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APPLICATION NUMBER:

211810Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



FOOD AND DRUG ADMINISTRATION
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MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: Tuesday, March 20, 2018 at 2:00pm-3:00pm (EST)
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 117332
Product Name: pexidartinib (PLX3397)
Indication: Treatment of pigmented villonodular synovitis or giant cell tumor of the tendon sheath
Applicant Name: Daiichi Sankyo, Incorporated

Meeting Chair: Steven Lemery, M.D., M.H.S.
Meeting Recorder: Felicia M. Diggs, R.N., B.S.N., M.S.N.

FDA ATTENDEES

Steve Lemery, MD, MHS	Associate Director, Division of Oncology Products 2, Office of Hematology Products
Jeff Summers, MD	Deputy Director for Safety, Division of Oncology Products 2, Office of Hematology Products
Denise Casey, MD	Clinical Reviewer, Division of Oncology Products 2, Office of Hematology Products
Suzanne Demko, PA-C	Clinical Team Lead, Division of Oncology Products 2, Office of Hematology Products
John Senior, MD	Medical Officer, Office of Pharmacovigilance & Epidemiology
Shawna Weis, PhD	Non-Clinical Reviewer, Division of Hematology & Toxicology, Office of Hematology Products
Whitney Helms, PhD	Non-Clinical Team Lead, Division of Hematology & Toxicology, Office of Hematology Products
Brian Furmanski, PhD	Senior Clinical Pharmacology Reviewer, Division of Clinical Pharmacology V, Office of Clinical Pharmacology
Jiang Liu, PhD	Pharmacometrics Team Lead, Division of Pharmacometrics, Office of Clinical Pharmacology

Hong Zhao, PhD	Clinical Pharmacology Team Lead, Division of Clinical Pharmacology, Office of Clinical Pharmacology
Naomi Redd	Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology
Elizabeth Everhart	Safety Regulatory Project Manager, Office of Surveillance and Epidemiology
Manasi Sheth-Chandra, PhD	Statistical Reviewer, Division of Biometrics V, Office of Biostatistics
Kun He, PhD	Statistical Associate Division Director, Division of Biometrics V, Office of Biostatistics
Felicia Diggs, RN, BSN, MSN	Regulatory Health Project Manager, Division of Oncology Products 2, Office of Hematology Products

SPONSOR ATTENDEES

Glenn Gormley, MD, PhD	Senior Executive Officer, Global Head R&D
Sandra Hamelsky, PhD, MPH	Director, Regulatory Affairs, Oncology
Eric Richards, MS, MPH	Vice President, Global Affairs, Oncology
Dale Shuster, PhD	Executive Director, Clinical Development, Oncology
Antoine Yver, MD, MSc	Executive Vice President and Global Head Oncology R&D
(b) (4) (Consultant)	(b) (4)
Qiang Wang, PhD	Director, Biostatistics

BACKGROUND

Regulatory

Since the submission of Investigational New Drug Application (IND) 117332, for PLX3397, clinical trials have been conducted under three INDs held by Plexxikon and its affiliates across Daiischi Sankyo Incorporated (DSI), to treat patients with solid tumors, acute myeloid leukemia, and prostate cancer.

- On July 21, 2009, Plexxikon submitted Investigational New Drug Application (b) (4) containing the protocol for Study PLX108-01, a dose-finding study of PLX3397 in patients with refractory solid tumors. The IND was deemed safe to proceed on August 19, 2009, and the study initiated in October 2009. This study is ongoing and includes an expansion cohort for patients with inoperable pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS).
- On March 11, 2013, pre-IND 117332 was opened with the submission of a Type B meeting request that was granted and subsequently withdrawn.

- On November 27, 2013 Plexxikon submitted a pre-IND/pre-Phase 2/3 meeting request to discuss a proposed clinical protocol and registration plan for PLX3397 for patients with symptomatic PVNS or GCT-TS for whom surgery is not a feasible option.
- On February 14, 2014, PLX3397 HCl was granted orphan drug status for the “Treatment of pigmented villonodular synovitis/giant cell tumor of tendon sheath” (Office of Orphan Product Development).
- On February 27, 2014, Plexxikon met with FDA to discuss the design of Study PLX108-10, intended to support a marketing application for PLX3397 in patients with PVNS and GCT-TS. The following key points were made:
 - Durable objective response (DOR) of sufficient magnitude supported by reliably detected effects on clinically important patient functional status and patient reported outcomes (PROs) may serve as a basis to support approval.
 - Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be the primary efficacy endpoint, and response rate according to the protocol specific Tumor Volume Score (TVS), will be assessed as a secondary endpoint.
 - PRO endpoints could provide useful supportive data if it can be shown that they reliably measure an improvement in pain or function in patients with PVNS.
 - A post-marketing study might be required to establish an optimal dose because the product may be administered chronically.
 - Given the rarity of the disease, the estimated safety database of patients treated with PLX3397 in conjunction with the safety database accumulated in clinical trials of PLX3397 in other patient populations may be sufficient to support a marketing application provided that no unusual toxicities are identified.
 - A single trial could support an application for registration if the results show a highly statistically significant effect on a measure of clinical benefit and are sufficiently robust and so compelling that it would be unethical to repeat the study in this rare disease population.
 - FDA recommended that DSI incorporate a reliable objective measure of functional improvement.
 - FDA emphasized that the results of PRO endpoints may not be interpretable if there are substantial missing data or due to inadvertent unblinding issues.
- On September 29, 2014, Plexxikon submitted IND 117332 which contained the protocol for Study PLX108-10 entitled, “A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath.” It was deemed safe to proceed.

- Also submitted on September 29, 2014, was a Special Protocol Assessment (SPA) request for Study PLX108-10. Clinical and statistical concerns pertaining to the proposed eligibility criteria, the methods of collecting and analyzing key patient reported outcomes, secondary endpoints, and the proposed statistical test for the primary efficacy analysis, were communicated to Plexxikon during a teleconference on November 4, 2014. A Special Protocol No Agreement letter was issued on November 12, 2014, with comments detailing the necessary protocol revisions for an SPA agreement to be reached. On January 30, 2015, Plexxikon informed FDA that they would not re-submit the SPA request.
- On February 10, 2015, Plexxikon transferred the legal and regulatory obligations for PLX3397 under IND 117332 to Daiichi Sankyo, Incorporated.
- On June 26, 2015, FDA and DSI participated in a teleconference as part of the Office of Hematology and Oncology Products Preliminary Breakthrough Therapy Designation Request (BTDR) process, to discuss the preliminary efficacy results from patients with PVNS or GCT-TS treated in Study PLX108-01. FDA informed DSI that the preliminary data was sufficient to support the submission of a formal Breakthrough Therapy Designation Request. The BTDR was submitted to FDA on September 3, 2015.
- On October 28, 2015, PLX3397 was granted Breakthrough Therapy Designation for the treatment of patients with PVNS or GCT-TS where surgical resection is associated with potentially worsening functional limitation or severe morbidity. The BTDR was based on evidence of durable response rate in patients treated in Study PLX108-01.
- On February 19, 2016, DSI submitted a request for a Type B/multidisciplinary Breakthrough Therapy meeting, as a result of the October 28, 2015, Breakthrough Therapy designation. The meeting purpose was to present an overview of the pexidartinib development program for the treatment of patients with symptomatic tenosynovial giant cell tumor (TGCT) and to obtain FDA's feedback on proposals to expedite the development program. Preliminary responses were sent to DSI on April 7, 2017, and the meeting subsequently was cancelled.
- On March 29, 2016, a Type B meeting was held to discuss topics related to the CMC development for PLX3397.
- On October 12, 2016, FDA placed IND 117332 on partial clinical hold and halted further enrollment into Study PLX108-10 due to reported serious adverse events (SAEs) of hyperbilirubinemia with concurrent liver enzyme elevation in patients with TGCT and in patients with cancer treated under other INDs. On March 16, 2017, DSI provided a complete response to the partial clinical hold that satisfactorily addressed the issues, and the hold was removed on April 10, 2017.
- On July 24, 2017, DSI submitted a Type B meeting request to obtain the Agency's feedback on the proposal to revise the order of the sequential hierarchy for testing of

secondary efficacy endpoints in Study PLX108-10. On September 6, 2017, FDA provided DSI with preliminary comments, and the meeting subsequently was cancelled.

- On October 16, 2017, DSI submitted a Type A meeting request to discuss the best way to move forward regarding clinical pharmacology study (PL3397-A-U126) and to obtain FDA feedback on the suitability of the tenosynovial giant cell tumor data package for New Drug Application (NDA) review. The meeting was denied because the information contained in the meeting request did not meet the criteria for a stalled development program. However, FDA provided a response to question #1 in the meeting package to facilitate DSI's drug-drug interaction program.
- On November 9, 2017, DSI requested a Type B meeting to discuss the clinical pharmacology program for pexidartinib for the treatment of patients with symptomatic TGCT. The meeting was held via teleconference on January 12, 2018.
- On November 13, 2017, FDA placed IND 117332 on partial clinical hold and halted further enrollment into other trials across the development program for pexidartinib, due to additional reports of serious adverse events of hepatotoxicity. DSI provided a complete response to the partial clinical hold on December 20, 2017, that satisfactorily addressed the hold issues by revising the protocol to increase frequency of monitoring for hepatotoxicity, incorporating additional risk mitigation strategies in the protocol, and amending the informed consent and Investigator's brochure. The hold was removed on January 12, 2018.
- On January 19, 2018, DSI submitted a Type B pre-New Drug Application (pNDA) meeting request to obtain guidance for a planned NDA submission for pexidartinib for the treatment of symptomatic tenosynovial giant cell tumor.

The purpose of this meeting is to discuss a planned NDA submission based on the results of Study PLX108-10 (ENLIVEN). The background package was received on February 13, 2018, and included objectives on clinical efficacy and safety, clinical pharmacology, data format and submission, and administrative topics.

Clinical Pharmacology

Per DSI, 14 clinical pharmacology studies with pexidartinib have been completed including formulation comparison, food effect, acid reducing agent effect, relative bioavailability, mass balance, CYP enzyme inhibition and induction, UGT and P-gp inhibition, QT, and renal and hepatic impairment studies (see table below). DSI has 1 ongoing study (PL3397-A-U126) to evaluate the induction and inhibition effects of pexidartinib on CYP3A4 and the inhibition effect on CYP2C9 following multiple doses of pexidartinib. The study report of PL3397-A-U126 will be submitted post-marketing. In a previous IND submission (IND 117332 SDN 101), DSI provided a plan to evaluate the oral contraceptive drug-drug interaction potential with pexidartinib as the perpetrator based on the results from Study PL3397-A-U126 and submit the study report post marketing.

