program, a Risk Evaluation and Mitigation Strategy (REMS) is not required and will not be planned to be included in the proposed NDA.

Deciphera proposes to submit the potential 90-day or 120-day safety update using data from INVICTUS and Study 01-001 with a data cut-off date of August 31, 2019, in April 2020. Deciphera states that labeling may be updated to reflect the updated safety data.

The SCE will present both side-by-side data and pooled data from both INVICTUS and Study 01-001, and the Integrated Summary of Efficacy (ISE) will include pooled efficacy analyses datasets.

The proposed eCTD content of the planned NDA was provided in the meeting package.

Proposed Post-Marketing Studies

Deciphera proposes to submit four clinical pharmacology components as post-marketing requirements/commitment after the NDA approval, as follows:

- assessment of hepatic impairment
- assessment of renal impairment
- assessment of effects of induction of CYP metabolism on ripretinib
- assessment of effects of ripretinib on pharmacokinetics of a CYP2C8 substrate

Product Quality

DCC-2618 is supplied in 10 mg and 50 mg tablets for oral administration. The drug substance is formulated as (b) (4) hydroxypropylmethylcellulose acetate succinate (b) (4) (HPMCAS (b) (4) (b) (4). (b) (4) DCC-2618/HPMCAS (b) (4) is further formulated with other excipients to produce DCC-2618 tablets. The final tablets contain (b) (4) DCC-2618 together with microcrystalline cellulose, lactose (b) (4), crospovidone, (b) (4), and magnesium stearate. The manufacturing process consists (b) (4) (b) (4) (b) (4). The tablets are packaged in HPDE bottles with child resistant closure and (b) (4) liner. Each bottle contains 30 DCC-2618 tablets and a (b) (4) (b) (4) desiccant (b) (4). The recommended storage condition is 25°C/60% RH.

Nonclinical
DCC-2618 (ripretinib) is an orally administered inhibitor of the KIT and PDGFRA kinases. To support the NDA, Deciphera plans to submit GLP-compliant toxicology studies of up to 13-weeks duration in two species (rat and dog) with SEND datasets, as well as in vitro and in vivo pharmacology and pharmacokinetic/ADME studies, a full battery of GLP-compliant genotoxicity studies, a photoxicity study, as well as dose-range findings in embryo-fetal development studies in rats and rabbits, and a GLP-compliant embryo-fetal development study in rats.

Clinical/Statistical
Study DCC-2618-03-001 is a randomized (2:1), double-blind, placebo-controlled study evaluating DCC-2618 (ripretinib) versus placebo in up to 120 patients with advanced GIST (including wild-type). Key inclusion criteria include: age ≥18 years, a histologic diagnosis of GIST, progression on imatinib, sunitinib, and regorafenib or have documented intolerance to any of these treatments despite dose modifications, and ECOG PS of 0 to 2. Key exclusion criteria include known active central nervous system metastases and left ventricular ejection fraction <50%, The primary efficacy endpoint is progression-free survival (PFS) according to modified RECIST (mRECIST) and as assessed by independent radiologic review (IRR). The key secondary efficacy endpoint is objective response rate (ORR). There were no interim analyses planned.

The primary analysis for PFS was a stratified log-rank test. With 90 PFS events planned at the final analysis, the study had at least 90% power to detect a difference in PFS between DCC-2618 and placebo assuming a median PFS of 4.5 months for DCC-2618 and 1 month for placebo. To control the family-wise type I error rate, the hypothesis tests for the treatment difference were performed at a two-sided significance level of 0.05 sequentially in the following order:

1. PFS
2. ORR
3. overall survival (OS)
4. quality of life (QOL) as determined by changes from baseline to Day 1 of cycle 2 in EORTC-QLQ-C30 Role function and Physical function (each at 0.025 level significance)

Enrollment has been completed; treatment and follow-up is ongoing. As of May 31, 2019, a total of 129 patients were randomized to receive ripretinib (N=85) or placebo (N=44). The efficacy results from the double-blind period of the study are summarized in Table 1; however, the reported p-value for OS is nominal. There is no alpha provided for the test of OS because the test for ORR was not statistically significant in the hierarchy.

Table 1 Efficacy Results (Study DCC-2618-03-001; INVICTUS)

	Ripretinib (N=85)	Placebo (N=44)
Progression-Free Survival (PFS)		
Number of Events (%)	51 (60.0)	37 (84.1)
Number of Censored Events (%)	34 (40.0)	7 (15.9)
Median PFS (weeks) (95% CI)	27.6 (20.0, 29.9)	4.1 (4.0, 7.3)
HR (95% CI)	0.15 [95% CI (0.09, 0.25)]	
p-value	< 0.0001	
Objective Response Rate		
Objective Response, N (%)	8 (9.4)	0 (0)
p-value	0.0504	
Overall Survival (OS)		
Number of Deaths (%)	26 (30.6)	26 (59.1)
Number of Censored Deaths (%)	59 (69.4)	18 (40.9)
Median OS (weeks) (95% CI)	65.6 (53.6, 65.6)	28.6 (17.9, 50.4)
HR (95% CI)	0.36 [95% CI (0.21, 0.62)]	
p-value	0.0004*	

HR=Hazard Ratio; CI=Confidence Interval; NE=Not Estimable
* Statistical significance can't be claimed according to the prespecified testing order. Hypothesis of OS can only be formally tested if the test for ORR is statistically significant

Source: Table 6 in the sponsor's meeting background materials.

SPONSOR QUESTIONS AND FDA RESPONSES

Regulatory

1. **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: The proposed table of contents appears complete except as noted in FDA's response to Question 14. Prior to submission, ensure all hyperlinks, including in the annotated labeling, are functional.

   Deciphera's Email Response on 10/7/19: The Sponsor thanks the FDA for their response. The Sponsor would like to inform the FDA that the comparability protocol as discussed at the EOP2, CMC meeting (dated November 27, 2018) will be submitted post-approval due to a shift in the timing of implementation for the changes proposed (i.e., reassignment of drug product date of manufacturing based upon (b) (4) the tablet manufacturing process).

Discussion During the 10/9/19 Teleconference: FDA stated that Deciphera's proposal is acceptable.

2. **Does the Agency agree that the safety and efficacy data summarized in the briefing package could justify a request for priority review of the planned NDA?**

   FDA Response: Yes; however, the determination of priority review status will be made after review of the justification submitted to the NDA.

   Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

   Discussion During the 10/9/19 Teleconference: No discussion occurred.

Product Quality

3. At the time of NDA submission, Deciphera expects to have primary stability through 12 months of testing for drug substance and 9 months of testing for drug product (as outlined in Table 5). In order to provide a comprehensive data set that will support commercial shelf-life, Deciphera intends to update the drug product stability with results from the 12-month stability time-point at the long-term condition within 90 days after the submission of the original application. We acknowledge the Agency response to the same question (Question 7) documented in the official EOP2, CMC meeting minutes (dated November 28, 2018, reference ID: 4355838). However, since the EOP2, CMC meeting, Fast Track Designation was granted on June 21, 2019 and compelling topline results from the Phase 3 INVICTUS study are available.

   a. **Deciphera is seeking Agency feedback on the proposal to provide 9M drug product data (from 3 production scale registration stability lots) in the initial application followed by a stability update during the NDA review cycle within 90-days of the original application (without impacting the NDA review period/PDUFA date).**

      FDA Response: The proposed timeline is reasonable. While Deciphera indicates 12-month data may be provided 90 days after the original submission, Table 1 of the proposed real-time oncology review (RTOR) timeline provided by Deciphera through an email on September 16, 2019, appears to indicate that the data would be available in about 60 days. FDA may not be able to review data submitted 30 days after the initial NDA submission. Review of the 12-month data will depend upon the extent of the submission and Agency resources. If the Agency is unable to review the 12-month data during the review cycle, FDA will assign the shelf life based on the 9-month data.

Table 1: Drug Product Primary (Registration Batches)

Batch No.	Date of Manufacture[1]	Date (b) (4) (b) (4)	Date Stability Initiated	Earliest Availability of 12-Month Stability Data
18-0320	24Jul2018	28Aug2018	03Jan2019	End Feb. 2020
18-0321	29Jul2018	03Sep2018	03Jan2019	End Feb. 2020
18-0402	21Sep2018	02Oct2018	28Dec2018	End Feb. 2020

The date of manufacture of the tablets is assigned (b) (4) (b) (4)

Deciphera's Email Response on 10/7/19: The Sponsor appreciates the FDA's willingness to accept the NDA with 9 months of drug product stability data. Please note that the availability of the 12-month stability data noted in the table above of the email dated September 16, 2019 was reflective of the earliest availability of the stability data.

Based on the projected 12-month pull date from the stability chambers (end of December 2019) and required testing, the data will not be available for submission in an amendment within 30-days of the initial NDA submission. The Sponsor acknowledges that the FDA might not be able to review the 12-month data during the review cycle and could assign the shelf life based on the 9-month data.

The 12-month stability data will be provided in an amendment as soon as possible after NDA submission based on data availability (*anticipated by end of February 2020*).

Discussion During the 10/9/19 Teleconference: FDA stated that Deciphera's proposal appeared acceptable. FDA reiterated that FDA cannot guarantee review of any information submitted more than 30 days after submission of the original NDA.

b. If the Agency is in agreement with the acceptability of an initial application on the basis of 9M drug product stability data, Deciphera anticipates an NDA submission in December 2019. In this scenario, Deciphera is considering a concurrent approach to process validation for drug product. Based on the ODD (#14- 4474) for ripretinib, does the Agency agree that a concurrent validation is acceptable?

FDA Response: FDA does not object to Deciphera's proposal of a concurrent approach to process validation for the drug product. Although the Agency

does not approve process validation approaches, protocols, or number of specific batches used in process validation studies, FDA encourages Deciphera to submit the process validation protocol and any available data at the time of NDA submission. The actual protocols, acceptance criteria, and study outcomes (as applicable) will be evaluated during an inspection of the manufacturing facilities. The product design and the suitability of manufacturing processes and control strategy will be evaluated during the NDA review cycle. It is Deciphera's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. The process validation protocol should be built on an understanding of the process gathered from experience executing development batches (Process Validation (PV) Stage 1). Subsequent design of the facility and qualification of equipment/utilities and operational performance qualification (PV Stage 2) should be incorporated into the proposed commercial scale manufacturing process and control strategy. Likewise, knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy. Successful process validation should also include a plan for continued process verification (PV Stage 3).

For additional information on process validation, refer to the FDA Guidance for Industry, entitled "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.

For further information on FDA's drug compliance and pre-approval inspection programs, refer to the following links on FDA's website: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm.

Deciphera's Email Response on 10/7/19: The Sponsor appreciates the opportunity to apply a concurrent approach to process validation for the drug product. The Sponsor acknowledges the FDA's preference to receive the PPQ protocol and any available data at the time of the initial NDA submission. Based on current timing, drug product PPQ will not start until the end of January 2020. Although the drug product PPQ protocol will not be available until after NDA submission, information relating to the validation approach will be provided in Module 3.2.P.3.5.

If acceptable to the FDA, the Sponsor commits to submitting the drug product PPQ protocol within 30 days after the initial NDA submission. The protocol will be available at the site during pre-approval inspection.

Discussion During the 10/9/19 Teleconference: FDA stated Deciphera's proposal appeared reasonable. FDA considered the PPQ protocol to be a minor component and submission of the protocol within 30 days after submission of the original NDA will not count as a late submission.

4. Over the course of dissolution method development, Deciphera has comprehensively evaluated method parameters to identify the optimal operating conditions for the dissolution analysis of ripretinib tablets, 50 mg. Subsequently, multiple studies were performed to demonstrate that the dissolution method is adequately sensitive to detect meaningful variations for certain critical manufacturing variables and process parameters. These studies are captured in a method development report which shall be submitted to the IND [as requested by the Agency as an option for seeking feedback as documented in EOP2, CMC meeting minutes (dated November 28, 2018, reference ID: 4355838)] in advance of the pre-NDA meeting.

Deciphera acknowledges that the Agency will require up to 3 months for review of the dissolution method development report. However, if the Agency has had the opportunity to review prior to the pre-NDA meeting does the Agency agree that a) the dissolution method for ripretinib tablets, 50 mg provides sufficient discriminatory capacity and b) that the dissolution method is a suitable and adequate tool for release and stability testing of ripretinib tablets, 50 mg?

FDA Response: The dissolution method development report is under review. FDA's assessment will be completed within 3 months of the August 22, 2019, IND submission. Based on the preliminary review, it appears that Deciphera has not included data to support the discriminatory ability of the method with respect to drug substance particle size distribution. Please submit this data to the IND and include a request for feedback in the cover letter and state that the amendment is part of the dissolution development report. FDA reiterates that the selection of the dissolution sampling time point should be where Q = (b) (4) % dissolution occurs based on the proposed immediate release tablet formulation. Additionally, to set the appropriate dissolution acceptance criterion, FDA recommends that Deciphera collect and report dissolution data at all sampling times (e.g., 5, 10, 15, 20, 30, 40 and 60 minutes) of the primary registration/commercial/stability batches throughout the stability program.

Deciphera's Email Response on 10/7/19: The Sponsor acknowledges the request to submit additional data to support the discriminatory ability of the dissolution method to the IND.

If acceptable to the FDA, the Sponsor proposes to submit the requested information in an amendment to the IND no later than November 1, 2019. Information regarding this request will also be provided in the updated dissolution method development report to be submitted in the NDA.

Discussion During the 10/9/19 Teleconference: FDA agreed with Deciphera's proposal. FDA requested earlier submission if possible. FDA stated that the cover letter should clearly state that the submission is related to the August 22, 2019, amendment and provide the submission type to facilitate routing to the appropriate review discipline.

5. Ripretinib tablets, 50 mg are white to off-white, oval tablets debossed with 'DC1' on one face of the tablet. The 'DC1' debossing serves as a unique identifier for the drug product.

   Does the Agency agree with the use of 'DC1' as the product identifier for ripretinib tablets, 50 mg?

   FDA Response: Yes, FDA agrees with the use of "DC1."

   Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

   Discussion During the 10/9/19 Teleconference: No discussion occurred.

Nonclinical

6. **Does the Agency agree that the nonclinical data package is adequate to support an NDA submission for the proposed indication?**

   FDA Response: Based on the list of studies included in the proposed Table of Contents, the nonclinical data package appears sufficient to support the submission of an NDA.

   Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

   Discussion During the 10/9/19 Teleconference: No discussion occurred.

7. **Deciphera intends to cross-reference IND 125279 for all nonclinical reports in Module 4 using cross-application links. Does the Agency agree with this approach?**

FDA Response: No, FDA does not agree. Submit or resubmit all the nonclinical data to the NDA. FDA recommends that Deciphera include a column in the Tabulated Summaries submitted in the nonclinical sections of Module 2 indicating whether a specific study was previously submitted to the IND.

Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: Please refer to the discussion under the **DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION** section below.

Clinical

8. **Does the Agency agree that the data from Phase 3 registration Study, DCC-2618-03-001 together with the data from the supportive Study, DCC-2618-01-001 are adequate to substantiate the efficacy and safety of ripretinib and support filing of the NDA for a full approval of the proposed indication?**

FDA Response: Based on the information provided, the proposed data from the registration trial and the supportive study appear adequate to support filing of the NDA.

Please confirm that the proposed NDA will contain a mock-up define file to show the variables that will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRR-determined PFS events or censoring, and variables for subgroup analyses, etc. Variables used for sensitivity analyses in the statistical analysis plan should also be included.

Please include in the submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, and (c) SAS programs by which the derived variables were produced from the raw variables.

Deciphera's Email Response on 10/7/19: The Sponsor confirms that the proposed NDA will contain a mock-up define file to show the variables that will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRR-determined PFS events or censoring, and variables for subgroup analyses, etc. Variables used for sensitivity analyses in the statistical analysis plan will also be included. Additionally, the Sponsor confirms that the SAS programs that produced all the efficacy results, all raw as well as derived variables in.xpt format, and SAS programs by which the derived variables were produced from the raw variables will be included in the NDA submission.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

9. **Does the Agency agree with the safety analyses planned for the NDA submission?**

FDA Response: FDA agrees with the overall safety analyses planned for inclusion in the NDA submission. FDA advises Deciphera that while it is acceptable to submit analyses of "drug-related TEAEs", for the purpose of labeling, FDA will consider all TEAEs regardless of assigned attribution.

Clarify how patients enrolled into the INVICTUS Study who crossed over and received at least 1 dose of ripretinib will be identified in the ISS dataset.

Deciphera's Email Response on 10/7/19: The crossed over patients from the placebo arm who received at least 1 dose of ripretinib in the open label period of the INVICTUS Study will be identified by the variable in the integrated ADSL dataset which represents the actual treatment arm in the INVICTUS study.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

10. **Does the Agency agree with the efficacy analyses planned for the NDA submission?**

FDA Response: No. Section 3.4.2 of the meeting package stated that the number of PFS events required to conduct the planned analysis for the study were 90 events and the study had reached these events in May 2019. However, in Table 6 in the meeting package, the total number of events reported was 88. Please explain this discrepancy. In the NDA submission, Deciphera should submit the correct dataset with the planned number of events. If the number of events in the dataset submitted for the NDA does not include the planned number of events, this will be a review issue and the O'Brien-Fleming method will be applied to recalculate the alpha level instead of using the pre-specified significance level.

FDA notes that the pooling of the two study populations proposed for the ISE may not be appropriate due to potential population heterogeneity; therefore, these analyses will be considered exploratory.

Deciphera's Email Response on 10/7/19: The Sponsor acknowledges the FDA's feedback. At the time of the data cutoff of the INVICTUS Study database (May 31, 2019), the count of PFS events was 92. During the data cleaning period between May 31, 2019 and Aug 9, 2019, four patients of the 92 who had PFS event were identified to have received new anti-cancer therapy or surgery before the PFS event occurred. Hence, these four patients were censored for PFS according to the pre-specified PFS censoring rules in the SAP. Therefore, there

are 88 events in the primary PFS analysis which will be submitted in the NDA. Censored events with the reason for censoring will be also included in the datasets. Since the PFS results are highly significant ($p<0.0001$), the testing for PFS will still be statistically significant after applying O'Brien-Fleming method.

Discussion During the 10/9/19 Teleconference: FDA stated that Deciphera's response was acceptable. FDA reiterated that Deciphera should use the O'Brien-Fleming method.

(FDA original response continued) FDA notes that the pooling of the two study populations proposed for the ISE may not be appropriate due to potential population heterogeneity; therefore, these analyses will be considered exploratory.

Deciphera's Email Response on 10/7/19: The Sponsor acknowledges the FDA's feedback that the pooling of the two patient populations is not appropriate. The Sponsor will not include the planned ISE datasets and the pooled analyses of ORR and DOR in the Module 2.7.3 [Summary of Clinical Efficacy (SCE)]. The Sponsor still plans to present the side-by-side data of the endpoints, PFS, ORR, and DOR from the INVICTUS Study and the Phase 1 Study, DCC-2618-01-001 in the SCE.

Discussion During the 10/9/19 Teleconference: FDA clarified that FDA would prefer to receive the ISE dataset for the purpose of conducting exploratory analyses, even though it will not be used for the primary analysis or in support of labeling claims.

11. **Does the Agency concur with the revised proposal regarding patient safety narratives criteria for inclusion in the NDA submission?**

FDA Response: Yes.

Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

12. **Does the Agency agree to the proposed data cutoff, content and format of the 120-day safety update and timing of the submission in the case of priority review?**

FDA Response: FDA agrees with the proposed data cutoff, content, and format of the 120-day (90-day if priority review) safety update. Typically, the 90-day safety update is submitted approximately 90 days after the original NDA submission; however, FDA will accept this update early if Deciphera chooses. The safety update, in addition to cumulative safety information, should include a flag in the safety datasets indicating the newly recorded events.

FDA does not agree with the proposed submission of an updated label (Sections 5 and 6). An updated label should only be submitted if the safety update changes the overall safety profile of ripretinib in a meaningful way.

Although FDA agrees with the proposed data cut-off date of August 31, 2019, FDA expects that Deciphera will notify FDA of any notable new safety issues (e.g., death due to toxicity that arises at any time during the review).

Deciphera's Email Response on 10/7/19: The Sponsor acknowledges and accepts the FDA's requests. The Sponsor will provide a listing of safety information including death and SAEs that occur after August 31, 2019 in the Module 2.7.4 addendum as part of the safety update.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

Clinical Pharmacology

13. **Does the Agency agree with the plans to evaluate excretion and metabolism of ripretinib and its metabolites in the absence of an AME study?**

FDA Response: Yes, Deciphera's plan appears acceptable.

Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

14. **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 ripretinib for the proposed indication?**

FDA Response: FDA has the following concerns regarding the proposed plan:

a. Dose adjustments for concomitant use with CYP3A inhibitors and organ impairment need to be based on drug interaction trials or dedicated organ impairment trials (and population PK analysis for organ impairment) and not based on exposures achieved in the concentration QT analyses. In a response to the current meeting, provide a summary of how many patients within each hepatic (using NCI-ODWG criteria) and renal impairment category are planned to be included in the population PK analysis to be submitted in the initial NDA submission. Submit the study reports for the dedicated renal and hepatic impairment trials within the original NDA submission to allow for adequate dose adjustment and labeling recommendations in these patient populations with different degrees of organ impairment.

Deciphera's Email Response on 10/7/19: The Sponsor agrees that dose adjustments for concomitant use with CYP3A inhibitors and organ impairment should be based on results from drug interaction trials or dedicated organ impairment trials (and population PK analysis for organ impairment).
The population PK analysis is currently ongoing and will be included in the initial NDA submission. A preliminary summary of the patients with hepatic and renal impairment at baseline that will be included in the population PK analysis (study DCC-2618-01-001 and DCC-2618-01-003 combined) is presented in *[Table 1 and Table 2]*.

Table 1: Preliminary Summary of Patients with Hepatic Impairment included in PopPK Analysis

Covariate	Hepatic Function Groups	No. of Patients (N = 350)
Hepatic Impairment Category (using NCI-ODWG criteria)	Normal	257 (73.4%)
	Mild	91 (26.0%)
	Moderate	2 (0.571%)

Note: Baseline total bilirubin & AST were used to define hepatic function groups

Table 2: Preliminary Summary of Patients with Renal Impairment included in PopPK Analysis

Covariate	Renal Function Groups	No. of Patients (N = 350)
Renal Impairment Category	Normal (CrCl ≥90 mL/min)	178 (50.9%)
	Mild impairment (60 ≤ CrCl < 90 mL/min)	112 (32.0%)
	Moderate impairment (30 ≤ CrCl < 60 mL/min)	54 (15.4%)
	Severe impairment (15 ≤ CrCl < 30 mL/min)	4 (1.14%)
	Unknown[a]	2 (0.571%)

Note: Baseline creatinine clearance was used to define renal function groups.
a The baseline creatinine clearance of two patients are missing.

The dedicated hepatic impairment study (DCC-2618-01-004) in mild and moderate (and possibly severe) hepatic impairment is currently ongoing. As of October 7, 2019, 8 subjects with mild hepatic impairment have been enrolled and treated. In October 2019, the Investigators participating in this study and the Sponsor plan to review safety data for the mild impairment group and decide if the safety data is sufficient to proceed with enrolling subjects with moderate hepatic impairment. The PK results from the mild and moderate hepatic impairment groups in this study are anticipated to be available in March 2020. At that time, a decision will be made whether to enroll the severe hepatic impairment group, as outlined in the protocol.

The dedicated renal impairment cohort of study DCC-2618-01-001 (creatinine clearance between 20 and 50 mL/min) is currently ongoing. As of October 7, 2019, 8 patients have been enrolled in this cohort. The PK results for patients with moderate and severe renal impairment in this study are anticipated to be available in March 2020.

The Sponsor believes that the planned analyses to be included in the initial NDA submission will provide sufficient data to guide dose adjustments based on organ function. Proposed labeling will be limited to organ impairment categories that have sufficient PK and/or safety data at the time of the initial NDA.

Discussion During the 10/9/19 Teleconference: FDA stated that Deciphera's proposals were acceptable.

b. The proposal to submit planned drug interaction trials and PBPK modeling subsequent to a potential initial approval is not acceptable, as this will not allow for adequate dose adjustment recommendations in labeling. Submit protocols for the proposed drug interaction trials needed based on in vitro screens for FDA review prior to their initiation and initiate these trials as soon as possible.

Deciphera's Email Response on 10/7/19: The Sponsor acknowledges the FDA's request and agrees to submit the protocols for the proposed drug interaction trials based upon in vitro screens for FDA review as soon as possible. One drug interaction study has already been completed and two drug interaction studies are currently planned as listed below:

- The ripretinib drug interaction study DCC-2618-01-004 evaluated the effects of pantoprazole (a proton pump inhibitor) and itraconazole (a strong CYP3A inhibitor). This study has been completed and will be included in the initial NDA submission.

(b) (4)

(b) (4)

Discussion During the 10/9/19 Teleconference: FDA acknowledged Deciphera's proposals. FDA stated that the adequacy of the proposed drug-drug interaction potential data to permit for dose adjustments in labeling would be a review issue. FDA clarified that incomplete drug interaction characterization at the time of original NDA submission would not preclude filing.

c. The proposal to submit the proposed PBPK modeling data subsequent to an initial approval is not acceptable. Submit a summary of the plan and objectives of the PBPK modeling for FDA comment within 30 days of the current meeting and submit the modeling data as part of the initial NDA submission.

Deciphera's Email Response on 10/7/19: The Sponsor plans to evaluate the effect of ripretinib as a potential inhibitor of various CYP substrates including a clinical evaluation of the potential inhibitory effect of ripretinib on the most sensitive CYP substrate (CYP2C8), consistent with FDA Guidance for Clinical Drug Interaction Studies. Other less sensitive substrates 2C9, 2C19 and 2D6 probes may be evaluated in the clinical study. Alternatively, PBPK modeling may be conducted to address the other probe substrates only as needed, depending upon the magnitude of inhibitory effector on the CYP2C8 probe substrate. If PBPK modeling is needed, the in vivo drug interaction data will be used to optimize model parameters and specific details will be included in a PBPK modeling plan.

The Sponsor will provide an outline of the study design (i.e. either cocktail approach that includes 2C8, 2C9, 2C19 and 2D6 or CYP2C8 alone followed by PBPK modeling) in the initial NDA submission.

Discussion During the 10/9/19 Teleconference: FDA stated that Deciphera should submit a detailed proposal for the PBPK analysis and rationale for conducting it for FDA's feedback as soon as possible and prior to the original NDA submission.

d. Concentration-QTc analysis based on study DCC-2618-01-001 appears reasonable to characterize the effect of ripretinib on the QTc interval at the

proposed therapeutic dose. Whether the data would be adequate to exclude a large mean increase (i.e. >20 ms) on the QTc interval is a review issue. See additional Clinical Pharmacology comments below.

Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

ADDITIONAL COMMENTS

Regulatory

15. FDA agrees with Deciphera's September 23, 2019, proposed RTOR submission plan content and timelines, except as noted above in Question 12 regarding the 90-day safety update. After further internal discussions, FDA agrees that Deciphera may submit any other data early as Deciphera wishes as described in the September 23, 2019, proposal. FDA may review these components early as time permits.

Deciphera's Email Response on 10/7/19: The Sponsor thanks the FDA for their response. The Sponsor would like to inform that the timelines for submission of the following NDA components under RTOR have shifted:

- ISS datasets and documentation submission: November 25, 2019
- PK report for Phase 1 Study: November 29, 2019
- Module 2.7.4 (SCS): December 13, 2019

Discussion During the 10/9/19 Teleconference: FDA stated that Deciphera's proposed revised timelines were acceptable.

Post-Meeting Addendum*: On October 24, 2019, Deciphera submitted a revised RTOR submission plan, which included the following revisions:*

- *Addition of bioanalytical and PK method validation reports to the November 8, 2019 submission*
- *ISE datasets submission timeline has been shifted from November 25, 2019 to December 13, 2019*
- *Population pharmacokinetics and exposure-response analyses reports submission timeline has been shifted from November 29, 2019 to December 13, 2019*

FDA found this revised RTOR submission plan acceptable.

Clinical Pharmacology

16. Provide the following information in the concentration-QTc study report:

    a. the number of subjects at each dose level and in each study cohort;

    b. the ECG sampling schedule relative to the last dose in the dose expansion cohort; and

    c. justification for pooling data from the dose escalation and dose expansion cohorts in the presence of differences in ECG acquisition and baseline selection.