Protocol No.	Protocol Title	Status
PLX108-11	A Phase 1, Open-label, Randomized, Three-Treatment, Three-Period, Three-Sequence, Crossover Study to Evaluate the Effect of Food and the Proton Pump Inhibitor Esomeprazole on the Pharmacokinetics of PLX3397 in Healthy Subjects	Completed
PL3397-A-U114	A Phase 1, Open-Label, Randomized, 3-Period, 3-Way Crossover Study to Assess the Relative Bioavailability and Food Effect of a New Formulation of PLX3397 in Healthy Subjects	Completed
PL3397-A-U115	An Open-label, Single-dose, Mass-balance Study to Assess the Disposition of ¹⁴ C-labeled Pexidartinib in Healthy Male Volunteers	Completed
PL3397-A-U116	A Phase 1, Open-Label, Randomized, 2-period, 2-way Crossover Study to Assess the Relative Bioavailability of Pexidartinib in Healthy Subjects	Completed
PL3397-A-U117	An Open-Label Randomized Phase 1, Three-Treatment, Three-Period Crossover Study to Assess the Dose Proportionality of Pexidartinib (200 to 600 mg) in Healthy Subjects	Completed
PL3397-A-U118	An Open-Label, 2-Treatment, 2-Period, Single-Sequence Study to Evaluate the Effect of Itraconazole on the Pharmacokinetics of Pexidartinib in Healthy Subjects	Completed
PL3397-A-U119	An Open-Label, 2-Treatment, 2-Period, Single-Sequence Study to Evaluate the Effect of Rifampin on the Pharmacokinetics of Pexidartinib in Healthy Subjects	Completed
PL3397-A-U120	An Open-Label, Randomized, 2-Treatment, 2-Period, Crossover Study to Evaluate the Effect of Esomeprazole on the Pharmacokinetics of Pexidartinib in Healthy Subjects	Completed
PL3397-A-U121	A Phase 1, Single-Blind, Placebo-Controlled, Single-Dose Escalation Study to Assess the Pharmacokinetics of Pexidartinib in Healthy Subjects	Completed
PL3397-A-U122	An Open-label, Randomized, 2-treatment, 2-Period, Crossover Study to Evaluate the Effect of Probenecid on the Pharmacokinetics of Pexidartinib in Healthy Subjects	Completed
PL3397-A-U123	An Open-label, Single-dose Study to Assess the Pharmacokinetics of Pexidartinib in Subjects with Hepatic Impairment Compared to Healthy Subjects	Completed
PL3397-A-U124	An Open-label, Single-dose Study to Assess the Pharmacokinetics of Pexidartinib in Subjects with Various Degrees of Renal Function	Completed
PL3397-A-U125	A Double-blind, Placebo- and Active-controlled (Open-label Moxifloxacin), 3-treatment Crossover Study to Determine the Effect of Pexidartinib on QTc Interval in Healthy Subjects	Completed
PL3397-A-U126	An Open-Label, Single Sequence, Crossover Drug-Drug Interaction Study Assessing The Effect of Pexidartinib on the Pharmacokinetics of CYP3A4 and CYP2C9 Substrates in Patients	Study start-up
PL3397-A-U127	An Open-label, 4-treatment, 4-period, Single-sequence Drug-drug Interaction Study to Determine the Effect of Pexidartinib on the Pharmacokinetics of Omeprazole and Digoxin in Healthy Subjects	Completed

Source: Page 1 and 2 of appendix 3 in the current meeting package

Nonclinical

Pexidartinib is a multi-kinase inhibitor that exhibits activity against CSF1R (Fms), cKit, and FLT3. Under IND (b) (4) DSI has submitted a full panel of GLP-compliant toxicology studies, including 6- and 9-month studies in the rat and dog, respectively; a full panel of reproductive toxicology studies (embryo fetal studies in rats and rabbits, PPNF and fertility studies in the rat); and a full panel of genetic toxicology studies. A 26-week carcinogenicity study in the Tr.rasH2 mouse model has also been completed and submitted under IND (b) (4) In the

responses to DSI's Type B meeting, dated 04 April 2016, FDA agreed to DSI's request to submit the reports of the Segment III reproductive toxicology study as a post-marketing requirement. The final report of this study was submitted on 28 April 2017. FDA also agreed that the report of the 2-year carcinogenicity study in the rat could be submitted as a post-marketing requirement if the weight of evidence, including data from the 6-month carcinogenicity study in the mouse, indicated a lack of carcinogenic risk with pexidartinib.

Clinical

Disease Background

PVNS and GCT-TS are rare diseases and are considered subtypes of tenosynovial cell giant tumor. According to the briefing package, PVNS and GCT-TS have an estimated annual incidence of 1.8 cases per million and 9.2 cases per million, respectively, in the United States. Patients are usually diagnosed between the ages of 20 and 60 years and most often present with pain and swelling at the affected joint. The knee is the most frequently involved joint for patients with PVNS, while GCT-TS often presents in the wrist and finger joints. The clinical course is generally not life threatening; however, if left untreated, the tumor continues to expand within the limited intraarticular space and can lead to worsening pain, swelling, stiffness, and limitation in range of motion (ROM) at the involved joint. The current standard of care is surgical resection using arthroscopic synovectomy or open resection. External beam radiation can be administered in select cases where surgery is not feasible. The goals of treatment are to reduce tumor-related symptoms of pain, stiffness, and immobility and to lessen the risk of recurrence. The overall recurrence rate for patients with focal localized disease is low, ranging from 0% to 6%; however, in patients with diffuse forms of the disease, recurrence is estimated to be in the range of 40% or higher. Multiple recurrences and repeated surgical resections can lead to decreased joint function, chronic pain and stiffness, and disfigurement or other postsurgical morbidities. There are no systemic therapies approved for treatment of patients with PVNS or GCT-TS.

PVNS and GCT-TS have a common immunophenotype, pathogenesis, and genetic profile. The tumors consist of collections of mononuclear and multinucleated giant cells, and tumor growth appears to be driven by a mutation involving chromosome 1p13 which induces overexpression of colony stimulating factor-1 (CSF-1) on the tumor cells triggering migration of non-neoplastic monocytes and macrophages expressing the CSF-1 receptor (CSF1R) to the tumor site. The bulk of the tumor mass appears to consist of these inflammatory cells.

Pexidartinib: Clinical Development Program in TGCT

Patients with TGCT were treated in two studies: PLX108-01 under IND (b)(4) and PLX108-10 under IND 117332.

Study PLX108-01

Study PLX108-01 is an open-label, two-part, dose-escalation study with disease-specific expansion cohorts. In the dose-escalation part of the study, patients with advanced solid tumors received daily pexidartinib at oral doses ranging from 200 to 1200 milligrams (mg). The identified recommended dose was 1000 mg/day administered as a split dose. A total of 39 patients were enrolled and treated in a TGCT expansion cohort. The primary endpoint was ORR. The secondary efficacy endpoints included response rate according to volumetric magnetic

resonance imaging (MRI), progression free survival, and DOR. According to the briefing document, 23 of the 37 evaluable patients had a confirmed response based on investigator assessments using RECIST 1.1, for an ORR of 62% (95% CI: 44.8 to 77.5) and a median duration of response of 18 months at the data cutoff date of March 7, 2017.

The most common treatment emergent adverse events (TEAEs) were fatigue, hair color changes, nausea, arthralgia, periorbital edema, dysgeusia, diarrhea, pruritus, headache, rash, and peripheral edema. The most frequent Grade 3 or 4 adverse events (AEs) were hypophosphatemia, increased alanine aminotransferase (ALT) or alkaline phosphatase (AST), and diarrhea. There were six treatment-related SAEs in five patients: acute kidney injury, renal cell carcinoma, neck pain, elevated transaminases, hyponatremia, and cholecystitis.

Study PLX108-10 (ENLIVEN)

Study PLX108-10, entitled “A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered Pexidartinib in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath” was a two part, randomized, double-blind, placebo-controlled trial in patients with symptomatic TGCT with recurrence or for whom planned surgery may result in worsening function, limitation, or severe morbidity.

A total of 120 of a planned 126 patients were randomized in a 1:1 ratio to receive either pexidartinib or placebo for 24 weeks. Randomization was stratified by U.S. versus non-U.S. sites and by upper extremity versus lower extremity joint involvement. For the first two weeks of the trial, patients randomized to the pexidartinib arm received 1000 mg daily followed by 800 mg daily thereafter administered as a split dose. In Part 1, tumor assessment by MRI was performed at Weeks 13 and 25; range of motion assessments were performed at the same times. PRO measures were reported at Weeks 9, 17, and 25. Patients who completed Part 1 were eligible for enrollment into Part 2, an open-label extension phase in which all patients received pexidartinib.

The primary endpoint was centrally reviewed ORR per RECIST 1.1 at Week 25 on the intent to treat (ITT) analysis set. Secondary endpoints included mean change from baseline in range of motion, response rate using tumor volume score (TVS), and multiple PROs, including the patient-reported outcomes measurement information system (PROMIS) physical function scale, the worst stiffness numerical rating score (NRS) item and the BPI worst pain NRS item. A hierarchical (“gatekeeping”) testing procedure was to be applied to secondary endpoints.

The ORR for the 61 patients treated with pexidartinib during Part 1 was 39% (95% CI: 28, 52) with no responders experiencing disease progression after a median follow-up of six months. The following tables, copied from the briefing document, provide a summary of the efficacy results for Study PLX108-10.

Table 4.6: Overall Response Rate in Part 1

End of Part 1 Assessment	Randomized to Placebo (N=59)	Randomized to Pexidartinib (N=61)	Difference in % (Pexidartinib – Placebo)
Complete Response			
n (%)	0 (0.0)	9 (14.8)	
95% CI	0.00, 6.11	7.96, 25.72	
Partial Response			
n (%)	0 (0.0)	15 (24.6)	
95% CI	0.00, 6.11	15.51, 36.68	
Stable Disease			
n (%)	46 (78.0)	24 (39.3)	
95% CI	65.87, 86.65	28.07, 51.88	
Progressive Disease			
n (%)	1 (1.7)	1 (1.6)	
95% CI	0.30, 9.00	0.29, 8.72	
Not Evaluable			
n (%)	12 (20.3)	12 (19.7)	
95% CI	12.04, 32.27	11.63, 31.31	
ORR (CR or PR)			
n (%)	0 (0.0)	24 (39.3)	39.34
95% CI	0.00, 6.11	28.07, 51.88	26.52, 51.88
Fisher's Exact Test <i>P</i> -value (1-sided)			<0.0001

CI = confidence interval; CR = complete response; PR = partial response

Table 4.7: Results for Secondary Efficacy Endpoints of Phase 3 Study PLX108-10

Secondary Endpoint in Sequential Hierarchy	Placebo (SE) [95% CI]	Pexidartinib (SE) [95% CI]	<i>P</i> -value
Range of Motion (LS mean change from baseline in % normal reference for corresponding joint and plane of motion)	6.20% (2.374) [1.49, 10.91]	15.07% (2.086) [10.93, 19.22]	0.0043 (2-sided)
Tumor Volume Score Response	0% (NC) [0.00, 6.11]	55.7% (NC) [43.30, 67.49]	<0.0001 (1-sided)
PROMIS LS mean change from baseline; NIH Instrument; Normal Average = 50	-0.89 (1.038) [-2.95, 1.16]	4.06 (1.132) [1.82, 6.30]	0.0077 (2-sided)
Worst Stiffness NRS Change from Baseline; 0 (normal) – 10	-0.28 (0.292) [-0.86, 0.30]	-2.45 (0.293) [-3.03, -1.87]	<0.0001 (2-sided)
BPI-30 Pain Response, ≥30% Improvement from Baseline w/o Increased Analgesic Use	15.3% (NC) [8.24, 26.52]	31.1% (NC) [20.94, 43.59]	0.032 (1-sided)