    Deciphera's Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

    Discussion During the 10/9/19 Teleconference: No discussion occurred.

17. When Deciphera submits the QT assessment report, please include the following items:

    a. Clinical study report

    b. Statistical analysis plan

    c. Clinical study protocol

    d. Investigator's brochure

    e. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (https://www.fda.gov/media/129685/download)

    f. Annotated case report form

    g. A data definition file which describes the contents of the electronic data sets

    h. Electronic data set. The QT-IRT has updated the specification on how data sets should be submitted. These specifications are posted at the FDA Study Data Standards Resources webpage under 'Technical Guides'. Please refer to the QT Technical Specifications (https://www.fda.gov/media/128187/download) before submitting reports for QT studies.

i. Adverse Event analysis using the MedDRA SMQ “Torsade de pointes/QT Prolongation” and include the preferred term “Seizure” by treatment and dose level.

j. Narrative summaries and case report forms for any
   i. Deaths possibly related to cardiac toxicity
   ii. Serious adverse events (cardiac)
   iii. Episodes of ventricular tachycardia or fibrillation
   iv. Episodes of syncope
   v. Episodes of seizure
   vi. Adverse events (cardiac) resulting in the subject discontinuing from the study

k. Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

Deciphera’s Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

18. FDA is also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

Deciphera’s Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

19. Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).

Deciphera’s Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred.

20. Please see the QT-IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt) for up-to-date links to relevant guidances and select references to consider for QT evaluation.

Deciphera’s Email Response on 10/7/19: The Sponsor has no further comments and thanks the FDA for their response.

Discussion During the 10/9/19 Teleconference: No discussion occurred

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Discussion During the 10/9/19 Teleconference: FDA and Deciphera agreed to conduct the review using the Assessment Aid and Real Time Oncology Review (RTOR) pilots. Decision regarding participation in the Project Orbis pilot is pending and depends upon agreement from Australian and Canadian regulatory authorities.

FDA stated that if an agreement is reached, and this NDA will be reviewed under Project Orbis, a separate assessment aid for the Chemistry, Manufacturing and Controls (CMC) portion may be needed. In such case, FDA will communicate this information along with the CMC assessment aid template to Deciphera. FDA stated that an example of a completed CMC assessment aid is not available. FDA stated that the submission of the CMC assessment aid could potentially occur after the initial NDA submission; however, FDA requested Deciphera to provide timing of the planned submission of the CMC assessment aid as soon as possible after receipt of the template. FDA clarified that there is no page limit to the CMC assessment aid.

FDA stated that an informal teleconference could be scheduled to discuss the specifics once the decision regarding Project Orbis is made.

Deciphera asked whether an early application orientation meeting should be considered for this application. FDA stated that an early application orientation meeting is not needed and clarified that the timing of the application orientation meeting would not affect the review. FDA stated that the application orientation meeting will be scheduled based on availability. Deciphera asked whether the FDA considered participation in these pilots to be material information of interest to shareholders; FDA declined to comment.

The content of a complete application was discussed. The summary of the discussion and agreements are represented below.

Proposed Submission	Proposed Submission Component	Deciphera Proposed Date*	Agreed Upon Date
1	Module 3 (Quality) • 3.2.S.2.1 & 3.2.P.3.1 (Manufacturers) • *Establishment information*[a]	10/25/19 or earlier	10/25/19 or earlier
2	Portion of Module 1 • Field copy certification, debarment certification, financial certification and disclosure information, patent information, statements of claimed exclusivity, letter of authorization(s), environmental assessment	11/8/19	11/8/19
	Module 5.3.1.2		

	• Complete Clinical Pharmacology Phase 1 Study, DCC-2618-01-002 CSR • Datasets and documentation *Module 5.3.1.4*[a] *Bioanalytical Reports and PK Method Validation reports* Module 5.3.5 • Phase 1 Study (DCC-2618-01-001) and Phase 3 Study (DCC-2618-03-001; INVICTUS) datasets & documentation • Full BIMO datasets (Phase 1 and Phase 3) & OSI package Module 5.3.5.2 • Complete Phase 1 Study (DCC-2618-01-001) CSR without the PK report		
3	Module 1.14 • Draft Carton and Container Label • Draft Labeling Text (Word and SPL format) Module 4 and Module 2 (Nonclinical) • Nonclinical Study Reports will be submitted in Module 4 as per the proposal included in the pre-NDA meeting package (submitted on September 9, 2019 as SN 0211). Reports that were not previously submitted to the IND will be submitted in this rolling submission • Modules 2.6.1, 2.6.2, 2.6.3, 2.6.4, and 2.6.5 Draft Modules 2.4, 2.6.6, and 2.6.7 (without some hyperlinks) Module 5.3.5.1 Complete INVICTUS Study CSR	11/19/19	11/19/19 (Decipher a clarified that all nonclinical data will be submitted to the NDA)
4	Module 5.3.5.3 • ISS datasets	11/25/19	11/25/19
5	Module 2 (Clinical) (without all hyperlinks) • 2.7.3 (SCE) and 2.7.1 (SBP) Module 5.3.3.4 • Clinical Pharmacology Phase 1 Study, DCC-2618-01-003 CSR (without some hyperlinks and appendices) • Datasets and documentation Module 5.3.3.2 • Phase 1 Study (DCC-2618-01-001) CSR with the hyperlink to the PK report	11/29/19	11/29/19
6	Remaining Module 1 documents Module 2 Clinical Summaries • 2.5 (CO), 2.7.2 (SCP), and 2.7.4 (SCS) • 2.7.3 (SCE) and 2.7.1 (SBP) (complete with all hyperlinks) Module 3 and Module 2 (Quality) Module 4 and Module 2 (Nonclinical) • Final Study Report for Study DCC-2618-04-0014 (In Vitro Phototoxicity Assessment of DCC-2618 in Balb/c 3T3 Mouse Fibroblasts) • Modules 2.4, 2.6.6, and 2.6.7 (complete with all	12/13/19	12/13/19

	hyperlinks) Module 5.3.3.4 • Complete Clinical Pharmacology Phase 1 Study, DCC-2618-01-003 CSR (with all hyperlinks and appendices) *Module 5.3.3.5*[a] • *Population Pharmacokinetic (PopPK) datasets and Analysis Report* • *Exposure-Response (E-R) datasets and Analysis Report* *Module 5.3.5.3*[a] • *ISE datasets* Assessment Aid		
Process Validation Protocol[a]		*1/12/20*	*1/12/20*
Stability Update (12 months stability)		Anticipated by end of Feb 2020	by end of Feb 2020
90 Day Safety Update • Module 2.7.4 addendum • Module 5.3.5 o Cumulative datasets and documentation for Phase 1 Study (DCC-2618-01-001) and INVICTUS Study o Any additional narratives and CRFs • Module 5.3.5.3 o ISS datasets and appendices		3/12/20	3/12/20

[a]*Post-Meeting Addendum based on Deciphera's revised RTOR submission plan received 10/24/19*

The application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

It was concluded that at this time, a REMS submission is not required to file the application. FDA will determine the need for a REMS during the review of the NDA.

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).

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 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 contain the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Since ripretinib was granted orphan drug designation for treatment of GIST (Designation No.: 14-4474 on October 4, 2014, the planned NDA submission (prior to August 18, 2020) for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib, is exempt from the requirements of PREA. In the NDA, please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions). If there are any changes to the development plans that would cause the application to trigger PREA, this exempt status would change.

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 Information[1] and Pregnancy and Lactation Labeling Final Rule[2] 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

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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*.

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.[3]

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.[4]

[3] http://www.fda.gov/ectd
[4] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

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* (February 2018) and the associated *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*.[5]

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

None

[5] https://www.fda.gov/media/85061/download

ATTACHMENTS AND HANDOUTS

- Document tiled “20191024 Ripretinib Final NDA Submission Plan (RTOR),” received via email on 10/24/19 post pre-NDA meeting
- Document titled “20191007 Ripretinib Revised NDA Submission Plan (RTOR),” received via email on 10/7/19
- Document titled “20191007 Deciphera Responses to FDA Preliminary Comments_Pre-NDA Meeting,” received via email on 10/7/19

Reference is made to the Type B, pre-NDA meeting (teleconference) held with the FDA on October 9, 2019 to discuss the planned NDA submission for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. As agreed at the pre-NDA meeting, Deciphera is providing the final NDA submission plan (see Table 1). The post-initial NDA submission updates are summarized in Table 2.

Following the teleconference with the FDA, Deciphera has made following revisions to the submission plan:

- Addition of bioanalytical and PK method validation reports to the November 8th submission
- ISE datasets submission date has been shifted from November 25th to December 13th
- Population pharmacokinetics and exposure-response analyses reports submission date has been shifted from November 29th to December 13th

Table 1: Ripretinib (DCC-2618) - Final NDA Submission Plan (RTOR)

Submission	Modules	Sponsor Proposed Submission Date
1	**Module 3 (Quality)** • 3.2.S.2.1 & 3.2.P.3.1 (Manufacturers) • Establishment information	October 25, 2019
2	**Portion of Module 1** • Field copy certification, debarment certification, financial certification and disclosure information, patent information, statements of claimed exclusivity, letter of authorization(s), environmental assessment	November 8, 2019
	Module 5.3.1.2 • Complete Clinical Pharmacology Phase 1 Study, DCC-2618-01-002 CSR • Datasets and documentation	
	Module 5.3.1.4 Bioanalytical Reports and PK Method Validation reports	

Submission	Modules	Sponsor Proposed Submission Date
	Module 5.3.5 • Phase 1 Study (DCC-2618-01-001) and Phase 3 Study (DCC-2618-03-001; INVICTUS) datasets & documentation • Full BIMO datasets (Phase 1 and Phase 3) & OSI package	
	Module 5.3.5.2 • Phase 1 Study (DCC-2618-01-001) CSR without the PK report	
3	**Module 1.14** • Draft Carton and Container Label • Draft Labeling Text (Word and SPL format)	November 19, 2019
	Module 4 and Module 2 (Nonclinical) • Nonclinical Study Reports • Modules 2.6.1, 2.6.2, 2.6.3, 2.6.4, and 2.6.5 • Draft Modules 2.4, 2.6.6, and 2.6.7 (without some hyperlinks)[a]	
	Module 5.3.5.1 Complete INVICTUS Study CSR	
4	**Module 5.3.5.3** ISS datasets	November 25, 2019
5	**Module 2 (Clinical) (without some hyperlinks)** • 2.7.3 (SCE) and 2.7.1 (SBP)	November 29, 2019
	Module 5.3.3.4 • Clinical Pharmacology Phase 1 Study, DCC-2618-01-003 CSR (without some hyperlinks and appendices) • Datasets and documentation	

Submission	Modules	Sponsor Proposed Submission Date
	Module 5.3.5.2 • Phase 1 Study (DCC-2618-01-001) PK report and CSR with the hyperlink to the PK report	
6	**Remaining Module 1 documents**	December 13, 2019
	Module 2 Clinical Summaries • 2.5 (CO), 2.7.2 (SCP), and 2.7.4 (SCS) • 2.7.3 (SCE) and 2.7.1 (SBP) (complete with all hyperlinks)	
	Module 3 and Module 2 (Quality)	
	Module 4 and Module 2 (Nonclinical) • Final Study Report for Study DCC-2618-04-0014 (*In Vitro* Phototoxicity Assessment of DCC-2618 in Balb/c 3T3 Mouse Fibroblasts) • Modules 2.4, 2.6.6, and 2.6.7 (complete with all hyperlinks)	
	Module 5.3.3.4 • Complete Clinical Pharmacology Phase 1 Study, DCC-2618-01-003 CSR (with all hyperlinks and appendices)	
	Module 5.3.3.5 • Population Pharmacokinetic (PopPK) datasets and Analysis Report • Exposure-Response (E-R) datasets and Analysis Report	
	Module 5.3.5.3 ISE datasets	
	Assessment Aid	

Abbreviations: BIMO=Bioresearch Monitoring Program; CO=Clinical Overview; CSR=Clinical Study Report; ISE=Integrated Summary of Efficacy; ISS=Integrated Summary of Safety; PK=Pharmacokinetics; OSI=Office of Scientific Investigations; SBP=Summary of Biopharmaceutic Studies and Associated Analytical Methods; SCE=Summary of Clinical Efficacy; SCP=Summary of Clinical Pharmacology Studies; SCS=Summary of Clinical Safety

a. Drafts of modules 2.4, 2.6.6, and 2.6.7 is planned to be submitted on November 19, 2019 as the final study report for Study DCC-2618-04-0014 (*In Vitro* Phototoxicity Assessment of DCC-2618 in Balb/c 3T3 Mouse Fibroblasts) will not be available until December 2019. In the draft modules, the hyperlinks to the aforementioned study report will not be active; the final modules will have all hyperlinks active.

Table 2: Post-Initial NDA Submission Updates

Modules and Documents	Sponsor Anticipated Submission date
Module 3 – 30 Day Update • Process Validation Protocol	January 12, 2020
Module 3 • Stability Update (12 months stability)	Anticipated by end of February 2020

Module 2 and 5 - 90 Day Safety Update
• Module 2.7.4 addendum
• **Module 5.3.5.1 and 5.3.5.2**
  ○ Cumulative datasets and documentation for Phase 1 Study (DCC-2618-01-001) and INVICTUS Study
  ○ Any additional narratives and CRFs
• **Module 5.3.5.3**
  ○ ISS datasets and appendices
	March 12, 2020

Abbreviations: CRF=Case Report Forms; ISS=Integrated Summary of Safety

Deciphera has proposed the revised NDA submission plan (see Table 1) in preparation of the pre-NDA meeting (teleconference) with the FDA scheduled on October 9, 2019. Deciphera requests Agency's feedback and agreement on the proposed revised NDA submission plan for the RTOR pilot.

Table 1: Ripretinib (DCC-2618) - Revised Proposed Submission NDA Plan

Submission	Modules	Sponsor Proposed Submission Date
1	**Module 3 (Quality)** • 3.2.S.2.1 & 3.2.P.3.1 (Manufacturers)	October 25 or earlier
2	**Portion of Module 1** • Field copy certification, debarment certification, financial certification and disclosure information, patent information, statements of claimed exclusivity, letter of authorization(s), environmental assessment	November 8, 2019
	Module 5.3.1.2 • Complete Clinical Pharmacology Phase 1 Study, DCC-2618-01-002 CSR • Datasets and documentation	
	Module 5.3.5 • Phase 1 Study (DCC-2618-01-001) and Phase 3 Study (DCC-2618-03-001; INVICTUS) datasets & documentation • Full BIMO datasets (Phase 1 and Phase 3) & OSI package	
	Module 5.3.5.2 • Phase 1 Study (DCC-2618-01-001) CSR without the PK report	
3	**Module 1.14** • Draft Carton and Container Label • Draft Labeling Text (Word and SPL format)	November 19, 2019
	Module 4 and Module 2 (Nonclinical) • Nonclinical Study Reports will be submitted in Module 4 as per the proposal included in the pre-NDA meeting package (submitted on September 9, 2019 as SN 0211). Reports that were not previously submitted to the IND will be submitted in this rolling submission • Modules 2.6.1, 2.6.2, 2.6.3, 2.6.4, and 2.6.5 • Draft Modules 2.4, 2.6.6, and 2.6.7 (without some hyperlinks)[a]	

Reference is made to IND 125279 and the preliminary FDA responses (dated October 4, 2019) to Deciphera's pre-NDA meeting questions submitted on August 8, 2019 as part of the Type B, pre-NDA meeting request to discuss the planned submission of a New Drug Application (NDA) for ripretinib for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib. Deciphera thanks the FDA for their preliminary responses and provides responses to FDA's feedback below.

Deciphera's pre-NDA meeting questions and FDA's preliminary responses are in *italic text* and Deciphera's responses are provided in plain text.

Regulatory

1. 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*: The proposed table of contents appears complete except as noted in FDA's response to Question 14. Prior to submission, ensure all hyperlinks, including in the annotated labeling, are functional.*

Deciphera Response: The Sponsor thanks the FDA for their response. The Sponsor would like to inform the FDA that the comparability protocol as discussed at the EOP2, CMC meeting (dated November 27, 2018) will be submitted post-approval due to a shift in the timing of implementation for the changes proposed (i.e., reassignment of drug product date of manufacturing based upon (b) (4) (b) (4) the tablet manufacturing process).

2. Does the Agency agree that the safety and efficacy data summarized in the briefing package could justify a request for priority review of the planned NDA?

FDA Response*: Yes; however, the determination of priority review status will be made after review of the justification submitted to the NDA.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

Product Quality

3. At the time of NDA submission, Deciphera expects to have primary stability through 12 months of testing for drug substance and 9 months of testing for drug product (as outlined in Table 5). In order to provide a comprehensive data set that will support commercial shelf-life, Deciphera intends to update the drug product stability with results from the 12-month stability time-point at the long- term condition within 90 days after the submission of the original application. We acknowledge the Agency

response to the same question (Question 7) documented in the official EOP2, CMC meeting minutes (dated November 28, 2018, reference ID: 4355838). However, since the EOP2, CMC meeting, Fast Track Designation was granted on June 21, 2019 and compelling topline results from the Phase 3 INVICTUS study are available.

a. Deciphera is seeking Agency feedback on the proposal to provide 9M drug product data (from 3 production scale registration stability lots) in the initial application followed by a stability update during the NDA review cycle within 90-days of the original application (without impacting the NDA review period/PDUFA date).

***FDA Response**: The proposed timeline is reasonable. While Deciphera indicates 12-month data may be provided 90 days after the original submission, Table 1 of the proposed real-time oncology review (RTOR) timeline provided by Deciphera through an email on September 16, 2019, appears to indicate that the data would be available in about 60 days. FDA may not be able to review data submitted 30 days after the initial NDA submission. Review of the 12-month data will depend upon the extent of the submission and Agency resources. If the Agency is unable to review the 12- month data during the review cycle, FDA will assign the shelf life based on the 9-month data.*

Table 1: Drug Product Primary (Registration Batches)

Batch No.	Date of Manufacture[1]	Date (b) (4) (b) (4)	Date Stability Initiated	Earliest Availability of 12-Month Stability Data
18-0320	24Jul2018	28Aug2018	03Jan2019	End Feb. 2020
18-0321	29Jul2018	03Sep2018	03Jan2019	End Feb. 2020
18-0402	21Sep2018	02Oct2018	28Dec2018	End Feb. 2020

The date of manufacture of the tablets is assigned (b) (4) (b) (4)

Deciphera Response: The Sponsor appreciates the FDA's willingness to accept the NDA with 9 months of drug product stability data. Please note that the availability of the 12-month stability data noted in the table above of the email dated September 16, 2019 was reflective of the *earliest* availability of the stability data.

Based on the projected 12-month pull date from the stability chambers (end of December 2019) and required testing, the data will not be available for submission in an amendment within 30-days of the initial NDA submission. The Sponsor acknowledges that the FDA might not be able to review the 12-month data during the review cycle and could assign the shelf life based on the 9-month data.

The 12-month stability data will be provided in an amendment as soon as possible after NDA submission based on data availability (*anticipated by end of February 2020*).

b. If the Agency is in agreement with the acceptability of an initial application on the basis of 9M drug product stability data, Deciphera anticipates an NDA submission in December 2019. In this scenario, Deciphera is considering a concurrent approach to process validation for drug product. Based on the ODD (#14- 4474) for ripretinib, does the Agency agree that a concurrent validation is acceptable?

FDA Response*: FDA does not object to Deciphera's proposal of a concurrent approach to process validation for the drug product. Although the Agency does not approve process validation approaches, protocols, or number of specific batches used in process validation studies, FDA encourages Deciphera to submit the process validation protocol and any available data at the time of NDA submission. The actual protocols, acceptance criteria, and study outcomes (as applicable) will be evaluated during an inspection of the manufacturing facilities. The product design and the suitability of manufacturing processes and control strategy will be evaluated during the NDA review cycle. It is Deciphera's responsibility to conduct all studies necessary to assure that the commercial manufacturing process is capable of consistently delivering quality product. FDA requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] but does not prescribe how that is to be accomplished as it will depend on multiple factors, some of which are specific to the complexity of the product and process. The process validation protocol should be built on an understanding of the process gathered from experience executing development batches (Process Validation (PV) Stage 1). Subsequent design of the facility and qualification of equipment/utilities and operational performance qualification (PV Stage 2) should be incorporated into the proposed commercial scale manufacturing process and control strategy. Likewise, knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy. Successful process validation should also include a plan for continued process verification (PV Stage 3).*

For additional information on process validation, refer to the FDA Guidance for Industry, entitled "Guidance for Industry, Process Validation: General Principles and Practices" posted at the following link. *http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070336.pdf.*

For further information on FDA's drug compliance and pre-approval inspection programs, refer to the following links on FDA's website: *http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm252671.htm.*

Deciphera Response: The Sponsor appreciates the opportunity to apply a concurrent approach to process validation for the drug product. The Sponsor acknowledges the FDA's preference to receive the PPQ protocol and any available data at the time of the initial NDA submission. Based on current timing, drug product PPQ will not start until the end of January 2020. Although the drug product PPQ protocol will not be available until after NDA submission, information relating to the validation approach will be provided in Module 3.2.P.3.5.

If acceptable to the FDA, the Sponsor commits to submitting the drug product PPQ protocol within 30 days after the initial NDA submission. The protocol will be available at the site during pre-approval inspection.

4. *Over the course of dissolution method development, Deciphera has comprehensively evaluated method parameters to identify the optimal operating conditions for the dissolution analysis of ripretinib tablets, 50 mg. Subsequently, multiple studies were performed to demonstrate that the dissolution method is adequately sensitive to detect meaningful variations for certain critical manufacturing variables and process parameters. These studies are captured in a method development report which shall be submitted to the IND [as requested by the Agency as an option for seeking feedback as documented in EOP2, CMC meeting minutes (dated November 28, 2018, reference ID: 4355838)] in advance of the pre-NDA meeting.*

Deciphera acknowledges that the Agency will require up to 3 months for review of the dissolution method development report. However, if the Agency has had the opportunity to review prior to the pre-NDA meeting does the Agency agree that a) the dissolution method for ripretinib tablets, 50 mg provides sufficient discriminatory capacity and b) that the dissolution method is a suitable and adequate tool for release and stability testing of ripretinib tablets, 50 mg?

FDA Response*: The dissolution method development report is under review. FDA's assessment will be completed within 3 months of the August 22, 2019, IND submission. Based on the preliminary review, it appears that Deciphera has not included data to support the discriminatory ability of the method with respect to drug substance particle size distribution. Please submit this data to the IND and include a request for feedback in the cover letter and state that the amendment is part of the dissolution development report. FDA reiterates that the selection of the dissolution sampling time point should be where Q =* (b) (4) *% dissolution occurs based on the proposed immediate release tablet formulation. Additionally, to set the appropriate dissolution acceptance criterion, FDA recommends that Deciphera collect and report dissolution data at all sampling times (e.g., 5, 10, 15, 20, 30, 40 and 60 minutes) of the primary registration/commercial/stability batches throughout the stability program.*

Deciphera Response: The Sponsor acknowledges the request to submit additional

data to support the discriminatory ability of the dissolution method to the IND.

If acceptable to the FDA, the Sponsor proposes to submit the requested information in an amendment to the IND no later than November 1, 2019. Information regarding this request will also be provided in the updated dissolution method development report to be submitted in the NDA.

5. *Ripretinib tablets, 50 mg are white to off-white, oval tablets debossed with 'DC1' on one face of the tablet. The 'DC1' debossing serves as a unique identifier for the drug product.*

Does the Agency agree with the use of 'DC1' as the product identifier for ripretinib tablets, 50 mg?

FDA Response*: Yes, FDA agrees with the use of "DC1."*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

Nonclinical

6. ***Does the Agency agree that the nonclinical data package is adequate to support an NDA submission for the proposed indication?***

FDA Response*: Based on the list of studies included in the proposed Table of Contents, the nonclinical data package appears sufficient to support the submission of an NDA.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

7. ***Deciphera intends to cross-reference IND 125279 for all nonclinical reports in Module 4 using cross-application links. Does the Agency agree with this approach?***

FDA Response*: No, FDA does not agree. Submit or resubmit all the nonclinical data to the NDA. FDA recommends that Deciphera include a column in the Tabulated Summaries submitted in the nonclinical sections of Module 2 indicating whether a specific study was previously submitted to the IND.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

Clinical

8. Does the Agency agree that the data from Phase 3 registration Study, DCC- 2618-03-001 together with the data from the supportive Study, DCC-2618- 01-001 are adequate to substantiate the efficacy and safety of ripretinib and support filing of the NDA for a full approval of the proposed indication?

***FDA Response**: Based on the information provided, the proposed data from the registration trial and the supportive study appear adequate to support filing of the NDA.*

Please confirm that the proposed NDA will contain a mock-up define file to show the variables that will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRR-determined PFS events or censoring, and variables for subgroup analyses, etc. Variables used for sensitivity analyses in the statistical analysis plan should also be included.

Please include in the submission (a) SAS programs that produced all efficacy results, (b) all raw as well as derived variables in .xpt format, and (c) SAS programs by which the derived variables were produced from the raw variables.

Deciphera Response: The Sponsor confirms that the proposed NDA will contain a mock-up define file to show the variables that will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRR-determined PFS events or censoring, and variables for subgroup analyses, etc. Variables used for sensitivity analyses in the statistical analysis plan will also be included. Additionally, the Sponsor confirms that the SAS programs that produced all the efficacy results, all raw as well as derived variables in .xpt format, and SAS programs by which the derived variables were produced from the raw variables will be included in the NDA submission.

9. Does the Agency agree with the safety analyses planned for the NDA submission?

***FDA Response**: FDA agrees with the overall safety analyses planned for inclusion in the NDA submission. FDA advises Deciphera that while it is acceptable to submit analyses of "drug-related TEAEs", for the purpose of labeling, FDA will consider all TEAEs regardless of assigned attribution.*

Clarify how patients enrolled into the INVICTUS Study who crossed over and received at least 1 dose of ripretinib will be identified in the ISS dataset.

Deciphera Response: The crossed over patients from the placebo arm who received at least 1 dose of ripretinib in the open label period of the INVICTUS Study will be identified by the variable in the integrated ADSL dataset which represents the actual treatment arm in the INVICTUS study.

10. Does the Agency agree with the efficacy analyses planned for the NDA submission?

FDA Response*: No. Section 3.4.2 of the meeting package stated that the number of PFS events required to conduct the planned analysis for the study were 90 events and the study had reached these events in May 2019. However, in Table 6 in the meeting package, the total number of events reported was 88. Please explain this discrepancy. In the NDA submission, Deciphera should submit the correct dataset with the planned number of events. If the number of events in the dataset submitted for the NDA does not include the planned number of events, this will be a review issue and the O'Brien-Fleming method will be applied to recalculate the alpha level instead of using the pre-specified significance level.*

Deciphera Response: The Sponsor acknowledges the FDA's feedback. At the time of the data cutoff of the INVICTUS Study database (May 31, 2019), the count of PFS events was 92. During the data cleaning period between May 31, 2019 and Aug 9, 2019, four patients of the 92 who had PFS event were identified to have received new anti-cancer therapy or surgery before the PFS event occurred. Hence, these four patients were censored for PFS according to the pre-specified PFS censoring rules in the SAP. Therefore, there are 88 events in the primary PFS analysis which will be submitted in the NDA. Censored events with the reason for censoring will be also included in the datasets. Since the PFS results are highly significant ($p<0.0001$), the testing for PFS will still be statistically significant after applying O'Brien-Fleming method.

FDA notes that the pooling of the two study populations proposed for the ISE may not be appropriate due to potential population heterogeneity; therefore, these analyses will be considered exploratory.

Deciphera Response: The Sponsor acknowledges the FDA's feedback that the pooling of the two patient population is not appropriate. The Sponsor will not include the planned ISE datasets and the pooled analyses of ORR and DOR in the Module 2.7.3 [Summary of Clinical Efficacy(SCE)]. The Sponsor still plans to present the side-by-side data of the endpoints, PFS, ORR, and DOR from the INVICTUS Study and the Phase 1 Study, DCC-2618-01-001 in the SCE.

11. Does the Agency concur with the revised proposal regarding patient safety narratives criteria for inclusion in the NDA submission?

FDA Response*: Yes.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

12. Does the Agency agree to the proposed data cutoff, content and format of the 120-day safety update and timing of the submission in the case of priority review?