CI = confidence interval; LS = least squares; NC = not calculated; NIH = National Institutes of Health; NRS = numerical rating system; SE = standard error

Table 4.8: Tumor Response in the Cohort that Crossed Over to Pexidartinib at Week 25 of Part 2

	Pexidartinib Crossover in Part 2 (n=30)
RECIST 1.1 CR+PR	
n (%)	9 (30.0)
95% CI	16.7, 47.9
TVS Response	
n (%)	17 (56.7)
95% CI	39.2, 72.6

CI = confidence interval; CR = complete response; PR = partial response; NRS = numerical rating system;

The safety data reported from Study PLX108-10 were generally consistent with the results from PLX108-01. Fourteen patients (15%) discontinued pexidartinib due to an AE; eight of these patients experienced liver toxicity and six patients experienced non-liver AEs. Eight patients (9%) had treatment-related SAEs six of which were hepatic AEs. Four of the six patients experienced concurrent hyperbilirubinemia and three of these patients had a total bilirubin greater than 2 times the upper limit of normal (ULN). In most cases, the laboratory abnormalities resolved with discontinuation of the drug and time; however, one patient in PLX108-10 experienced cholestatic liver injury which lasted approximately seven months. Across the pexidartinib development program, there have been other serious cholestatic liver events in patients with various cancers including one fatal event and another prolonged cholestatic liver injury that required liver transplantation.

DISCUSSION

Clinical Efficacy and Safety

- The pexidartinib clinical development program to date comprises 27 studies sponsored by DSI or its subsidiary Plexxikon (Table 3.1). Across these studies, 630 subjects with cancer or TGCT received pexidartinib and were assessed for safety and efficacy in 13 sponsored clinical studies, two of which were focused in the target indication, TGCT. A total of 338 healthy subjects have received pexidartinib in 14 sponsored clinical pharmacology studies and, in addition, 138 subjects have received pexidartinib in eight investigator-initiated studies. Additional detail for all clinical studies is available in Appendix 1.*

Summary of the Pexidartinib Clinical Development Program*

Study	Subjects Treated	Population	IND Number
Studies in TGCT Indication			

PLX108-10 (ENLIVEN)	120 (91 with pexidartinib)	TGCT	117,332
PLX108-01 (TGCT Cohort)	39	TGCT	(b) (4)
Studies of Pexidartinib Monotherapy in Patients with Cancer			
PLX108-01 (non-TGCT Cohort)	93	Non-TGCT solid tumor	(b) (4)
PLX108-03	20	Hodgkin's lymphoma	(b) (4)
PLX108-04	38	Glioblastoma multiforme	(b) (4)
PLX108-05	90	Acute myeloid leukemia (AML)	(b) (4)
PLX108-06	6	Prostate cancer	(b) (4)
PLX108-13	6	Kinase receptor (KIT)-mutant Melanoma	Non-IND study
PL3397-A-A103	11	Solid tumors, one TGCT subject	Non-IND study
Studies of Pexidartinib as Combination Therapy in Patients with Cancer			
PLX108-07 (+ paclitaxel)	74 (68 with pexidartinib)	Solid tumors	(b) (4)
PLX108-08 (+ temozolomide, RT)	65	Glioblastoma multiforme	(b) (4)
PLX108-09 (+ vemurafenib)	13	BRAF mutant melanoma	(b) (4)
PLX108-14 (+ pembrolizumab)	78	Solid tumors	(b) (4)
PLX121-01 (+PLX9486)	12	Solid tumors	(b) (4)
Other Pexidartinib Studies			
Clinical pharmacology studies (14 studies)	338	Healthy subjects	(b) (4)
Investigator-initiated studies (8 studies)	138	Solid and hematologic tumors	IIS IND

DSI position on question #1 may be found on pages 17-20 of the meeting background package.

The Sponsor believes that with a restricted indication, proper labeling, and an appropriate risk evaluation and mitigation strategies (REMS), pexidartinib offers a relevant treatment option for select TGCT patients and, therefore, consideration of an NDA seeking approval for treatment in this population is warranted. Does the FDA agree?

FDA Response:

FDA agrees that consideration of an NDA seeking approval for pexidartinib in an appropriate subgroup of patients with TGCT in which the likelihood of obtaining clinical benefit from pexidartinib outweighs the risks associated with pexidartinib treatment is warranted. In the NDA, include adequate justification for the proposed restricted indication and a robust benefit:risk assessment for pexidartinib for this subgroup. FDA will review the totality of the efficacy and safety data in the application and if necessary, may seek advice from an Advisory Committee (AC) prior to taking an action on the application for pexidartinib in TGCT.

See question # 9 regarding the proposed REMS.

DSI Response sent electronically March 15, 2018:

DSI would like to further discuss question #1.

Discussion during the meeting:

DSI asked FDA if the Agency had preliminary thoughts regarding potential discussion items in an advisory committee. FDA anticipated that an advisory committee would discuss risk versus benefit. FDA also anticipated that an advisory committee would discuss the appropriate population if pexidartinib is approved. FDA recommended that DSI discuss why the totality of the available evidence overcomes the limitations in the collection of PRO information.

FDA recommended that DSI provide any supportive information they have to support efficacy, which may include pictures.

- 2. The dose regimen of 800 mg/day (400 mg twice a day (BID)) to be proposed in the NDA is revised from the dose regimen of 1000 mg/day for two weeks followed by 800 mg/day (400 mg BID) used in Part I of PLX108-10. The Sponsor acknowledges that it is unknown whether a starting dose of 800 mg/day will attenuate the risk of hepatotoxicity. But it is unlikely that a starting dose of 800 mg/day versus 1000 mg/day for the first two weeks of treatment will substantively reduce the overall efficacy, given the long-term duration of therapy for most patients and the clinical activity observed in the crossover cohort of 30 subjects who began treatment with pexidartinib at 800 mg/day (Section 4.2.3). With this in mind, and the serious nature of the hepatotoxicity primarily observed in the first eight weeks of therapy, the initial two-week treatment with the higher (1000 mg/day) dose of pexidartinib would appear unjustifiable.*

In the proposed NDA, modeling and simulation analyses will explore the exposure-response relationship for efficacy and safety (Question 11); however, the robustness of the efficacy analysis will be limited because of the narrow dose range used in TGCT patients studied to date. Dose response data for the pharmacodynamic biomarker, CSF-1, will be included. Preclinical results in various animal disease models will also be submitted, but it should be noted there is no

established correlation between the biomarker or preclinical results and safety or efficacy in the TGCT population. The Sponsor recognizes acceptance of this dose will be a review issue and is seeking advice as to any additional analyses that would assist FDA in its review.

The Sponsor is proposing a dose of 800 mg /day (400 mg BID), which is different than the dose used in the randomized part of the Phase 3 study. The NDA will include the rationale for the proposed dose, available clinical data at that dose, as well as modeling and simulation analyses. Are there any other analyses that would assist the FDA's review of the proposed dose and dosing regimen?

FDA Response:

Overall, FDA agrees with the dose justification approach. Please see the response to Question 11 for FDA's recommendations on additional analyses to support the proposed dose and dosing regimen.

DSI Response sent electronically March 15, 2018:

Question #2 is clear and no further discussion is needed.

3. *DSI position for question #3 may be found on pages 21-23 of the meeting background package.*

Does the FDA agree with the Sponsor's plan for summarizing clinical efficacy (M2.7.3) from PLX108-10 and the TGCT cohort of PLX108-01?

FDA Response:

Efficacy Populations

FDA acknowledges and agrees with the rationale for not pooling the primary efficacy data from Studies PLX108-01 and PLX108-10, which were designed differently, evaluated different dosing regimens and endpoints, and used different formulations of pexidartinib.

Presenting efficacy results by the following groups appears reasonable: the 61 patients who received pexidartinib as compared to the 59 patients who received placebo during Part 1 of PLX108-10; the 30 patients who initially received placebo and then crossed over to receive pexidartinib in Part 2 of PLX108-10, the 61 patients who received pexidartinib and were followed on study during Part 1 and Part 2 of PLX108-10 (i.e., those initially randomized to pexidartinib for the randomized portion of the trial and who continued on the single arm Part 2 of the study); and the 39 patients who were treated in the TGCT cohort of PLX108-01.

Response rate and duration of response

FDA agrees with DSI's plan to evaluate and summarize the radiographic response rate and DOR results according to RECIST and TVS for Studies PLX108-01 and PLX108-10 by the patient groups listed above. Note that response rates should be calculated based on the intent-to-treat population and should not exclude patients who were treated with pexidartinib but did not have evaluable disease based on the absence of a baseline or post-baseline scan. Provide side by side summary tables in the Summary of Clinical Efficacy (SCE) to present these results. If there are

differences in the ORR and DOR results between the groups, provide a robust analysis of why these cohorts might respond differently to pexidartinib.

Include exploratory analyses of response rate and DOR that pools the 91 patients treated with pexidartinib in PLX108-10 with the 39 patients who received pexidartinib in PLX108-01.

Clinical Outcomes Assessments

FDA agrees with DSI's general proposal for evaluating the clinical outcomes data from PLX108-10; however, FDA requests confirmation that the following analyses will be conducted and included in the SCE (or Integrated Summary of Efficacy if appropriate):

- a comparison of the mean change from baseline for range of motion, PROMIS, and worst stiffness and worst pain assessments between all patients treated with pexidartinib versus placebo during the randomized portion (Part1) of PLX108-10
- a comparison of the mean change from baseline for range of motion, PROMIS, and worst stiffness and worst pain measures between the patients treated during the randomized portion of PLX108-10 who had a valid baseline and at least one post-baseline assessment
- associations between tumor response rate and range of motion, PROMIS, and worst stiffness and worst pain endpoints to demonstrate that tumor shrinkage correlates with improvement in clinical outcomes
- a sensitivity analysis that addresses the missing PRO and range of motion data on both arms of Part 1 of PLX108-10

In addition to the assessment of mean change from baseline in ROM relative to a reference standard for the same joint, a thorough discussion of the actual clinical benefit of improved ROM in individual patients based upon the specific joint involved and the extent of impairment at baseline should be included in the SCE.

FDA acknowledges and agrees to the submission of a separate PRO report in Module 5.3.5.3 to support the use of the selected PRO measures in PLX108-10; however, it is unlikely that labeling claims can be made if there is significant missing data even if the tools are validated for the study population.

Patient Narratives and Photographic Data

FDA agrees with the submission of individual patient efficacy narratives for patients treated during PLX108-10. These narratives should provide the patient's best response to pexidartinib (if any) and discuss any correlative improvements observed in the patient's disease-related symptoms and functional status. If the patient is considered to have had clinical benefit during treatment with pexidartinib, include examples of this benefit (e.g., ability to ambulate following tumor shrinkage during treatment with study drug). Include available and relevant photographic assessments in the narratives. Alternatively, you may include photographic data in a separate file in the application with active hyperlinks in the narratives.

Provide individual patient narratives for patients treated with pexidartinib during PLX108-01 in addition to the planned narratives for patients in PLX108-10. FDA acknowledges that this was a single-arm trial during which relevant clinical outcomes were not routinely measured in the same way as during PLX108-10; however, additional correlations between radiographic responses and improvements in symptomatology and/or functional impairments could be supportive in the overall risk:benefit assessment. Include relevant photography as part of these narratives when available.

FDA agrees with the proposal to submit available photographic data from Studies PLX108-01 and PLX108-10 as supportive evidence of the clinical benefit provided with pexidartinib.

Updated efficacy data

All primary and updated efficacy data to support the application should be included in the original NDA. Clarify the content of the proposed updated efficacy data with a data cutoff date of January 31, 2018, and confirm that these data will be included in the original NDA.

DSI Response sent electronically March 15, 2018:

Question #3 requires no further discussion. DSI confirms that updated efficacy and safety data based on the January 31, 2018 datacut will be included in the original NDA submission. In terms of datasets, DSI will provide the following datasets for both PLX108-01 and PLX108-10 (ENLIVEN):

- SDTM and ADaM datasets for the March 2017 datacut
- ADaM datasets for the Jan 31, 2018 datacut

Discussion during the meeting:

No further discussion was necessary.

4. *DSI position on question #4 may be found on pages 23-25 of the meeting background package.*

Does the FDA agree with the Sponsor's plan to pool and summarize safety data (M2.7.4, Summary of Clinical Safety) across the pexidartinib clinical development program?

FDA Response:

FDA agrees with DSI's plan to pool the safety data from Studies PLX108-01 and PLX108-10 to provide the primary integrated safety analyses for the Summary of Clinical Safety (SCS) and to pool safety data from patients with non-TGCT solid tumor malignancies who received single-agent pexidartinib across the pexidartinib development program to conduct supportive safety analyses. Safety analyses from Study PLX108-05 (AML trial) should also be included, though these data need not be pooled with the solid tumor data. FDA may additionally request exploratory analyses of pooled data across both the TGCT and cancer populations that have been exposed to pexidartinib for specific safety signals that are observed during the review of the NDA.

Provide side-by-side summary tables to present key safety information from all patients with TGCT, non-TGCT solid tumors, and AML treated with pexidartinib, regardless of dose.

It is acceptable to include the updated safety results for the 80 patients with TGCT who were continuing pexidartinib after the March 2017 cutoff date as amendments to the respective clinical study reports. These data should be included in the original NDA submission. For the SCS, in addition to a thorough discussion of these updated results in the context of the primary analyses, provide side-by-side tables of key safety analyses (exposure, adverse events, discontinuations, and dose interruptions and reductions) for safety results as of the March 2017 cutoff and as of the January 2018 cutoff.

DSI Response sent electronically March 15, 2018:

Question #4 is clear and no further discussion is needed.

5. *DSI position on question #5 may be found on pages 25-26 of the meeting background package.*

Does the FDA agree with the proposed approach to summarize hepatic safety, including cases of cholestatic liver injury?

FDA Response:

DSI's approach to evaluating the pexidartinib development program for the hepatotoxicity signal appears reasonable; however, FDA may request additional analyses based on review of the data in the application. DSI should provide a thoughtful assessment of this risk that discusses the mechanism of liver injury, ways to mitigate risk for patients, and how this toxicity impacts the overall benefit:risk assessment for pexidartinib in the intended indication. Include this information in the SCS.

Provide summary tables that list all patients in the TGCT development program and all patients in the non-TGCT pexidartinib program who experienced elevation of transaminases and elevation of bilirubin concurrent with or following transaminitis. Include columns for patient identification (ID), diagnosis, risk factors, concomitant medications, pexidartinib dose, time of initial event, presenting symptoms, peak laboratory values, duration of transaminitis and hyperbilirubinemia in days, actions taken with study drug, other medical interventions (e.g., hospitalization, liver biopsy, etc.), and whether there was resolution.

Provide copies of all liver biopsy reports with hyperlinks in the respective patient narratives.

Provide a flag in the safety dataset for patients who experienced laboratory abnormalities that met (the laboratory components of) Hy's Law criteria.

Please view the eDISH data specifications for the proposed eDISH plots available via Firefox at: <http://edish.fda.gov/edish>.

DSI Response sent electronically March 15, 2018:

Question #5 is clear and no further discussion is needed.

Clinical

- The Sponsor proposes that the narrative portion of the Integrated Summary of Safety (ISS) be located in Module 2.7.4, including the in-text tables and figures. Additional tables, listings, and figures will be included in Module 5 with hyperlinks provided in Module 2.7.4. Given the size of the pooled analysis set, Module 2.7.4 will allow sufficient space to adequately describe the results with tables (non in-text), appendices, and datasets located in Module 5.*

Does the FDA agree with the Sponsor's plan to include the narrative portion of the integrated summary of safety in Module 2.7.4 with a hyperlink to the tables, listings, and figures of the integrated analysis of pooled data located in Module 5?

FDA Response:

The plan to include the narrative portion of the ISS in Module 2.7.4 with a hyperlink to the tables, listings, and figures of the integrated analyses of pooled data located in Module 5 could be acceptable if there is sufficient space to provide a robust and thoughtful discussion of the integrated safety data that permits a thorough assessment of the risks and benefits of pexidartinib in the proposed population. Summary tables of key results from the pooled analyses (with footnotes and hyperlinks to the relevant Module 5 tables/listings) should be included in Module 2 to support the relevant text discussions in the SCS.

DSI Response sent electronically March 15, 2018:

Question #6 is clear and no further discussion is needed.

- DSI position on question #7 may be found on pages 27-28 of the meeting background package.*

Does the FDA agree with the proposed approach to summarize safety data related to cognitive disorder, cardiac function, and myelosuppression?

FDA Response:

DSI's proposal to evaluate cardiac function and myelosuppression as categories of adverse events of special interest (AESI) across the pooled safety data from TGCT and non-TGCT patient cohorts and to specifically analyze frequency, severity, relationship to study drug, and action taken with regard to study drug and study appears acceptable. Patient narratives for all AESIs that occurred up until the January 2018 cutoff date should be included in the application.

Provide a rationale, including examples of the specific types of cognitive disorders that have occurred in patients treated with pexidartinib, for evaluating the broad category of "cognitive disorder" as an AESI. What methods were used to create the list of preferred terms (PTs) that will be included in the cognitive disorder category?

DSI Response sent electronically March 15, 2018:

Question #7 is clear and no further discussion is needed.

8. *The Sponsor will submit safety narratives for all of the following events:*

- All deaths during treatment or within 30 days of treatment discontinuation
- All deaths after 30 days of treatment discontinuation reported as related to pexidartinib treatment
- All SAEs
- All discontinuations due to AEs, excluding disease progression
- All AEs judged to be of special interest (See Question 7)
- All events meeting liver function test (LFT) signature criteria of transaminases increased with hyperbilirubinemia (see Question 5)

Does the FDA agree with the Sponsor's submission plan for safety narratives?

FDA Response:

FDA agrees with the plan to submit safety narratives for the events listed above. Narratives for any of these events that occurred up until the January 2018 data cutoff date should be included in the application.

DSI Response sent electronically March 15, 2018:

Question #8 is clear and no further discussion is needed.

9. *DSI position on question #9 may be found on pages 29-30 of the meeting background package.*

Does the FDA have any comments or suggestions regarding the Sponsor's proposal for a REMS, or on the proposed draft REMS included in Appendix 2 of this briefing document?

FDA Response:

At this time, we have no comments on the proposed REMS. A full review of the REMS will be made upon submission during review of the NDA. At the time of submission, include the REMS Supporting Document, relevant prescriber certification, and training materials as well as any patient materials that will support the REMS.

DSI Response sent electronically March 15, 2018:

DSI would like to further discuss question #9.

Discussion during the meeting:

DSI asked FDA regarding its thinking concerning the potential for an ETASU (Elements to Assure Safe Use). DSI does not want this drug to be administered by physicians who do not understand the disease and could not be able to hold a substantive discussion regarding risk and

benefit. FDA asked DSI who would prescribe pexidartinib, and DSI indicated oncologists would most likely be the prescribers.

FDA stated the Agency will review the prescriber training program in the proposed REMS. FDA will also review the language in the labeling and whether this information is sufficient to communicate the risk.

Content and Location of NDA Documents

10. *A list of pexidartinib clinical studies with their status for the NDA is provided in Appendix 1. The clinical study reports (CSRs) for all completed studies will be included in the NDA submission. The CSRs for the two studies conducted in subjects with TGCT (PLX108-01 and PLX108-10) are based on locked datasets with a clinical cut-off of 03 Mar 2017 and 27 Mar 2017, respectively. To provide more mature data for the NDA, an additional cut of the study data will be performed with a clinical cut-off of 31 Jan 2018. These data will be locked and select tables, listings, and figures will be generated and included in the CSRs by amendment.*

In addition to the two ongoing TGCT studies above, other ongoing Sponsor studies of pexidartinib include:

- PL3397-A-A103 (solid tumors): enrollment closed with one TGCT subject ongoing
- PLX108-13 (kit-mutant melanoma): enrollment closed with three subjects ongoing
- PLX121-01 (PLX9486 combination): enrolling with 12 subjects to date
- PLX108-14 (pembrolizumab combination): enrollment closed with three subjects ongoing
- PLX108-126 (drug-drug interaction [DDI] study in patients with tumors, including TGCT): in start-up and expected to commence enrollment of 30 subjects prior to the Day -120 safety cut

For the Day 120 safety update, data will be provided for subjects enrolled or continuing after the 31 Jan 2018 data cut for the NDA. The cut-off date for the Day 120 update will be approximately five months prior to the submission of the update. The following data will be presented in listings and tables along with a brief summary for these studies: subject disposition, demographics, medical history, prior and concomitant medications, treatment exposure, AEs, SAEs, and laboratory data. Tables of TEAEs and SAEs summarized by system organ class (SOC), PT, and worst Common Terminology Criteria for Adverse Events grade will also be provided.

For the Investigator-initiated studies (Appendix 1), an updated study synopsis and SAEs from the Sponsor's pharmacovigilance database will be provided. The Sponsor does not have access to other data from these studies.

The Day 120 safety report will comprise summary and discussion of these updated safety results. Because of the limited amount of new data, the Sponsor does not plan to update the integrated safety analyses.

Does the FDA agree with the Sponsor's proposed content and format for the Day 120 safety update?

FDA Response:

The proposed cutoff date for the safety update may be acceptable. With regard to the proposed content of this report, also include any updates to the patient narratives submitted with the original application and any new patient narratives describing safety events for the categories listed under question #8 occurring after the January 2018 data cutoff date. Additionally, reports of any life threatening or fatal hepatotoxicity events across the development program should be submitted to both the respective IND(s) and the NDA, even if these occur after the proposed data cutoff date (i.e., these safety events should be reported as they occur throughout the NDA review clock).