FDA Response*: FDA agrees with the proposed data cutoff, content, and format of the 120-day (90-day if priority review) safety update. Typically, the 90-day safety update is submitted approximately 90 days after the original NDA submission; however, FDA will accept this update early if Deciphera chooses. The safety update, in addition to cumulative safety information, should include a flag in the safety datasets indicating the newly recorded events.*

FDA does not agree with the proposed submission of an updated label (Sections 5 and 6). An updated label should only be submitted if the safety update changes the overall safety profile of ripretinib in a meaningful way.

Although FDA agrees with the proposed data cut-off date of August 31, 2019, FDA expects that Deciphera will notify FDA of any notable new safety issues (e.g., death due to toxicity that arises at any time during the review).

Deciphera Response: The Sponsor acknowledges and accepts the FDA's requests. The Sponsor will provide a listing of safety information including death and SAEs that occur after August 31, 2019 in the Module 2.7.4 addendum as part of the safety update.

Clinical Pharmacology

13. Does the Agency agree with the plans to evaluate excretion and metabolism of ripretinib and its metabolites in the absence of an AME study?

FDA Response*: Yes, Deciphera's plan appears acceptable.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

14. 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 ripretinib for the proposed indication?

FDA Response*: FDA has the following concerns regarding the proposed plan:*

a. Dose adjustments for concomitant use with CYP3A inhibitors and organ impairment need to be based on drug interaction trials or dedicated organ impairment trials (and population PK analysis for organ impairment) and not based on exposures achieved in the concentration QT analyses. In a response to the current meeting, provide a summary of how many patients within each hepatic (using NCI-ODWG criteria) and renal impairment category are planned to be included in the population PK analysis to be submitted in the

initial NDA submission. Submit the study reports for the dedicated renal and hepatic impairment trials within the original NDA submission to allow for adequate dose adjustment and labeling recommendations in these patient populations with different degrees of organ impairment.

Deciphera Response: The Sponsor agrees that dose adjustments for concomitant use with CYP3A inhibitors and organ impairment should be based on results from drug interaction trials or dedicated organ impairment trials (and population PK analysis for organ impairment).

The population PK analysis is currently ongoing and will be included in the initial NDA submission. A preliminary summary of the patients with hepatic and renal impairment at baseline that will be included in the population PK analysis (study DCC-2618-01-001 and DCC-2618-01-003 combined) is presented in **Error! Reference source not found.** and **Error! Reference source not found.**.

Table 1: Preliminary Summary of Patients with Hepatic Impairment included in PopPK Analysis

Covariate	Hepatic Function Groups	No. of Patients (N = 350)
Hepatic Impairment Category (using NCI-ODWG criteria)	Normal	257 (73.4%)
	Mild	91 (26.0%)
	Moderate	2 (0.571%)

Note: Baseline total bilirubin & AST were used to define hepatic function groups

Table 2: Preliminary Summary of Patients with Renal Impairment included in PopPK Analysis

Covariate	Renal Function Groups	No. of Patients (N = 350)
Renal Impairment Category	Normal (CrCl ≥90 mL/min)	178 (50.9%)
	Mild impairment (60 ≤ CrCl < 90 mL/min)	112 (32.0%)
	Moderate impairment (30 ≤ CrCl < 60 mL/min)	54 (15.4%)
	Severe impairment (15 ≤ CrCl < 30 mL/min)	4 (1.14%)
	Unknown[a]	2 (0.571%)

Note: Baseline creatinine clearance was used to define renal function groups.
a The baseline creatinine clearance of two patients are missing.

The dedicated hepatic impairment study (DCC-2618-01-004) in mild and moderate (and possibly severe) hepatic impairment is currently ongoing. As of October 7, 2019, 8 subjects with mild hepatic impairment have been enrolled and treated. In October 2019, the Investigators participating in this study and the Sponsor plan to review safety data for the mild impairment group and decide if the safety data is sufficient to proceed with enrolling subjects with moderate hepatic impairment. The

PK results from the mild and moderate hepatic impairment groups in this study are anticipated to be available in March 2020. At that time, a decision will be made whether to enroll the severe hepatic impairment group, as outlined in the protocol.

The dedicated renal impairment cohort of study DCC-2618-01-001 (creatinine clearance between 20 and 50 mL/min) is currently ongoing. As of October 7, 2019, 8 patients have been enrolled in this cohort. The PK results for patients with moderate and severe renal impairment in this study are anticipated to be available in March 2020.

The Sponsor believes that the planned analyses to be included in the initial NDA submission will provide sufficient data to guide dose adjustments based on organ function. Proposed labeling will be limited to organ impairment categories that have sufficient PK and/or safety data at the time of the initial NDA.

b. The proposal to submit planned drug interaction trials and PBPK modeling subsequent to a potential initial approval is not acceptable, as this will not allow for adequate dose adjustment recommendations in labeling. Submit protocols for the proposed drug interaction trials needed based on in vitro screens for FDA review prior to their initiation and initiate these trials as soon as possible.

Deciphera Response: The Sponsor acknowledges the FDA's request and agrees to submit the protocols for the proposed drug interaction trials based upon in vitro screens for FDA review as soon as possible. One drug interaction study has already been completed and two drug interaction studies are currently planned as listed below:

- The ripretinib drug interaction study DCC-2618-01-004 evaluated the effects of pantoprazole (a proton pump inhibitor) and itraconazole (a strong CYP3A inhibitor). This study has been completed and will be included in the initial NDA submission.

(b) (4)

[redacted]

c. The proposal to submit the proposed PBPK modeling data subsequent to an initial approval is not acceptable. Submit a summary of the plan and objectives of the PBPK modeling for FDA comment within 30 days of the current meeting and submit the modeling data as part of the initial NDA submission.

Deciphera Response: The Sponsor plans to evaluate the effect of ripretinib as a potential inhibitor of various CYP substrates including a clinical evaluation of the potential inhibitory effect of ripretinib on the most sensitive CYP substrate (CYP2C8), consistent with FDA Guidance for Clinical Drug Interaction Studies. Other less sensitive substrates 2C9, 2C19 and 2D6 probes may be evaluated in the clinical study. Alternatively, PBPK modeling may be conducted to address the other probe substrates only as needed, depending upon the magnitude of inhibitory effector on the CYP2C8 probe substrate. If PBPK modeling is needed, the in vivo drug interaction data will be used to optimize model parameters and specific details will be included in a PBPK modeling plan.

The Sponsor will provide an outline of the study design (i.e. either cocktail approach that includes 2C8, 2C9, 2C19 and 2D6 or CYP2C8 alone followed by PBPK modeling) in the initial NDA submission.

d. Concentration-QTc analysis based on study DCC-2618-01-001 appears reasonable to characterize the effect of ripretinib on the QTc interval at the proposed therapeutic dose. Whether the data would be adequate to exclude a large mean increase (i.e. >20 ms) on the QTc interval is a review issue. See additional Clinical Pharmacology comments below.

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

ADDITIONAL COMMENTS

Regulatory

15. FDA agrees with Deciphera's September 23, 2019, proposed RTOR submission plan content and timelines, except as noted above in Question 12 regarding the 90-day safety update. After further internal discussions, FDA agrees that Deciphera may submit any other data early as Deciphera wishes as described in the September 23, 2019, proposal. FDA may review these components early as time permits.

Deciphera Response: The Sponsor thanks the FDA for their response. The Sponsor would like to inform that the timelines for submission of the following NDA components under RTOR have shifted:

- ISS datasets and documentation submission: November 25, 2019
- PK report for Phase 1 Study: November 29, 2019
- Module 2.7.4 (SCS): December 13, 2019

Clinical Pharmacology

16. *Provide the following information in the concentration-QTc study report:*

    a. *the number of subjects at each dose level and in each study cohort;*

    b. *the ECG sampling schedule relative to the last dose in the dose expansion cohort; and*

    c. *justification for pooling data from the dose escalation and dose expansion cohorts in the presence of differences in ECG acquisition and baseline selection.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

17. *When Deciphera submits the QT assessment report, please include the following items:*

    a. *Clinical study report*

    b. *Statistical analysis plan*

    c. *Clinical study protocol*

    d. *Investigator's brochure*

    e. *A completed Highlights of Clinical Pharmacology and Cardiac Safety Table (https://www.fda.gov/media/129685/download)*

    f. *Annotated case report form*

    g. *A data definition file which describes the contents of the electronic data sets*

    h. *Electronic data set. The QT-IRT has updated the specification on how data sets should be submitted. These specifications are posted at the FDA Study Data Standards Resources webpage under 'Technical Guides'. Please refer to the QT Technical Specifications (https://www.fda.gov/media/128187/download) before submitting reports for QT studies.*

    i. *Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.*

    j. *Narrative summaries and case report forms for any*

        i. *Deaths possibly related to cardiac toxicity*

        ii. *Serious adverse events (cardiac)*

        iii. *Episodes of ventricular tachycardia or fibrillation*

        iv. *Episodes of syncope*

        v. *Episodes of seizure*

vi. *Adverse events (cardiac) resulting in the subject discontinuing from the study*

k. *Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

18. *FDA is also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

19. *Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com).*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

20. *Please see the QT-IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt) for up-to-date links to relevant guidances and select references to consider for QT evaluation.*

Deciphera Response: The Sponsor has no further comments and thanks the FDA for their response.

Submission	Modules	Sponsor Proposed Submission Date
	Module 5.3.5.1 Complete INVICTUS Study CSR	
4	**Module 5.3.5.3** ISS and ISE datasets	November 25, 2019
5	**Module 2 (Clinical) (without some hyperlinks)** • 2.7.3 (SCE) and 2.7.1 (SBP)	November 29, 2019
	Module 5.3.3.4 • Clinical Pharmacology Phase 1 Study, DCC-2618-01-003 CSR (without some hyperlinks and appendices) • Datasets and documentation	
	Module 5.3.3.5 • Population Pharmacokinetic (PopPK) Analysis Report • Exposure-Response (E-R) Analysis Report	
	Module 5.3.5.2 • Phase 1 Study (DCC-2618-01-001) CSR with the hyperlink to the PK report	
6	**Remaining Module 1 documents**	December 13, 2019
	Module 2 Clinical Summaries • 2.5 (CO), 2.7.2 (SCP), and 2.7.4 (SCS) • 2.7.3 (SCE) and 2.7.1 (SBP) (complete with all hyperlinks)	
	Module 3 and Module 2 (Quality)	
	Module 4 and Module 2 (Nonclinical) • Final Study Report for Study DCC-2618-04-0014 (*In Vitro* Phototoxicity Assessment of DCC-2618 in Balb/c 3T3 Mouse Fibroblasts) • Modules 2.4, 2.6.6, and 2.6.7 (complete with all hyperlinks)	
	Module 5.3.3.4 • Complete Clinical Pharmacology Phase 1 Study, DCC-2618-01-003 CSR (with all hyperlinks and appendices)	
	Module 5.3.3.5 • PopPK and E-R datasets and documentation	

Submission	Modules	Sponsor Proposed Submission Date
	Assessment Aid	
Post-Initial NDA Submission Updates		
Stability Update (12 months stability)		Anticipated by end of February 2020
90 Day Safety Update • Module 2.7.4 addendum • **Module 5.3.5** o Cumulative datasets and documentation for Phase 1 Study (DCC-2618-01-001) and INVICTUS Study o Any additional narratives and CRFs • **Module 5.3.5.3** o ISS datasets and appendices		March 12, 2020

Abbreviations: BIMO=Bioresearch Monitoring Program; CO=Clinical Overview; CSR=Clinical Study Report; ISE=Integrated Summary of Efficacy; ISS=Integrated Summary of Safety; OSI=Office of Scientific Investigations; SBP=Summary of Biopharmaceutic Studies and Associated Analytical Methods, SCE=Summary of Clinical Efficacy, SCP=Summary of Clinical Pharmacology Studies, SCS=Summary of Clinical Safety

a. Drafts of modules 2.4, 2.6.6, and 2.6.7 is planned to be submitted on November 19, 2019 as the final study report for Study DCC-2618-04-0014 (*In Vitro* Phototoxicity Assessment of DCC-2618 in Balb/c 3T3 Mouse Fibroblasts) will not be available until December 2019. In the draft modules, the hyperlinks to the aforementio ned study report will not be active; the final modules will have all hyperlinks active.

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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10/31/2019 08:12:07 AM

CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	125279
Request Receipt Date	August 21, 2019
Product	Ripretinib (DCC-2618)
Indication	Advanced gastrointestinal stromal tumor (GIST)
Drug Class/Mechanism of Action	Inhibitor of KIT and platelet-derived growth factor receptor alpha (PDGFRα) kinases
Sponsor	Deciphera Pharmaceuticals, LLC
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	October 18, 2019

Note: This document must be uploaded into CDER's electronic document archival system as a ***clinical review: REV-CLINICAL-24 (Breakthough Therapy Designation Determination) even if the review is attached to the MPC meeting minutes and*** *will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR)****.*** *Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. **Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):**

Deciphera requests Breakthrough Therapy Designation for ripretinib for the proposed indication of the treatment of patients with advanced gastrointestinal stromal tumor (GIST) who have received prior treatment with imatinib, sunitinib, and regorafenib.

2. **Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?** ☐YES ☒NO

3. **Was the BTDR submitted to a PIND?** ☐YES ☒NO
   If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. **Consideration of Breakthrough Therapy Criteria:**

   a. Is the condition serious/life-threatening[1])? ☒YES ☐NO

If 4a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

[1] For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf

b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

- ☒ YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- ☐ Undetermined
- ☐ NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked "No", BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC's input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTD Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked "Yes" or "Undetermined", proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation ☐

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug's mechanism of action (if known), the drug's relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Disease Background

Gastrointestinal stromal tumors (GISTs) are rare neoplasms though they represent the most common mesenchymal tumors of the gastrointestinal tract. (1) The estimated incidence is approximately 3,000 to 6,000 new cases per year in the U.S. (2, 3, 4) GISTs are driven by activating mutations in KIT (~80%) or PDGFRα (~10%) receptor tyrosine kinases. (4, 5) Patients typically present with primary mutations in KIT exon 9 or 11. Surgery is the mainstay of treatment for localized disease; however, local or distant recurrences occur in more than half of these patients. (6) Approximately 50% of patients present with metastatic or unresectable disease. The 5-year survival for patients with metastatic disease is 48%. (7) Chemotherapy and radiation have not been shown to be effective. (1, 5) For patients with unresectable or metastatic GIST, initial therapy is with KIT directed tyrosine kinase inhibitors (TKIs) including imatinib, sunitinib, and regorafenib; these therapies are FDA approved based upon improvement in overall survival (OS) or progression free survival (PFS) as shown in Table 1. However, many patients develop secondary drug-resistance mutations in KIT resulting in disease relapse or progression. (2) There are currently no approved therapies that broadly inhibit secondary drug-resistant mutations. Imatinib targets primary mutations in KIT exon 9 and 11, but has demonstrated limited activity in patients harboring other KIT or PDGFRα mutations. (8, 9) Sunitinib has limited efficacy against KIT exon 13 and 14. (9) Regorafenib is the only approved therapy that has activity against GIST with mutations in KIT exon 17. (10) The sponsor hypothesizes that DCC-2618's ability to inhibit the broad range of primary and secondary mutants of KIT and PDGFRA kinases makes it a promising therapeutic option for patients with advanced GIST who have become resistant to the currently approved agents.