Submit the safety update at 90 days rather than 120 days to facilitate a timely and thorough review of the additional safety data.

DSI Response sent electronically March 15, 2018:

DSI requires no additional discussion, and confirms that the safety update will be submitted at 90 days, rather than 120 days, to facilitate a timely and thorough review of the additional safety data.

Clinical Pharmacology

11. *DSI position on question #10 may be found on pages 31-33 of the meeting background package.*

Does the FDA agree with the adequacy of the quantitative clinical pharmacology program and modeling and simulation analysis plan?

FDA Response:

Overall, FDA agrees with the proposed quantitative clinical pharmacology program and modeling and simulation analysis plan. Please also provide adequate model qualification. FDA recommends the following additional analyses to be performed:

Exposure-response analyses for efficacy:

- Conduct longitudinal pharmacokinetic (PK)/pharmacodynamic (PD) tumor growth modeling using data from both PLX108-10 (include both part 1 and part 2) and PLX108-01. Use data from the placebo control group to develop the natural tumor growth model. Integrate effects of baseline characteristics including but not limited to demographics, disease features, and lab measurements on tumor response. Incorporate dose reduction

and dose interruption data in modeling. Provide comparisons of tumor response with the proposed dosing regimen to that with the tested dosing regimen.

- Conduct multivariate exposure-response logistic regression analyses of data from Study PLX108-10 that include baseline characteristics. Provide a justification for the exposure metrics that are used in the exposure-response analyses. Drug exposure to be used in the analyses may include but not be limited to trough concentrations at steady-state, maximum concentrations at steady-state, average concentrations at steady-state or trough concentrations after the first dose. The use of either the parent drug exposure or metabolite exposure, or both, should be justified. If the rate of dose interruption and discontinuation was high in the clinical trials, DSI should conduct appropriate exposure-response analyses to minimize the confounding impact from dose modification and discontinuation. For example, for ORR, doses administered after the time of confirmed response or progressive disease should not be included for the calculations of the exposure metrics.

Exposure-response analyses for safety:

- Conduct a PK/PD model for LFTs. In addition to the pooled primary safety data, supportive safety data (see Question 4) can be also used for modeling. Integrate effects of baseline characteristics on LFTs. Provide comparisons of the LFTs with the proposed dosing regimen to that with the tested dosing regimen.
- Conduct multivariate exposure-response logistic regression analyses including baseline characteristics with a justification for the exposure metrics.

DSI Response sent electronically March 15, 2018:

DSI agrees to conduct the exposure-response analyses for efficacy and primary safety and submit this information in the original NDA. DSI will also conduct exposure-response analyses for supportive safety (page 20 of FDA's preliminary comments; 13 Mar 2018), including studies PLX108-03, PLX108-04, PLX108-05, and PL3397-A-A103, but requests to submit the exposure-response analyses for the supportive safety studies with the 90 day safety update.

Discussion during the meeting:

FDA stated that DSI's plan is acceptable.

Data Format and Submission

12. *The Sponsor proposes the following approach for submitting individual study data:*

- The Sponsor proposes to submit all clinical datasets as SAS® transport files delivered in Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) format 3.1.3 for the mono-therapy TGCT indication studies (PLX108-01 and PLX108-10: data cut-off as of 03 Mar 2017 and 27 Mar 2017, respectively). These study datasets will have bookmarked and hyperlinked define.xml files. The SDTM-annotated

case report forms (CRFs) will also be provided. Additionally, Office of Scientific Investigation (OSI) datasets and listings will be provided for the PLX108-10 study.

- The Sponsor proposes to submit all clinical datasets as SAS transport files delivered in CDISC SDTM format 3.1.3 for the monotherapy in other indication studies (PL3397-A-A103, PLX108-03, PLX108-04, PLX108-05, and PLX108-06). These study datasets will have bookmarked and hyperlinked define.xml files. The SDTM-annotated CRFs will also be provided.
- The Sponsor proposes to submit source data as SAS transport files, proc contents (pdf) and blank electronic CRF (eCRF) for the combination therapies in other indication studies (PLX108-07, PLX108-08, PLX108-09, and PLX108-14). Please note that these studies started before 17 Dec 2016 therefore, a Trial Summary (TS) dataset will also be submitted.
- The Sponsor proposes to submit all clinical datasets as SAS transport files delivered in CDISC SDTM format (versions are supported by guidelines included in the Data Standards Catalog) for the clinical pharmacology studies in healthy subjects. These study datasets will have bookmarked and hyperlinked define.xml files. The SDTM-annotated CRFs will also be provided.
- The Sponsor proposes to submit analysis datasets from the Phase 3 study PLX108-10 and the Phase 1 study PLX108-01 (data cut off as of 27 Mar 2017 and 03 Mar 2017, respectively) in the Analysis Data Model (ADaM) format, along with the define.xml and the Analysis Data Reviewer's Guide (ADRG). The SDTM to ADaM SAS programs and SAS programs from ADaM to key outputs will also be provided for the Phase 3 study PLX108-10.

For the ISS analysis datasets, the Sponsor proposes the following approach:

- ISS analysis datasets will be provided in the ADaM format, along with the define.xml and ADRG. With regard to the ongoing studies PLX108-10 and PLX108-01, data with a cut-off of 27 Mar 2017 and 03 Mar 2017, respectively, will be included in the ISS ADaM datasets. SAS programs that produce the key outputs for the ISS from these ADaM datasets will be provided.

Data from Jan 2018 data cut supporting tables, listings, and figures in CSR amendments of studies PLX108-10 and PLX108-01 will be provided upon request from the Agency.

Does the FDA agree with the proposed data formats and standards for the submission datasets that will be included in the proposed NDA?

FDA Response:

The proposed data format and standards for the submission datasets appears acceptable. Please submit SAS codes for producing the results in the efficacy section of the CSR; also provide SAS codes for deriving ORR from the raw data.

DSI Response sent electronically March 15, 2018:

Question #12 is clear and no further discussion is needed.

13. *The Sponsor proposes to submit the following as part of the pharmacometric datasets/documents:*

- SAS transport file (.xpt) for each NONMEM dataset used in the analysis.
- Data definition file (.pdf) corresponding to each NONMEM dataset /SAS transport file.
- NONMEM model /output files in ASCII format with a .txt extension.

Does the FDA agree with the Sponsor on the proposed formats for the pharmacometric datasets/documents in the proposed NDA?

FDA Response:

Overall, FDA agrees with the proposed formats for the pharmacometric datasets/documents. Please submit exposure-response datasets and code/output files. In addition, submit key simulation datasets and code/output files. Refer to the clinical pharmacology comments under “Additional Comments” regarding the structure and format of the clinical pharmacology sections of the planned application for pexidartinib.

DSI Response sent electronically March 15, 2018:

Question #13 is clear and no further discussion is needed.

Administrative

14. *In accordance with the Guidance for Clinical Investigators, Industry, and FDA Staff: Financial Disclosure by Clinical Investigators⁴ (Feb 2013), the Sponsor will include financial disclosure information for the pivotal Phase 3 study, PLX108-10, in Module 1.3.4 and does not plan to provide disclosure information for any other studies in the NDA.*

Does the FDA agree with the Sponsor’s proposal for handling financial disclosure information?

FDA Response:

No. Provide financial disclosure information for all investigators who participated in PLX108-10 or who treated patients in the TGCT expansion cohort of PLX108-01.

DSI Response sent electronically March 15, 2018:

Question #14 is clear and no further discussion is needed.

Additional Comments:

Clinical Pharmacology

15. Provide an update on the status of the planned oral contraceptive drug-drug interaction study.
16. FDA recommends the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry: *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format* (available at <https://go.usa.gov/xn4qB>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.
17. Address the following questions in the Summary of Clinical Pharmacology in the NDA:
 - a) What is the basis for selecting the doses and dosing regimen used in the trials intended to support the marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dosage and administration.
 - b) What are the exposure-response relationships for efficacy, safety, and biomarkers?
 - c) What is the effect of pexidartinib on the QT/QTc interval?
 - d) What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
 - e) What are the effects of food on the bioavailability? What are the dosing recommendations regarding meals or meal types? Provide justification for recommendations regarding meals or meal types.
 - f) How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?
18. Apply the following advice in preparing the clinical pharmacology sections of the original submission:
 - a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 - b) Provide final study reports for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric means with coefficients of variation (and mean \pm standard deviation) and medians with minimum and maximum values as appropriate.

- c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - i. Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - ii. Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; and the reasons for dose modifications in the datasets.
- d) Submit the following for the population pharmacokinetic analysis reports:
 - i. Standard model diagnostic plots
 - ii. Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
 - iii. Model parameter names and units in tables
 - iv. Summary of the report describing the clinical application of modeling results

Refer to the following pharmacometric data and models submission guidelines
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.

- e) Submit the following information and data to support the population pharmacokinetic analyses:
 - i. SAS transport files (*.xpt) for all datasets used for model development and validation
 - ii. A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - iii. Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
- f) Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for population PK;

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for exposure-response relationships; and <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and model submission guidelines.

19. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report. Provide the study report as PDF files (screenshots can be incorporated if required). Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software. Include appropriate supporting documentations such as any special instructions and file definitions.
20. Include the following items when submitting the QT study report:
 - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Electronic copy of the study report
 - c. Electronic or hard copy of the clinical protocol
 - d. Electronic or hard copy of the Investigator's Brochure
 - e. Annotated CRF
 - f. A data definition file which describes the contents of the electronic data sets
 - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
 - h. Please make sure that the electrocardiogram (ECG) raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
 - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
 - j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation
 - iv. Episodes of syncope
 - v. Episodes of seizure

- vi. Adverse events resulting in the subject discontinuing from the study
 - k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
 - l. A completed Highlights of Clinical Pharmacology Table
21. Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter available at: <http://cardiac-safety.org/ecg-database/>.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The content of a complete application was discussed during a telephone conference held on March 22, 2018. The following topics were discussed:

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan.

Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. FDA and DSI agreed that the exposure-response analyses for the supportive safety studies will be submitted with the 90-day safety updates. You stated you intend to submit a complete application except for the exposure-response analyses; therefore, the only agreement for late submission of application components are for these analyses. There are no other agreements for late submission of application components.