Ripretinib Mechanism of Action

Ripretinib is an orally administered inhibitor of KIT and PDGFRα kinases. Ripretinib inhibits a broad range of primary and secondary mutations of KIT and PDGFRα kinases, including primary mutations in exons 9 and 11 of KIT, secondary mutations in exons 13, 14, 17 and 18 of KIT, the primary exon 18 mutation D842V of PDGFRα, and exon 12 and 14 mutations of PDGFRα.

Ripretinib Relevant Regulatory Background

- May 26, 2017: Type B meeting held to discuss adequacy of the nonclinical and clinical pharmacology plans, and design of the pivotal study, Protocol DCC 2618-03-001, entitled "A Randomized, Multicenter Phase 3, Double Blind Study of DCC-2618 + Best Supportive Care (BSC) vs Placebo + BSC in Patients with Advanced Gastrointestinal Stromal Tumors after Prior Treatment with Imatinib, Sunitinib and Regorafenib," to support an NDA for DCC-2618.
- August 24, 2017: Fast Track designation (FTD) request denied for ripretinib for treatment of patients with GIST who have received prior treatment with approved therapies, due to lack of adequate information on how the development program will affect the serious aspect of the condition or address the unmet medical need.
- October 23, 2018: Preliminary Breakthrough Therapy Designation (BTDR) Advice teleconference held to discuss DCC-2618 for treatment of patients with advanced GIST who have received prior treatment with 1) imatinib, sunitinib, and regorafenib, and 2) imatinib. FDA stated that additional information was needed to determine whether a BTDR would be appropriate.
- February 13, 2019: Type C WRO Pre-NDA meeting to discuss procedural and administrative aspects of a planned New Drug Application (NDA) for ripretinib for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.
- June 21, 2019: FTD was granted for ripretinib for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib, to demonstrate clinically meaningful and statistically robust improvement in progression free survival (PFS) compared to placebo.
- August 8, 2019: Deciphera submitted a request for a Type B preNDA meeting which was granted as a face-to-face meeting to be held on October 9, 2019 to seek agreement from the Agency on the content and format of the NDA and to obtain advice and feedback on regulatory, Chemistry, Manufacturing, and Controls (CMC), nonclinical, and clinical questions.

Submission for BTDR

The following submission were evaluated as part of the BTDR review

- Application 125279 - Sequence 0205 - 0205 (241) 08/21/2019 GI-1 /Breakthrough Therapy/Designation Request

8. Information related to endpoints used in the available clinical data:

a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

Deciphera requests BTD based upon an improvement in PFS compared to placebo, which is the primary endpoint of the ongoing Trial DCC-2618-03-001.

b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:

- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
- *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*

- *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

PFS has been used as the primary endpoint to support traditional approval of agents for the treatment of unresectable GIST. DOP2 would also consider overall survival to be a clinical endpoint that directly measures the clinical benefit of a drug and would support traditional approval.

Depending on the context, DOP2 may consider a large effect on overall response rate (ORR) to support approval of the proposed indication; an ORR of 33-43%, depending on dose, was used as the basis for accelerated approval of imatinib in patients with unresectable GIST in 2002. At that time, there were no alternative effective therapies for unresectable GIST.

c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

Not applicable

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are no available FDA-approved therapies beyond the third-line setting for GIST. Table 1 lists all approved therapies for patients with GIST.

Table 1: Agents Approved for the treatment of GIST

Agent	Indication	Endpoint used to establish efficacy	Treatment Effect
Imatinib[a]	Unresectable and/or metastatic GIST that is Kit (CD117) positive	OS 400 mg vs 800 mg **PFS 400mg vs 800 mg** ORR 400 mg vs 800 mg	49.0 vs 48.7 months P=0.98 **18.9 vs 23.2 months** 51.4% vs 53.9%
Imatinib	Adjuvant treatment of patients following resection of Kit (CD117) positive GIST	RFS 12 months of therapy versus RFS 36 months treatment OS 12 months of therapy versus OS 36 months treatment	58% vs 75% HR (95%CI): 0.46 (0.32, 0.65) Median OS NR in either group 13% deaths vs 6% deaths HR (95% CI): 0.45 (0.22, 0.89)
Sunitinib	GIST after disease progression on or intolerance to imatinib	TTP versus placebo **PFS versus placebo** ORR versus placebo	27.4 vs 6.4 weeks HR (95%CI): 0.33 (0.23,0.47) **5.5 vs. 1.4 months** **HR (95% CI): 0.33 (0.24,0.47)** 6.8% (95% CI 3.7,11.1) vs. 0
Regorafenib	Locally advanced, unresectable, or metastatic GIST who have been previously treated with	OS versus placebo **PFS versus placebo**	NR vs NR HR (95%CI): 0.77 (0.42, 1.41) **4.8 vs 0.9 months** **HR (95% CI): 0.27 (0.19, 0.39)**

Agent	Indication	Endpoint used to establish efficacy	Treatment Effect
	imatinib and sunitinib		

Sources: Summarized from the USPI for imatinib; sunitinib; and regorafenib
Abbreviations: OS, Overall Survival; PFS, Progression Free Survival; ORR, Objective Response Rate; NR, not reached; CI, confidence interval; RFS, recurrence-free survival; TTP, Time to Tumor Progression; HR, Hazard Ratio
[a]initially received accelerated approval based on ORR, conversion to full approval based on PFS and OS

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation[2].

No other drugs have received breakthrough therapy designation for this proposed indication.

On June 1, 2017, FDA granted BTD to BLU-285 (avapritinib) for treatment of patients with unresectable or metastatic GIST harboring the PDGFRα D842V mutation regardless of number of prior therapies; 9 of the 12 patients who received prior therapy and had the PDFRα D842V mutation in the BLU-285 study had received prior imatinib. BTD was granted based on an ORR of 43% with DOR ranging from 2.9 to 16.2 months; eight of the ten responses were ongoing at the time of data cut off.

11. Information related to the preliminary clinical evidence:

a. Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design[3], trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

Deciphera provided data from Study DCC-2618-03-001, a randomized, multicenter, double-blind, placebo-controlled, cross-over study that evaluated ripretinib versus placebo for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib. The primary objective was to evaluate PFS as assessed by blinded independent review based on modified RECIST. The key secondary objective was ORR. Other secondary endpoints were time to progression, OS, time to best response, quality of life, and disease control rate.

A total of 129 patients were randomized to receive ripretinib (N=85) or placebo (N=44). Patients in the treatment arm received ripretinib 150 mg daily. Patients in the control arm received matching placebo. Randomization was stratified based on prior lines of therapy (3 vs >3) and ECOG (0 vs 1 or 2). Patients in both arms received treatment for 2 years or until disease recurrence, unacceptable toxicity, or withdrawal of consent. At the time of disease progression, patients who received ripretinib were allowed to remain on ripretinib at the same dose or increase to 150 mg twice daily, and patients receiving placebo were allowed to cross-over to receive ripretinib 150 mg daily.

The study met its primary endpoint of PFS. The results demonstrated a statistically significant and clinically meaningful improvement in PFS with a median of 6.3 (4.6, 6.9) months in the ripretinib arm compared to 1.0 (0.9, 1.7) month for the placebo arm (HR 0.15 [95% CI (0.09, 0.25)] p-value < 0.0001).

For the key secondary endpoint of ORR, ripretinib demonstrated an ORR of 9.4% compared with 0% for placebo (p-value=0.0504), which was not statistically significant. Ripretinib (nominally) showed a clinically meaningful improvement over placebo for the secondary endpoint OS (median OS 15.1 months vs. 6.6 months, HR = 0.36). Since statistical significance was not achieved for ORR, based on pre-specified hierarchical testing rules, the hypothesis testing of OS was not formally performed. The OS data for the placebo arm includes patients taking placebo who, following progression, were crossed over to ripretinib treatment.

[2] Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.
[3] Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Deciphera provided safety data from a total of 128 patients who received a dose of the assigned treatment per arm (ripretinib arm, N= 85; placebo arm, N=43). The most common adverse events (AEs) observed in the ripretinib arm were alopecia (44%), fatigue (36%), nausea (33%), abdominal pain (31%), constipation (29%), myalgia (27%), diarrhea (24%), decreased appetite (23%), palmar-plantar erythrodysesthesia syndrome (21%), and vomiting (21%). The most frequent Grade 3 or 4 AEs in the ripretinib arm were anemia (9%), abdominal pain (7%) and hypertension (7%). The most common serious AEs were abdominal pain (5%), anemia (4%), nausea (2%), and vomiting (2%). There were five (6%) deaths in the ripretinib arm and ten (23%) death in the placebo arm attributed to AEs. In the ripretinib arm the AEs were listed as death in three patients, and one patient each for general physical health deterioration and hypoglycemia.

12. Division's recommendation and rationale (pre-MPC review):

☒ GRANT:

Provide brief summary of rationale for granting:

Based on the data submitted by Deciphera, DOP2 recommends granting the proposed request for breakthrough therapy designation for the treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib.

GIST is a serious disease. The clinical evidence presented demonstrates a statistically significant and clinically meaningful improvement in PFS over placebo.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

☐ DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

Deciphera submitted results from the pivotal trail, DCC-2516-03-001. The results of this study will be used to support a future NDA submission. A pre-NDA meeting is scheduled.

b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

Not applicable.

14. List references, if any:

1. Aubin F and Blanke CD. Metastatic gastrointestinal stromal tumors. Cancer Chemother Pharmacol. 2011;67(Suppl 1):S9-S14.
2. Blay J-Y. A decade of tyrosine kinase inhibitor therapy: Historical and current perspectives on targeted therapy for GIST. 2010. http://dx.doi.org/10.1016/j.ctrv.2010.11.00.2.
3. Corless CL, Fletcher JA, and Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol. 2004;22(18):3813-25.
4. Corless CL, Barnett CM, and Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nature Reviews. Cancer. 2011;11:865-78.
5. Heinrich MC, Corless CL, Demetri GD, Blanke CD, von Mehren M, Joensuu H, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21(23):4342-9.
6. Eisenberg BL and Smith KD. Adjuvant and neoadjuvant therapy for primary GIST. Cancer Chemother Pharmacol. 2011;67 (Suppl 1):S3–S8.
7. Ma G, Murphy D, Martinez M, et. al., 2015, Epidemiology of gastrointestinal tumors in the era of histology codes; results of a population-based study. C. Epidemiol Biomarkers Prev; 24: 298.
8. Kee D, Zalcberg JR. Current and emerging strategies for the management of imatinibrefractory advanced gastrointestinal stromal tumors. Ther Adv Med Oncol 2012;4(5):255-70.
9. Demetri GD, Benjamin RS, Blanke CD, Blay JY, Casali P, Choi H, et al; NCCN Task Force. NCCN Task Force Report: Optimal management of patients with gastrointestinal stromal tumor (GIST) – update of the NCCN clinical practice guidelines. J Natl Compr Canc Netw 2007;5(2):S1-29.
10. Corless CL, Barnett CM, Heinrich MC. Gastrointestinal stromal tumours: origin and molecular oncology. Nat Rev Cancer 2011;17;11(12):865-78.

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES ☒ NO ☐

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation ☒
Deny Breakthrough Therapy Designation ☐

Reviewer Signature:	Leslie Doros, MD	{See appended electronic signature page}
Team Leader Signature:	Ashley Ward, MD	{See appended electronic signature page}
Division Director Signature:	Steven Lemery, MD	{See appended electronic signature page}

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/

LESLIE A DOROS
10/07/2019 05:36:38 PM

ASHLEY F WARD
10/08/2019 08:21:57 AM

STEVEN J LEMERY
10/08/2019 09:04:16 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 125279

MEETING MINUTES

Deciphera Pharmaceuticals LLC
Attention: Jama Pitman
500 Totten Pond Road 6th Floor
Waltham, MA 02451

Dear Dr. Pitman:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DCC-2618.

We also refer to the telecon between representatives of your firm and the FDA on May 26, 2017. The purpose of the meeting was to discuss your proposed clinical development plans for DCC-2618.

A copy of the official minutes of the 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 (240) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S., P.M.P.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End-of-Phase 1 / Pre-Phase 3
Meeting Date and Time:	May 26, 2017 / 1:00 – 2:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	125279
Product Name:	DCC-2618
Indication:	Treatment of patients with advanced GIST who have received prior treatment with imatinib, sunitinib, and regorafenib
Sponsor/Applicant Name:	Deciphera Pharmaceuticals LLC
Meeting Chair:	Marc Theoret
Meeting Recorder:	Leah Her

FDA ATTENDEES

Patricia Keegan	Director, DOP2
Steven Lemery	Associate Director, DOP2
Marc Theoret	Clinical Team Leader, DOP2
Leslie Doros	Clinical Reviewer, DOP2
Leah Her	Regulatory Health Project Manager, DOP2
Whitney Helms	Nonclinical Supervisor, DHOT
Anwar Goheer	Nonclinical Reviewer, DHOT
Hong Zhao	Clinical Pharmacology Team Lead, DCPV
Saeho Chong	Clinical Pharmacology Reviewer, DCPV
Joyce Crich	Product Quality Team Leader, NDBII

SPONSOR ATTENDEES

Eric Haltom	VP of Clinical Operations
Michael Kaufman	VP of Manufacturing and Preclinical Development
Jama Pitman	Sr. Director and Head of Regulatory, Quality and Pharmacovigilance
Oliver Rosen	Chief Medical Officer
Rodrigo Ruiz Soto	VP of Clinical Research and Translational Medicine

BACKGROUND

On March 24, 2017, Deciphera requested a meeting with FDA to discuss the proposed clinical development plans for DCC-2618. Specifically, Deciphera is seeking FDA's advice regarding the adequacy of the nonclinical and clinical pharmacology plans, and the design of the pivotal trial, Protocol DCC-2618-03-001, entitled "A Randomized, Multicenter Phase 3, Double Blind Study of DCC-2618 + Best Supportive Care (BSC) vs Placebo + BSC in Patients with Advanced Gastrointestinal Stromal Tumors after Prior Treatment with Imatinib, Sunitinib and Regorafenib," to support the filing of a New Drug Application (NDA) for DCC-2618 for the proposed indication:

> *Treatment of patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor (GIST) who have been previously treated with imatinib* (b) (4) *sunitinib* (b) (4)*, and regorafenib*

The meeting requested on March 24, 2017 was granted on April 14, 2017. The briefing document was received on April 28, 2017. Upon review of the preliminary comments issued on May 25, 2017, Deciphera requested the in-person meeting to be converted into a teleconference.

Deciphera stated their intent to request a separate meeting in the second half of 2017 to discuss the details of the Chemistry, Manufacturing and Controls (CMC) plans to support the planned NDA.

Key Regulatory History

- October 2, 2014: Orphan Drug Designation granted for DCC-2618 for treatment of GIST (Designation No.: 14-4474)
- March 4, 2015: Type B / Pre-IND held to discuss the adequacy of the CMC information and the planned and completed nonclinical studies to support the proposed first-in-human (FIH) study and the proposed overall development program for DCC-2618 in advanced solid tumors driven by c-KIT/PDGFR mutation or over-expression
- August 11, 2015: New IND with Protocol DCC-2618-01-001, entitled "A Multicenter Phase 1, Open-Label, Dose-Escalation Study of DCC-2618 to Assess Safety, Tolerability and Pharmacokinetics in Patients with Advanced Malignancies," received on July 17, 2015, allowed to proceed

Drug Product Information

DCC-2618 (lab code as (b) (4)) has a chemical name of 1-[4-Bromo-5-[1-ethyl-7-(methyl-amino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea. It has a molecular weight of 510.36 g/mol and a molecular formula of $C_{24}H_{21}BrFN_5O_2$. DCC-2618 is formulated as tablets for oral administration in strengths of 10 mg and 50 mg. (b) (4)

(b) (4)

DCC-2618 tablets are packaged in high-density polyethylene bottles with a (b) (4)

child-resistant cap for oral administration, and is stored tightly closed at room temperature (at or below 25°C / 77°F) and away from areas of high humidity.

Nonclinical
DCC-2618 is an orally administered inhibitor of the KIT and PDGFRA kinases. The pharmacology of DCC-2618 and its active metabolite, DP-5439, have been evaluated in vitro and in vivo. A PK/PD study was performed in a human GIST xenograft mouse model. There was no evidence of bacterial mutagenicity with or without metabolic activation. GLP-compliant 4-week oral toxicity studies were performed in rats and dogs.

Deciphera intends to conduct a GLP-compliant 13-week oral study in SD rat and Beagle dogs after initiation of Clinical Study 03-001 (a randomized, placebo-controlled trial intended to support registration). In addition, prior to NDA submission, Deciphera intends to conduct an embryo-fetal toxicology studies in two species (rat and rabbit).

Clinical
Deciphera submitted the proposed study design for Trial DCC-2618-03-001 which Deciphera intends to conduct to support an application for DCC-2618 for treatment of patients with advanced gastrointestinal stromal tumors (GIST) who have previously received treatment with imatinib, sunitinib, and regorafenib. In addition, Deciphera submitted preliminary safety and efficacy data from the ongoing Phase 1 trial, DCC-2618-01-001.

Ongoing Trial DCC-2618-01-001
Trial DCC-2618-01-001 is an ongoing, first-in-human, open-label, dose-escalation and expansion cohort trial of DCC-2618 in up to 250 patients with advanced malignancies (50 patients in the dose-escalation portion and up to 200 patients total in the expansion cohorts). The primary objective is to determine the safety, tolerability, and maximum tolerated dose (MTD) of DCC-2618. Trial DCC-2618-01-001 utilizes a 3+3 pharmacologically guided dose-escalation. Intrapatient dose-escalation is permitted at Cycle 3 day 1 and patients who experience disease progression may receive DCC-2618 at a higher dose. Expansion cohorts for patients with GIST harboring KIT or PDGFRα mutations are (1) cohort 1 for DCC-2618 as fourth line treatment (up to 40 patients), (2) cohort 2 for fifth line treatment (up to 35 patients), and (3) cohort 3 for earlier than fourth line treatment (up to 55 patients). Tumor response evaluations per modified RECIST v1.1 were performed by the investigator every two cycles.

As of March 17, 2017, 42 patients have been enrolled across eight dose-level cohorts, six cohorts with DCC-2618 administered twice daily (20, 30, 50, 100, 150 and 200 mg) and two cohorts with DCC-2618 administered once daily (100 mg and 150 mg) as shown in the below table reproduced from the meeting package:

Dose Cohort	Number of Patients Enrolled	Number of GIST Patients Enrolled
20 mg BID	4	3
30 mg BID	4	2
50 mg BID	5	4
100 mg BID	6	6
150 mg BID	6	6
200 mg BID	5	5
100 mg QD	6	2
150 mg QD	6	6
Total	42	34

There were 34 patients enrolled with advanced GIST (33 with known activating KIT/PDGFRα mutations). Patients with GIST received one to seven prior therapies. The expansion cohort phase of the trial has not begun enrollment.

Safety Results

The maximum administered dose (MAD) was 200 mg BID. There were three dose-limiting toxicities (DLTs) across the dose level cohorts:

- 100 mg BID: Grade 3 elevated lipase
- 200 mg BID: Grade 3 elevated lipase
- 150 mg daily: Grade 4 elevated CPK

The meeting package provides the incidence of treatment emergent adverse events by dose level in Trial DCC-2618-01-001. Across the dose-level cohorts, the most frequent (≥20%) treatment emergent adverse events were fatigue (41%), anemia (31%), lipase increase (24%), decrease appetite (21%), and dyspnea (21%). Serious adverse events occurred in 11 patients (26%); serious adverse events occurring in more than one patient were gastrointestinal hemorrhage, anemia, increased lipase, and hypoglycemia. There were six patients who had dose reductions; only one of these occurred at 150 mg daily (Grade 4 CPK elevation). The other five occurred at higher dose levels. Of the six patients who received DCC-2618 at the proposed dose of 150 mg daily for use in Trial DCC-2618-03-001, there were two reported treatment-emergent adverse events: alopecia and vomiting in one (17%) patient each.

Efficacy Results

According to the meeting package, the overall response rate as assessed by the investigator per RECIST 1.1 "is available for 23 patients with KIT- or PDGFRα-driven GIST. Patients included in this analysis include patients who made it to the C3D1 scan." There were three patients that experienced a partial response at the cycle 3 day 1 imaging assessment: one at the 100 mg BID dose level, one at the 150 mg BID dose level, and one noted after the data cut-off date at the

200 mg BID. The following efficacy summary per RECIST v1.1 at C3D1 for patients with KIT or PDGFRA-driven GIST is reproduced from the meeting package:

Dose Cohort	KIT or PDGFRA GIST Pts Enrolled by Cohort (N=23)	Pt ID	RECIST 1.1 Results			
			PR	SD	PD	SD +PR (%)
20 mg BID	2	(b) (6)	0	1	1	1
30 mg BID	2		0	2	0	2
50 mg BID	4		0	4	0	4
100 mg BID	5		1	3	1	4
150 mg BID	6		1	4	1	5
200 mg BID	1		0	0	1	0
150 mg QD	3		0	3	0	3
Total			**2**	**17**	**4**	**19 (83%)**

PR = Partial Response; SD = Stable Disease; PD = Progressive Disease; [1]Patient has PDGFRA-driven GIST;
Note: Patient (b) (6) (200 mg BID cohort), not included in Table 15, experienced clinical progression prior to the C3D1 scan.

The meeting package does not identify whether the responses have been confirmed on a subsequent tumor response evaluation performed at least 4 weeks after the initial determination of the response.

Proposed Trial DCC-2618-03-001

Trial DCC-2618-03-001 is a two-arm, randomized, double-blind, multicenter trial evaluating DCC-2618 versus placebo in up to 114 patients with advanced GIST after prior treatment with imatinib, sunitinib, and regorafenib. The primary objective is progression-free survival (PFS). Secondary objectives are:

- Overall survival (OS)
- Response rate
- Investigator assessed mPFS
- Assessment of disease-related symptoms and quality of life using patient reported outcome (PRO) measurements
- Safety

Key inclusion criteria include histologically confirmed diagnosis of GIST; received at least three prior lines of therapy but no more than four; patients with a KIT mutation must have received at least two of the following agents: imatinib, sunitinib, or regorafenib; patients with PDGFRα mutation who have received two prior treatments approved or investigational; and ECOG performance status of 0 to 2. Key exclusion criteria include patients with known KIT and PDGFRα wild-type GIST, baseline prolongation of QTc on repeated demonstration of >450 msec in females or >470 msec in males, concurrent treatment with proton-pump inhibitor, inability to swallow pills, malabsorption syndromes, requirement of intravenous alimentation, treatment of active peptic ulcer disease, and active gastrointestinal bleeding.

Patients will be randomized in a 2:1 fashion to receive DCC-2618 150 mg orally once daily in repeated 28-day cycles with best supportive care (BSC) or placebo with BSC. Randomization

will be stratified by line of treatment (4th line versus 5th line), and mutational status (KIT vs PDGFRα). Patient accrual will be conducted in approximately 30 centers globally.

Patients will be treated on their assigned arm until they develop progressive disease, experience unacceptable toxicity, or withdraw consent. Tumor response assessments per modified RECIST v1.1 will be conducted every cycle for the first four cycles and then every two cycles thereafter. The modifications to RECIST v1.1 (GIST-specific) are as follows:

- No lymph nodes chosen as target lesions; enlarged lymph nodes followed as non-target lesions
- No bone lesions chosen as target lesions
- Positron emission tomography (PET) not acceptable for radiological evaluation
- A progressively growing new tumor nodule within a pre-existing tumor mass must meet the following criteria to be considered as unequivocal evidence of progression on the modification to RECIST 1.1: (a) the lesion is at least 2 cm in size and definitively a new active GIST lesion (e.g., enhancing with contrast or other criteria to rule out artefact); or (b) the lesion has to be expanding on at least two sequential imaging studies

At time of progressive disease, patients on the placebo arm will be offered treatment with open-label DCC-2618. Determination of disease-progression will be based on investigator assessment. Patients on the DCC-2618 arm who develop disease progression will be offered the option to continue treatment on study at the escalated dose of 150 mg twice daily BID.

The primary endpoint is PFS as assessed by independent radiologic review per modified RECIST version 1.1 (modifications as described above). Assuming that the median PFS is 1 month in the placebo arm and 2 months in the DCC-2618 arm, a total of 98 events are needed to detect a hazard ratio of 0.5 with 90% power at a 2-sided alpha level of 5%. Recruitment is expected to take 9 months with 12 additional months for follow-up for an estimated trial duration of 21 months. One interim analysis for PFS will be performed after 49 (50%) events for efficacy and futility. The O'Brien Fleming (OBF) boundary method will be utilized to calculate the respective alpha allocations. If the interim analysis is positive and the benefit observed is considered clinically meaningful, the trial will be unblinded and patients who are on placebo will be allowed to receive DCC-2618 arm.

The key secondary endpoint is overall survival (OS). Assuming that the median OS is 6 months in the placebo arm and 11.5 months in the DCC-2618 arm, this trial allows for 80% power at a 1-sided alpha level of 2.5% to detect a statistically significant difference in OS.

DISCUSSION

FDA General Comment: The meeting package provides insufficient information on the safety and efficacy of DCC-2618 at the proposed dose of 150 mg orally once daily (QD) to determine whether this is the optimal dose for the proposed indication and appropriate for use in the clinical trial intended to support marketing approval. Specifically, Trial DCC-2618-01-001 is currently ongoing and is continuing to evaluate trough concentrations of the DCC-2618 100 mg QD and 150 mg QD dose levels; and the recommended phase 2 dose has not been determined. The safety data provided at the proposed recommended dose of 150 mg daily (n=6) or a total daily dose that exceeds 150 mg (n=17) is limited to 23 patients. Similarly, efficacy data for DCC-2618 is limited at the proposed dose. FDA would recommend continuing to evaluate data from the ongoing trial DCC-2618-01-001 to provide additional evidence supporting Deciphera's dose selection.

Nonclinical

1. *Background: Please refer to the Company Position on page 8 and Section 4.4.2 Planned Nonclinical Toxicology Studies of the Briefing Document.*

   Per ICH S9 Guidance for Industry, the Sponsor intends to conduct the 13-week repeat-dose nonclinical toxicology study and the reproductive embryo-fetal nonclinical study (as noted in Section 4.4.2), after initiation of Clinical Study 03-001. The results from the nonclinical toxicology studies will be included in the initial marketing application.

   Does the Division agree with the overall design and timing of the conduct of these studies?

   FDA Response: FDA does not agree that the timing of the planned nonclinical studies is sufficient to support the continued development of DCC-2618. As discussed in the ICH Guidance for Industry S9: Nonclinical Evaluation for Anticancer Pharmaceuticals, available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm085389.pdf, "results from repeat dose studies of 3 months duration following the intended clinical schedule should be provided **prior** to initiating Phase 3 studies." Thus, the study reports for the 13-week chronic toxicology studies should be submitted to the IND prior to initiation of Study 03-001. Deciphera did not provide details regarding the design of planned 13-week studies. While the high doses proposed for use in the planned 13-week GLP-compliant toxicology studies appear reasonable based on the data provided in the meeting package, FDA does not provide concurrence on doses to be used in nonclinical studies outside of carcinogenicity protocols submitted under a Special Protocol Assessment (SPA).

   FDA agrees with the timing of the proposed embryofetal development studies in 2 species. If there are clear findings of embryo-lethality or teratogenicity in one species, then an embryofetal development study in a second species may not be required.