PREA REQUIREMENTS

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

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that marketing applications for certain adult oncology drugs (i.e.,

those intended for treatment of an adult cancer and with molecular targets that FDA determines 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. 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 conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

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

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

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.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an electronic common technical document (eCTD) submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site

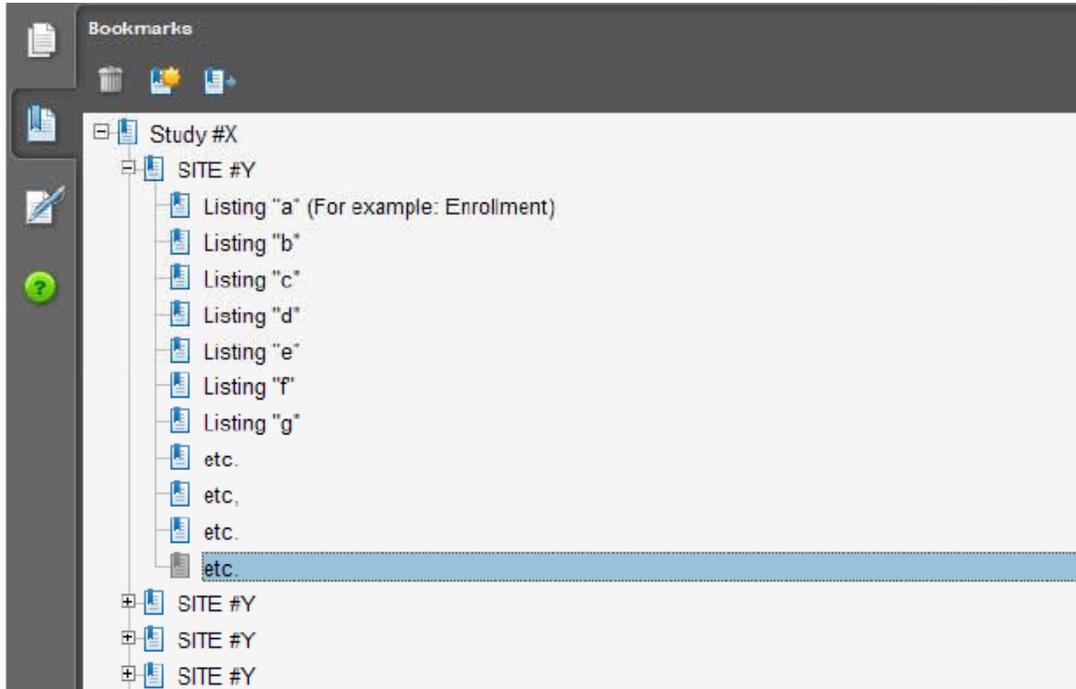
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).

5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

Issues Requiring Further Discussion

There are no issues requiring further discussion.

Action Items

There are no pending action items.

Attachments and Handouts

There were no attachments or handouts during the meeting.

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

/s/

FELICIA DIGGS
03/23/2018

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 117332
Request Receipt Date	September 3, 2015
Product	PLX 3397 (Pexidartinib)
Indication	Pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS) where surgical resection is associated with potentially worsening functional limitation or severe morbidity
Drug Class/Mechanism of Action	Small molecule receptor tyrosine kinase inhibitor that targets CSF1R
Sponsor	Daiichi Sankyo Pharma
ODE/Division	OHOP/DOP2
Breakthrough Therapy Request Goal Date (within <u>60</u> days of receipt)	November 2, 2015

Note: This document should be uploaded into CDER’s electronic document archival system as a clinical review and will serve as the official Clinical Review for the Breakthrough Therapy Designation Request (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.*Section I to be completed within 14 days of receipt for all BTDRs*

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):

The proposed indication for PLX3397 (pexidartinib) is for the treatment of patients with pigmented villonodular synovitis (PVNS) or giant cell tumor of tendon sheath (GCT-TS) where surgical resection may result in potentially worsening functional limitation or severe morbidity.

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

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:

3. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹? YES NO

If 3a 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:

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

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>

NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

N/A

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 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 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. 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}

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

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.

6. 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.

- *Information regarding the disease and intended population for the proposed indication.*
- *Disease mechanism (if known) and natural history (if the disease is uncommon).*

Disease Background

Pigmented villonodular synovitis (PVNS) and giant cell tumor of tendon sheath (GCT-TS) are two subtypes of a single condition referred to as “tenosynovial giant cell tumour, localised and diffuse type” (TGCT). PVNS usually refers to the more common and diffuse type of TGCT, and GCT-TS refers to the less common and localized TGCT. The two entities have a common immunophenotype, pathogenesis, and genetic profile. The tumors consist of collections of mononuclear and multinucleated giant cells, and tumor growth appears to be driven by a mutation involving chromosome 1p13 which induces overexpression of colony stimulating factor-1 (CSF-1) on the tumor cells which triggers migration of non-neoplastic monocytes and macrophages to the tumor site because of their expression of the CSF-1 receptor(CSF1R)¹. The bulk of the tumor mass appears to consist of the nonneoplastic inflammatory cells. The pigment that characterizes the tumor mass is thought to be due to the presence of hemosiderin-laden macrophages developing after repeated hemarthroses¹.

PVNS and GCT-TS are rare diseases, with an estimated annual incidence of 1.8 cases per million and 9.2 cases per million respectively, in the United States². Patients are usually diagnosed in between ages 20 and 60 and most often present with pain and swelling at the affected joint. The knee is the most commonly involved joint for patients with PVNS while GCT-TS often presents in the wrist and finger joints. The clinical course is indolent; however, if left untreated, the tumor continues to expand within the limited intraarticular space and will lead to worsening pain, swelling, stiffness, and limitation in range of motion at the involved joint. The current standard of care is surgical resection using arthroscopic synovectomy (partial or complete) or open resection. External beam radiation is employed in select cases where surgery is not feasible³. The goals of treatment are to reduce tumor-related symptoms of pain, stiffness and immobility and to lessen the risk of recurrence. The overall recurrence rate for patients with focal localized disease is low, ranging from 0% to 6%; however, in patients with diffuse forms of the disease, recurrence is estimated to be in the range of 40% or higher¹. In one of the larger retrospective analyses of 107 patients with GCT-TS or PVNS with relatively long follow-up (mean of seven years for patients with GCT-TS and mean of 14 years for patients with PVNS), a recurrence rate of 72% was reported for patients with PVNS⁴. Multiple recurrences and repeated surgical resections can lead to decreased function of the joint, chronic pain and stiffness, disfigurement and other postsurgical morbidities. There are no systemic therapies approved for treatment of patients with PVNS or GCT-TS.

Relevant Regulatory History

On July 21, 2009, Plexxikon submitted IND (b)(4) containing the protocol for Study PLX108-01, a dose-finding study of PLX3397 in patients with refractory solid tumors. The IND was deemed safe to proceed on August 19, 2009, and the study initiated in October 2009. This study is ongoing and includes an expansion cohort for patients with inoperable PVNS and GCT-TS.

On February 27, 2014, Plexxikon met with FDA to discuss the design of Study PLX108-10 which is intended to support a marketing application for PLX3397 in patients with PVNS and GCT-TS. The following key agreements were made at the pre-IND meeting:

- Durable objective response of sufficient magnitude supported by reliably detected effects on clinically important patient functional status and patient reported outcomes (PROs) may serve as a basis to support approval.
- ORR according to RECIST 1.1 will be the primary efficacy endpoint, and response rate according to the protocol specific Tumor Volume Score (TVS), will be assessed as a secondary endpoint.
- PRO endpoints could provide useful supportive data if it can be shown that they reliably measure an improvement in pain or function in patients with PVNS.
- A post-marketing study might be required to establish an optimal dose given that the product may be administered chronically.
- Given the rarity of the disease, the estimated safety database of patients treated with PLX3397 in conjunction with the safety database accumulated in clinical trials of PLX3397 in other patient populations, may be sufficient to support a marketing application provided that no unusual toxicities are identified.
- A single trial could support an application for registration if the results show a highly statistically significant effect on a measure of clinical benefit and are sufficiently robust and so compelling that it would be unethical to repeat the study in this rare disease population.

FDA recommended that Daiichi Sankyo incorporate a reliable objective measure of functional improvement such as a range of motion assessment conducted by a blinded third party. FDA additionally emphasized that the results of PRO endpoints may not be interpretable if there are substantial missing data or inadvertent blinding issues.

On September 29, 2014, Plexxikon submitted IND 117332 which included the protocol for Study PLX108-10 entitled, "A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath." It was deemed safe to proceed.

On September 29, 2014 Plexxikon also submitted a Special Protocol Assessment (SPA) request for PLX108-10. Clinical and statistical deficiencies pertaining to the proposed eligibility criteria, the methods of collecting and analyzing key patient reported outcome (PRO) secondary endpoints and the proposed statistical test for the primary efficacy analysis were identified and communicated to Daiichi Sankyo during a teleconference on November 4, 2014, and a Special Protocol No Agreement letter was issued on November 12, 2014 with comments detailing the necessary protocol revisions for a SPA agreement to be reached.

On January 30, 2015, Plexxikon informed FDA that they would not re-submit the SPA request. Although the majority of the SPA deficiencies were resolved, Daiichi Sankyo decided to maintain a responder definition of at least 30% reduction in the Brief Pain Inventory worst pain NRS score rather than a minimum 50% reduction as FDA had recommended. Additionally, Daiichi Sankyo opted not to incorporate an assessment of blinding success into the study and to not modify the sequence of secondary endpoints as FDA had recommended.

On February 10, 2015, Plexxikon transferred the legal and regulatory obligations to Daiichi Sankyo Inc. with respect to studies of PLX3397 conducted under IND 117,332

On June 26, 2015, FDA and Daiichi Sankyo had a teleconference as part of the Preliminary Breakthrough Therapy Designation Request program to discuss the preliminary efficacy results from patients with PVNS or GCT-TS treated in Study PLX108-01. FDA informed Daiichi Sankyo that this preliminary data could be sufficient to submit a formal BTDR.

PLX3397: Mechanism of Action and Clinical Development

PLX3397 is an oral small molecule receptor tyrosine kinase inhibitor that targets CSF1R, Kit, and oncogenic Flt3. According to Daiichi Sankyo, nonclinical studies have demonstrated anti-cancer activity in animal models. It is thought that the drug may have antitumor effects through inhibition of cell growth, survival, invasion and metastasis due to the product's ability to alter the composition of the tumor microenvironment. Daiichi Sankyo hypothesizes that PLX3397 selectively targets the CSF1R on the nonneoplastic inflammatory cells that comprise the majority of the tumor mass, thereby inhibiting further growth of the tumor.

There are two ongoing studies of PLX3397 in patients with PVNS and GCT-TS. Study PLX108-01, entitled, "A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology" is a study of PLX3397 in refractory solid tumors and includes an expansion cohort of patients with PVNS or GCT-TS. This is an open-label dose-escalation study with the objective of evaluating safety, pharmacokinetics (PK) and preliminary efficacy. The dose-escalation part of the study evaluated oral doses from 200 mg through 1200 mg daily and established a recommended phase 2 dose of 1000 mg daily given as a split dose (600 mg in the morning and 400 mg in the evening). The BTID request includes data from 31 patients with PVNS or GCT-TS treated with PLX3397 1000 mg daily given as a split dose during Study PLX108-01.