   FDA reminds Deciphera that the full battery of genotoxicity studies as described in ICH S2 ((ICH-S2A, April 1996 & ICH-S2B, July 1997) are expected to support a marketing application. If the in vitro assays are positive, then an in vivo assay might not be

warranted. The bacterial mutagenicity assay on its own is insufficient to support a marketing application. Finally, based on the information in the meeting package, Deciphera has not evaluated the potential for DP-5439 to inhibit the hERG potassium channel; Deciphera could consider whether such an evaluation would be useful to assess the overall safety of DCC-2618.

Deciphera's Emailed Response of 5/26/17: It is anticipated that at least 50 patients will have been dosed at 150 mg QD (or higher) in Clinical Study DCC-2618-01-001 when Clinical Study 03-001 is submitted to the IND. The Sponsor asserts that DCC-2618 has higher exposures in humans than rats or dogs. As a result, the full13-week toxicology study readout may provide limited predictive power for acute and chronic safety in humans and the final study report is not need to initiate clinical trial 03-001.

The skin changes observed in the 4-week dog studies, are readily monitorable with standard parameters and 13-week study results can be communicated ahead of clinical exposure (e.g. at 4, 8 and 13 weeks). Other safety findings posing a potential risk in this advanced GIST patient population of study 03-001 have neither been observed in the 4-week toxicology studies nor in clinical study DCC-2618-01-001.

The Sponsor respectfully requests endorsement from the Division to submit the 03-001 protocol to the IND while the 13-week toxicology study is ongoing and commits to providing the draft toxicology study report to the Division prior to dosing a patient in the 03-001 clinical study. The final toxicology report should be available approximately 3 months post-submission of the draft toxicology report. It is anticipated that <25% of patients will have enrolled into the 03-001 trial when the final toxicology report is available and thus there would be minimal exposure of DCC-2618 to patients in the 03-001 study until the final report is available.

Additionally, should sufficient long-term human efficacy and safety data at the 150 mg QD dose level (and higher) accompany the submission of the pivotal trial 03-001 to the IND, the Sponsor would like to request that the Division review this data and determine if it is appropriate to initiate the pivotal trial prior to submission of the draft 13-week toxicology report. Please see our comments dated May 25, 2017 below under Question 6.

Follow-up question 1a: Does the Division agree that the final 03-001 protocol can be submitted to the IND while the 13-week toxicology study is being conducted and that dosing of patients will be contingent upon submission of the draft 13-week toxicology report to the IND?

Follow-up question 1b: Does the Division agree that long term human data from clinical study DCC-2618-01-001 at the proposed 150 mg QD dose (and higher) may be considered when reviewing Clinical Protocol 3-001 and if deemed appropriate may provide an opportunity to initiate dosing in the pivotal trial prior to availability of the draft 13-week toxicology study report?

Discussion During the Teleconference on 5/26/17: FDA stated that the purpose of the chronic toxicology studies is to characterize the safety of a pharmaceutical by identifying side effects that may not have been observed in clinical studies. Therefore, FDA stated that only a limited number of patients (no more than 50 patients) should be enrolled in Study 03-001 prior to the submission of the draft toxicology reports with signed pathology reports. FDA stated that Clinical Study 03-001 will be placed on a partial hold consistent with this approach. Deciphera acknowledged FDA's response and that a partial hold would be placed on the planned study.

Clinical

2. *Background: Please refer to the Company Position on pages 8-9 and Attachment A Clinical Study Synopsis of the Briefing Document.*

The Sponsor proposes that Clinical Study 03-001, a Phase 3, randomized, placebo-controlled trial in patients who have received prior treatment with imatinib, sunitinib, and regorafenib be the first registration for DCC-2618. The active arm will be DCC-2618 monotherapy + Best Supportive Care (BSC) and the control arm will be a matching placebo + BSC.

Does the Division agree that a placebo comparator is appropriate for this trial?

FDA Response: FDA agrees that a placebo comparator is acceptable in this treatment-refractory population. If an effective treatment becomes available during the course of the trial, it may be unethical to continue the use of a placebo control. Please refer to FDA Guidance "E10 Choice of Control Group and Related Issues in Clinical Trials" at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073139.pdf.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division or their response.

3. *Background: Please refer to the Company Position on page 9 and Attachment A Clinical Study Synopsis of the Briefing Document.*

(b) (4)

Does the Division agree (b) (4)

(b) (4)

FDA Response: FDA does not agree. (b) (4)

(b) (4)

(b) (4)

For a single randomized trial to support an NDA, the trial should be well-designed, well-conducted, with a favorable study risk/benefit ratio, and provide statistically persuasive efficacy findings so compelling that a second trial would be unethical or practically impossible to repeat. Refer to the FDA Guidance for Industry entitled "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," available at https://www.fda.gov/ohrms/dockets/98fr/971OOgdl.pdf, and "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics," available at https://www.fda.gov/downloads/drugsGuidanceComplianceRegulatoyInformation/Guidance/UCM071590.pdf.

Deciphera's Emailed Response of 5/26/17: The Sponsor agrees (b) (4)
(b) (4)

Discussion During the Teleconference on 5/26/17: No discussion occurred.

4. *Background: Please refer to the Company Position on pages 9-10 and Attachment A Clinical Study Synopsis of the Briefing Document.*

Does the Division agree (b) (4)
(b) (4) **?**

FDA Response: FDA does not agree. (b) (4)
(b) (4)

See FDA Additional Comments 14 and 15.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division or their response.

5. *Background: Please refer to the Company Position on page 10 and Attachment A Clinical Study Synopsis of the Briefing Document.*

Does the Division agree that the proposed secondary efficacy endpoints DCC-2618-03-001 are appropriate and are clinically meaningful to support the primary endpoint of PFS?

FDA Response: The key secondary endpoint of OS is acceptable; however, DCR is not a considered by FDA to be a measure of clinical benefit, provides no useful information beyond that characterized by the primary endpoint of PFS, and would not be included in product labeling.

The secondary endpoint of ORR should be assessed by blinded independent central review with a confirmatory scan performed ≥4 weeks after response is observed to confirm durability.

Results of secondary endpoints will generally not be considered unless the analysis of the primary endpoint is statistically significant. A statistical analysis plan controlling the overall false positive rate for those secondary endpoints to be potentially included in the label at a level of two-sided 0.05 should be specified. In general, analyses of OS and ORR with duration of response may be included in the product labeling.

Please see FDA Additional Comment 16 regarding the PRO endpoint.

Deciphera's Emailed Response of 5/26/17: We confirm that there will be a detailed, pre-specified, statistical analysis plan that outlines the testing procedures whereby the

primary endpoint will be tested first and then step down to a family of key secondary endpoints. The overall Type I error rate will be controlled at the two-sided 0.5 level.

Discussion During the Teleconference on 5/26/17: No discussion occurred.

6. *Background: Please refer to the Company Position on pages 10-11 and Attachment A Clinical Study Synopsis of the Briefing Document.*

Does the Division agree that 150 mg QD is the appropriate dose for clinical study 03-001 and (b) (4) (b) (4)

FDA Response: No. There is insufficient information in the meeting package for FDA to determine (b) (4) (b) (4). See FDA General Comment above.

Deciphera's Emailed Response of 5/26/17: As outlined in the briefing book, the data collected to-date has demonstrated a favorable safety profile with no cumulative toxicity and a positive risk:benefit profile. The Sponsor anticipates that at least 50 patients will have received the 150 mg QD dose of DCC-2618 at the time of Clinical Protocol 03-001 submission to the IND. In addition, the sponsor agrees that a more comprehensive understanding of the Study DCC-2618-01-001 PK data will be beneficial in designing Study 03-001. Examination of individual DCC-2618 concentration-time profiles on Cycle 1 Day 1 (first dose) across all dose groups of Study DCC-2618-01-001 suggests potential nonlinear PK characteristics of DCC-2618. Population PK modeling along with exposure-response analyses with simulations using available data up to date will be conducted to aid the design of Study 03-001.

The Sponsor commits to providing a more mature summary of safety and efficacy data in addition to the modeling results in support of the dose justification upon submission of the pivotal protocol to the IND.

Discussion During the Teleconference on 5/26/17: No discussion occurred.

7. *Background: Please refer to the Company Position on page 11 and Section 5 Clinical Information of the Briefing Document.*

Does the Division agree that the anticipated safety database of ~240 patients with a diagnosis of GIST is acceptable to reasonably assess the safety profile of DCC-2618?

FDA Response: In general, FDA would request a minimum safety database of 300 patients to support an indication in the intended use population(s), which is sufficient to identify with 95% confidence serious adverse reactions that occur with a frequency of 1%.

If Deciphera intends to provide a smaller safety database, the application should contain justification as to why a safety database of approximately 240 patients treated at different dose levels would be adequate to make a risk:benefit determination during review of an NDA submission. Please refer to FDA Guidance for Industry, entitled "Premarketing Risk Assessment" available at https://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126958.pdf%20.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division or their response.

Clinical Pharmacology

8. *Background: Please refer to the Company Position on page 11 and Section 6 Clinical Pharmacology Information of the Briefing Document.*

Does the Division agree with the Sponsors plans as outlined in Table 16?

FDA Response: FDA generally agrees with the Clinical Pharmacology Plan submitted in the meeting package. FDA recommends that Deciphera conduct a dedicated study to assess food effect on the drug exposure following the FDA Food Effect Guidance, available at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126833.pdf.

The interim QT assessment plan is under review by FDA QT/IRT. Pending completion of FDA review, the proposed study should contain sufficient QT monitoring to characterize this risk. In addition, provide the justification for exclusion of patients with modest QT prolongation in the proposed trial.

See FDA Additional Comments 17-20 regarding the proposed study protocol.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division or their response.

ADDITIONAL COMMENTS

Chemistry, Manufacturing and Controls (CMC)

9. FDA strongly recommends that Deciphera requests an end-of-phase 2 (EOP2) CMC only meeting to ensure that the manufacturing program is adequate for this stage of clinical development.

Deciphera's Emailed Response of 5/26/17: The Sponsor will request and EOP2 CMC only meeting end of 2017/early 2018.

Discussion During the Teleconference on 5/26/17: No discussion occurred.

Clinical

10. In Trial DCC-2618-03-001, investigators and patients may be unmasked to assigned treatment arm based on toxicity. The plan to offer DCC-2618 to patients on the placebo arm who have investigator-assessed progression may result in an imbalance in censoring based on investigator-assessed progression events that are not confirmed by the blinded independent review committee (BIRC). FDA recommends that confirmation of progression of disease based on BIRC assessment be required prior to crossover for the placebo arm; the protocol should be amended to include this provision.

    Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment at this time and thanks the Division for the comment.

11. Please note that post-progression treatment with DCC-2618 may confound interpretation of treatment effects on overall survival, either positive or negative, if one exists.

    Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

12. Please note that the outcome of post-progression dose escalation in the DCC-2618 arm as measured with PK, FDG-PET, plasma cfDNA, and CT scans would be uninterpretable and considered exploratory.

    Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

13. Clarify how patients will be selected to enroll onto Trial DCC-2618-01-001 versus Trial DCC-2618-03-001. As per the meeting package, it is likely that both trials will be accruing KIT- and PDGFRα mutant GIST patients simultaneously.

    Deciphera's Emailed Response of 5/26/17: The Sponsor intends to close enrollment in to the DCC-2618-01-001 4th and 5th Line GIST cohorts on a per site basis once the site has the 03-001 study activated (assuming the site has both studies open for enrollment).

14. If patients will be enrolled based on KIT or PDGRFα mutation status, and if eligibility is limited to a specific mutation with KIT or PDGFRα, this should be stated as part of the inclusion criteria.

    Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

15. FDA recommends that Deciphera use an FDA-approved diagnostic test if possible for KIT testing. If Deciphera intends to ultimately limit DCC-2618 indication to a specific molecularly-determined subset of patients through use of a companion diagnostic, early consultation with the Center for Devices and Radiologic Health (CDRH) is strongly

recommended. For additional information on requesting feedback from CDRH, please refer to FDA Guidance "Requests for Feedback on Medical Device Submissions: The Pre-Submission Program and Meetings with Food and Drug Administration Staff" available at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

Statistics

16. Inclusion of PRO data in the product label will depend on the adequacy of submitted data, the strengths and limitations of the instrument within the given context of use, and the design and conduct of the trial.

    a. If a claim of superiority in a particular PRO concept is sought, Deciphera must pre-specify the PRO hypothesis and test it within the statistical testing procedure controlling the overall type I error rate for testing hypotheses based on primary and all secondary endpoints. Prospectively define the statistical analysis methods, especially procedures for handling missing values. Provide justification in advance for the endpoint definition, including what constitutes meaningful change, for FDA review and comment.

    b. PRO findings without a prospectively specified statistical analysis plan are considered descriptive. FDA will review these data as part of the totality of submitted information, and will evaluate and consider whether inclusion of descriptive PRO data in labeling is appropriate on a case-by-case basis, taking into consideration any factors that may affect the interpretability and reliability of the findings.

    Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

Clinical Pharmacology

Regarding the proposed Protocol DCC-2618-03-001:

17. Consider enrollment of patients with mild to moderate renal impairment (e.g., CLcr ≥30 mL/min) and mild to moderate hepatic impairment (e.g., total bilirubin <3 time the upper limit of normal) as Deciphera intends to evaluate organ impairment on the systemic exposure of DCC-2618 and DP-5439 in the proposed registration-enabling study. Include a blood sampling schedule and data analysis to assess the effect of hepatic and renal impairment on the systemic exposure of DCC-2618 and DP-5439.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

18. Consider restriction of the concomitant use of strong inhibitors and inducers of CYP3A4 as CYP3A4 is the major enzyme metabolizing DCC-2618.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

19. Collect sparse PK samples in all patients receiving DCC-2618 to perform population pharmacokinetics and exploratory exposure-response analyses.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

20. Record the timing of the concomitant histamine H2 receptor antagonists and antacids administration relative to DCC-2618 administration. Assess the effect of concomitant histamine H2 receptor antagonists and antacids on the systemic exposure of DCC-2618 and DP-5439.

Deciphera's Emailed Response of 5/26/17: The Sponsor has no further comment and thanks the Division for comment.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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, deferred, or inapplicable. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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 (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

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 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 Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, and BLA** must be submitted in eCTD format. **Master Files** and **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

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.

ISSUES REQUIRING FURTHER DISCUSSION
None

ACTION ITEMS
None

ATTACHMENTS AND HANDOUTS
None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEAH S HER
06/01/2017