The second ongoing Study PLX108-10 is entitled "A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath." It was initiated in May 2015. It is a randomized, double-blind, placebo-controlled study of PLX3397 in 126 patients with symptomatic PVNS or GCT-TS for whom surgery is not a feasible option because it will likely result in worsening function or severe morbidity. Patients will be randomized 1:1 to receive PLX3397 (loading dose of 1000 mg daily (400 mg AM dose and 600 mg PM dose) for two weeks followed by a dose of 800 mg daily (400 mg BID) or placebo for twenty-four weeks. Randomization is stratified by US versus non-US sites and by upper extremity versus lower extremity involvement. An MRI will be performed at Weeks 13 and 25 to assess tumor response. After Week 25 imaging, all patients will be eligible to enroll in an open-label longterm treatment phase. If patients receiving placebo demonstrate disease progression at Week 13, the protocol allows these patients to enter into the open-label arm early. The primary endpoint is objective response rate at Week 25 based on centrally reviewed MRI scans using RECIST 1.1. Secondary endpoints include response rate according to an alternative, protocol-specific radiographic criteria based on tumor volume (Tumor Volume Score) and duration of response according to both RECIST and the Tumor Volume Score. Clinical outcomes assessments will be evaluated as secondary endpoints and include measures to detect a change from baseline in range of motion, pain, stiffness and general physical function during treatment with PLX3397 as compared to placebo. The data generated from these clinical outcomes assessments may be used to support labeling claims for PLX3397. The following instruments will be used to measure changes in function and disease-related symptoms:

- *Range of motion:* Goniometers will be utilized to measure range of motion in degrees according to a standardized method based on American Medical Association disability criteria. This assessment will be performed by a qualified, independent, and blinded third party, such as an orthopedic surgeon or a physical therapist.
- *Pain:* Patients will complete the Brief Pain Inventory (BPI) Worst Pain NRS item questionnaire before their morning dose daily for seven days prior to Weeks 1, 9, 17 and 25 study visits and also prior to any invasive procedures.

- *Stiffness*: Patients will complete the Worst Stiffness NRS item questionnaire before their morning dose daily for seven days prior to Weeks 1, 9, 17 and 25 study visits and also prior to any invasive procedures. At the Week 25 visit, patients will also complete the Patient Global Impression of Change item for tumor-related stiffness
- *Physical function*: Patients will complete relevant physical function items from the Patient-reported Outcomes Measurement Information System (PROMIS) scale based on the location of their tumors (upper or lower extremity) at Weeks 1, 9, 17 and 25. The results of both sets of items will be combined and analyzed together.
- The EuroQol five-dimensional descriptive system (EQ-5D-5L) general health status instrument will also be administered at Weeks 1, 9, 17 and 25.

7. 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.

Daiichi Sankyo considers durable objective response rate to be a clinically meaningful endpoint supporting the BTDR. In the ongoing dose-finding Study PLX108-01, the primary endpoint is the analysis of safety and pharmacokinetics (PK) of PLX3397 in humans. Objective response rate according to RECIST 1.1 is a secondary endpoint. The data supporting the BTDR is derived from Study PLX108-01.

Study PLX108-10 is the ongoing efficacy study and is measuring radiographic response in addition to changes in patients' disease-related symptoms and physical function; however, this study was initiated in May 2015 and data from this trial are not included in the BTDR. The primary endpoint for Study PLX108-10 is independently reviewed objective response rate according to RECIST 1.1. Secondary endpoints for Study PLX108-10 are listed here in the hierarchy according to the protocol:

1. Response rate based on the BPI Worst Pain NRS item and analgesic use.
2. Response rate based on Tumor Volume Score using centrally evaluated MRI scans at Week 25.
3. Mean change from baseline in range of motion of the affected joint, relative to a reference standard for the same joint, at Week 25.
4. Mean change from baseline score in the PROMIS Physical Function Scale at Week 25.
5. Mean change from baseline score in the Worst Stiffness NRS item at Week 25
6. Duration of response (CR or PR) based on MRI and RECIST 1.1
7. Duration of response (CR or PR) based on MRI and TVS

- 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.*

DOP2 agrees that demonstration of a durable objective response rate according to RECIST 1.1 supported by a demonstration of an improvement in one or more disease-related symptoms or functional outcomes would be clinically meaningful and reasonably likely to predict clinical benefit of a drug in this disease.

- 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.

None.

8. 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 FDA-approved systemic therapies and no known curative treatments for patients with inoperable PVNS or GCT-TS. The current standard of care for primary disease is local control via arthroscopic synovectomy (partial or complete) or open resection. External beam radiation has been employed in select cases where surgery is not feasible.

The following table summarizes ongoing or completed studies of targeted drugs that have been or are being evaluated in patients with PVNS or GCT-TS.

Product	Mechanism of Action	Sponsor or reference	Comments
Imatinib	Tyrosine kinase inhibitor (one target is CSF1R)	Cassier, Philippe et al. ⁵	Retrospective multicenter review of 29 patients with inoperable PVNS. ORR 19% (1 CR, 4PR). Six patients withdrew for toxicity and 14 for “other” reasons. Authors concluded that there is proof of concept for targeting CSF1R in PVNS, but that the benefits must be weighed against toxicity.
Nilotinib	Tyrosine kinase inhibitor (one target is CSF1R)	Gelderblom, Hans et al. ⁶	Multicenter study of 56 patients with PVNS. No objective responses observed at 12 weeks. ORR at 48 weeks 6% (3 PRs of 47 evaluable patients). 12 week progression free rate of 93%.
RO5509554	Anti-CSF1R antibody	Hoffmann-La Roche ⁷	Ongoing first in human dose-finding study with expansion cohort including patients with PVNS.

Product	Mechanism of Action	Sponsor or reference	Comments
			2014 ASCO abstract reported ORR 70% (7 of 10 patients) at 6 weeks. Note that sponsor alerted FDA that there is no plan to continue development of this drug in PVNS.
MCS110	Anti-CSF1 antibody	Novartis	Double blind, randomized trial of patients with PVNS who are eligible for surgery ; consists of one dose 4 weeks prior to the scheduled surgery to evaluate change in tumor size prior to surgery.
FPA008	Anti-CSF1R antibody	Five Prime Therapeutics	Multicenter, dose-escalation with expansion study in patients with inoperable PVNS.

9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

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

10. 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 design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The data supporting the BTDR for PLX3397 comes from Study PLX108-01 entitled “A Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumors in which the Target Kinases Are Linked to Disease Pathophysiology.” The study was initiated in October 2009. This is an ongoing multicenter, single arm, dose-escalation study in patients with incurable solid tumors. The dose-escalation portion of the study is complete. There is an expansion cohort of patients with PVNS or GCT-TS who are being treated at the recommended phase 2 dose of 1000 mg daily (600 mg AM, 400 mg PM). An analysis was performed using data from thirty-one patients with PVNS who have enrolled in Study PLX108-01 as of December 31, 2014 with a data cutoff date of February 27, 2015.

The median exposure for the 31 patients with PVNS or GCT-TS was 254 days. Eighteen patients were treated for at least six months, and eleven patients were treated for at least one year. Of the 31 intent-to-treat (ITT) patients, 29 patients were evaluable for response using RECIST 1.1. All responses are according to local investigator assessment. Fourteen patients experienced a partial response (PR), for an objective response rate (ORR) of 45% (95% CI: 27, 64) for the ITT population and 48% (95% CI: 29, 67) for the evaluable patients. Six patients experienced at least 50% reduction in longest tumor diameter. Daiichi Sankyo notes that four patients who had prior use of imatinib or nilotinib experienced either PR (3 patients) or stable disease (1 patient). The median duration of response from onset of response until progression, discontinuation or data cutoff was seven months

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

⁴ 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.

Universities Arthritis Index (WOMAC) questionnaire. According to Daiichi Sankyo, an interim analysis from up to 18 patients with baseline and at least one post-baseline clinical outcome assessment value showed trends towards reductions in mean pain and stiffness scores over 24 weeks of treatment. On average, these patients experienced sustained decrease in the pain NRS over the 24 weeks of treatment, with a maximum decrease of 3 points at week 9 and week 13. The mean stiffness NRS reached a maximum decrease of 2.5 points at week 9 visit and remained below the baseline at 24 weeks of treatment. See Figures 3 and 4 copied from the briefing document below.

Figure 3: Mean Change from Baseline: Pain NRS

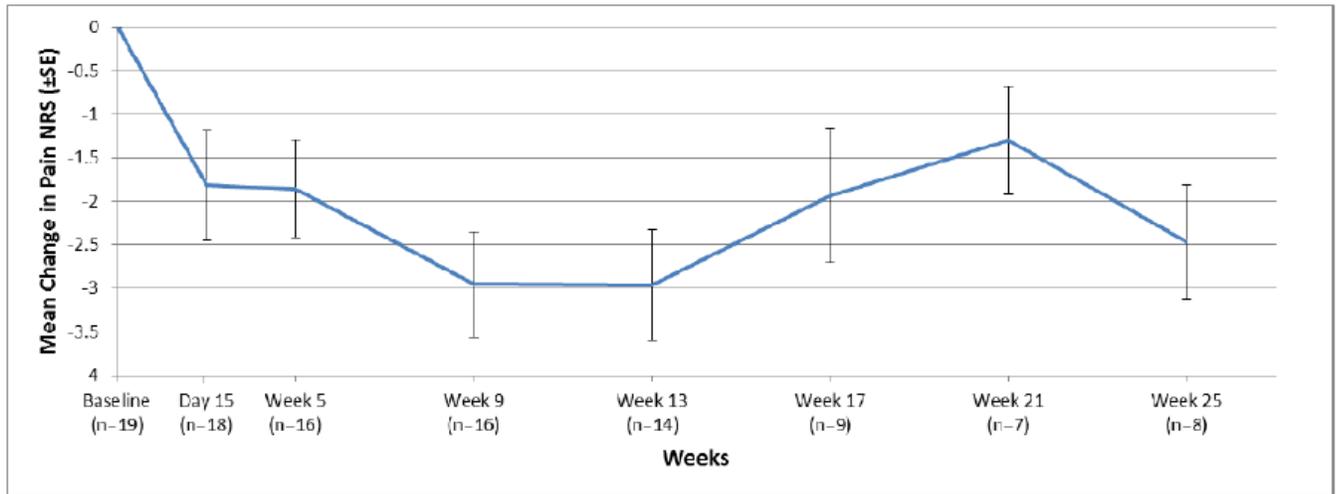
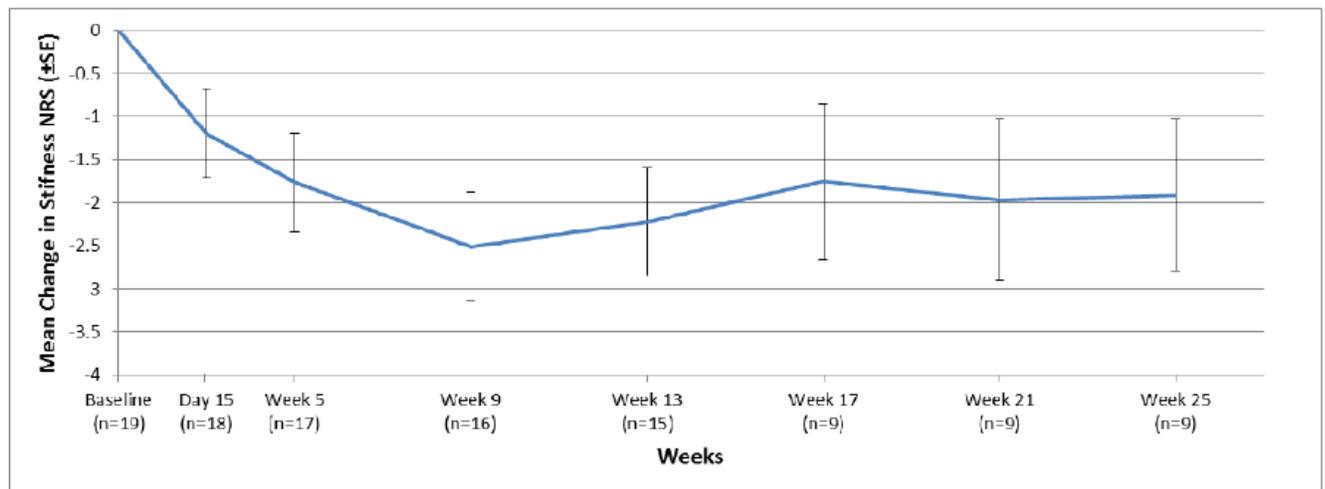


Figure 4: Mean Change from Baseline: Stiffness NRS



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.*

DOP2 considers the objective response and duration of response data in patients with PVNS or GCT-TS treated with PLX3397 provided in the BTDR and summarized above to be preliminary evidence of a substantial improvement over available local control treatment options.

DOP2 has considered the overall clinical development program for PLX3397 in patients with PVNS and GCT-TS during review of the BTDR. In addition to the data derived from Study PLX108-01 summarized in the BTDR, Daiichi Sankyo has designed and initiated a randomized, placebo-controlled trial to investigate the effect of PLX3397 on both tumor shrinkage and specific clinical outcome assessments relevant to this disease (i.e., pain and stiffness). A reliable assessment of an improvement in physical symptoms and/or function that parallels tumor shrinkage in patients with PVNS or GCT-TS treated with PLX3397 as compared to those treated with placebo could support a marketing application for PLX3397 for patients with inoperable disease.

The safety profile of PLX3397 was also reviewed. Daiichi Sankyo reports that 345 patients have been exposed to PLX3397 across eight clinical trials as of June 2014. The most frequent adverse events (AEs) observed across all studies included fatigue, nausea, decreased appetite, diarrhea, anemia, vomiting, and increases in liver enzymes. Hair color changes (often depigmentation) and constipation were also common in patients with solid tumors. Serious adverse events that occurred in more than one patient included neutropenia, dehydration, pneumonia, increased liver enzymes, anemia, increased INR, hyponatremia, rash and leukopenia. In the subset of 31 patients with PVNS, the most common AEs were similar to that of the pooled population and included hair color changes, fatigue, nausea, periorbital edema and dysgeusia. Grade 3 or higher AEs in patients with PVNS consisted of increased ALT/AST (n=2), hyponatremia (n=2), fatigue (n=1), neutropenia (n=1), anemia (n=1) and diarrhea (n=1). According to Daiichi Sankyo, all of observed AEs were reversible and improved with dose interruption or reduction. DOP2 has considered the potential for development of cumulative or new toxicities with chronic dosing of PLX3397 in patients with PVNS and GCT-TS, both relatively indolent diseases; however, given the seriousness of this condition, the associated morbidities and lack of available treatments for patients with inoperable disease, the potential clinical benefits appear to outweigh the risks of treatment with PLX3397 for patients with inoperable PVNS or GCT-TS.

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

GRANT :

Provide brief summary of rationale for granting:

There are no systemic therapies approved for patients with PVNS or GCT-TS who have inoperable tumors. Although surgical resection is the standard of care, recurrence of PVNS following surgery is frequent. Repeated surgeries can lead to further functional limitation at the affected joint, chronic pain, disfigurement and other postsurgical morbidities. Radiation can also cause further functional limitation and carries a small risk for development of secondary malignancies. Tyrosine kinase inhibitors that have been studied such as imatinib and nilotinib have not demonstrated a significant ORR in patients with PVNS.

DOP2 considers the effect size on durable response rate in patients with PVNS or GCT-TS demonstrated in Study PLX108-01 to be preliminary evidence of a substantial improvement over available local control treatment options. The trends noted in the subset of patients who were evaluated using clinical outcomes assessment tools in the amended protocol are considered supportive of the radiographic response data and warrant further evaluation in the context of a controlled trial.

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:

12. 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):

DOP2 has met with Daiichi Sankyo to discuss the design of the recently initiated study intended to support an NDA, Study PLX108-10. DOP2 and FDA's Clinical Outcome Assessments Staff have additionally had multiple teleconferences and provided written advice to Daiichi Sankyo regarding the design and endpoints of Study PLX108-10. DOP2 informed Daiichi Sankyo that a single, well-controlled study could support an application for registration if the results show a statistically significant effect on tumor shrinkage that correlates with an improvement in function or disease-related symptoms. DOP2 will continue to be available to Daiichi Sankyo for regulatory guidance to facilitate the development program for PLX3397 in this rare disease.

- 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:

13. List references, if any:

1. Ravi, V. et. al., Treatment of tenosynovial giant cell tumor and pigmented villonodular synovitis. *Curr Opin Oncol*, 2011. 23(4): p. 361-6.
2. Myers, B.W. and A.T. Masi, Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. *Medicine* (Baltimore), 1980. 59(3): p. 223-38.
3. Auregan, J.C., et al., Treatment of pigmented villonodular synovitis of the knee. *Arthroscopy*, 2014. 30(10): p. 1327-41.
4. Verspoor, F.G., et al., Long-term follow-up results of primary and recurrent pigmented villonodular synovitis. *Rheumatology* (Oxford), 2014. 53(11): p. 2063-70.

5. Cassier, P.A., et al., Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer*, 2012. 118(6): p. 1649-55.
6. Gelderblom, H. et al., An open-label international multicentric phase II study of nilotinib in progressive pigmented villo-nodular synovitis (PVNS) not amenable to a conservative surgical treatment. *Journal of Clin Oncology*, 2013, 31(15) (May 20 supplement) p. 10516.
7. Cassier, P., et. al., Phase 1 study of RG7155, a novel anti-CSF1R antibody, in patients with locally advanced pigmented villonodular synovitis (PVNS). *Journal of Clin Oncology*, 2013, 32(15) (May 20 supplement) p. 10504.
8. Dines JS, et al. Long-term follow-up of surgically treated localized pigmented villonodular synovitis of the knee. *Arthroscopy* 2007, 23: 930-937.
9. Chiari C, et al., What affects the recurrence and clinical outcome of pigmented villonodular synovitis? *Clin Orthop Rel Res* 2006; 450:172-178.

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

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

Grant Breakthrough Therapy Designation
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}

4-6-15/M. Raggio

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

/s/

DENISE A CASEY
10/27/2015

SUZANNE G DEMKO
10/27/2015

PATRICIA KEEGAN
10/28/2015



IND 117332

MEETING MINUTES

Plexxikon, Inc.
Attention: Stephanie Broome, Ph.D.
Vice President, Regulatory Affairs
91 Bolivar Drive
Berkeley, CA 94710

Dear Dr. Broome:

Please refer to your Pre-Investigational New Drug Application (PIND) file for PLX3397.

We also refer to the meeting between representatives of your firm and the FDA on February 27, 2014. The purpose of the meeting was to discuss the proposed protocol and registration plan for PLX3397.

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

If you have any questions please call me at (301) 796-0297.

Sincerely,

{See appended electronic signature page}

Deanne Varney
Senior Regulatory 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: Type B
Meeting Category: Pre-IND/pre-phase 2/3

Meeting Date and Time: Thursday, February 27, 2014, 11:30 AM
Meeting Location: White Oak Building 22, Room 1309

Application Number: IND 117332
Product Name: PLX3397
Indication: Treatment of Pigmented Villonodular Synovitis (PVNS) or giant cell tumor of the tendon sheath
Sponsor/Applicant Name: Plexxikon, Inc.

FDA ATTENDEES

Patricia Keegan, Division Director, DOP2
Denise Casey, Clinical Reviewer, DOP2
Amy Barone, Clinical Reviewer, DOP2
Martha Donoghue, Clinical Reviewer, DOP2
Suzanne Demko, Clinical Team Leader, DOP2
Deanne Varney, Regulatory Project Manager, DOP2
Ingrid Fan, Regulatory Project Manager, DOP2
Jonathan Jarow, Acting Deputy Office Director, OHOP
Gregory Reaman, Associate Director for Oncology Sciences, OHOP
Sirisha Mushti, Statistical Reviewer, DBV
Kun He, Statistical Team Leader, DBV
Lillian Zhang, Clinical Pharmacology reviewer, DCP5
Jun Yang, Clinical Pharmacology Acting Team Leader, DCP5
Shawna Weis, Pharmacology/Toxicology Reviewer, DHOT
Whitney Helms, Pharmacology/Toxicology Team Leader, DHOT
Larissa Lapteva, Medical Officer, OMPT

SPONSOR ATTENDEES

Stephanie Broome, Vice President Regulatory Affairs
Sandra Tong, Vice President Clinical Development
Henry Hsu, Chief Medical Officer
Laura Sanftner, Director, Nonclinical Development
Prabha Ibrahim, Sr. Vice President Chemistry & Nonclinical Development
Gideon Bollag, Chief Executive Officer
Paul Lin, Chief Operating Officer

(b) (4) CEO, (b) (4)
(b) (4) Senior Research Leader, (b) (4)

(b) (4) Section Chief, Sarcoma Oncology, Melanoma and Sarcoma Service. (b) (4)

BACKGROUND

On November 27, 2013, Plexxikon submitted a pre-IND/pre-Phase 2/3 meeting request to discuss the proposed protocol and registration plan for PLX3397. The meeting package, submitted on January 29, 2014, included updated specific goals aimed at reaching agreement with the agency on:

- The design of the proposed randomized registration trial, Study PLX108-10, for patients with symptomatic pigmented villonodular synovitis (PVNS) or giant cell tumor of the tendon sheath (GCT-TS) for whom surgery is not a feasible option
- The investigational plan for PLX3397 as a treatment for PVNS/GCT-TS
- Any additional information necessary to support a marketing application for PLX3397 for the proposed indication

Plexxikon states that PLX3397 is a small molecule receptor tyrosine kinase inhibitor that targets CSF1R, Kit, and oncogenic Flt3 with demonstrated anti-cancer activity in animal models. Plexxikon believes that because Fms and Kit regulate activities of mesenchymal cell populations (e.g. macrophages, osteoclasts, microglia and mast cells), the drug may block multiple aspects of tumorigenesis, including cell growth, survival, invasion and metastasis through its ability to alter the composition of the tumor microenvironment.

Plexxikon states that PLX3397 has a hERG IC₅₀ of 0.7 micromolar, but no effect was observed on action potential parameters when tested in the Purkinje fiber assay at a concentration of 3 micromolar. In the dog, a reduction in left ventricular contractility and arterial pulse pressure was observed at oral doses of 300 or 1000 mg/kg. No effects were observed on CNS or pulmonary function at oral doses of up to 200 mg/kg in the rat.

Plexxikon also states that PLX3397 was negative in the Ames assay, in the in vitro chromosome aberration assay, and in the in vivo micronucleus assay.

Plexxikon conducted 13-week repeat-dose toxicology studies with PLX3397 in the rat and the dog. According to the meeting package, the no observed adverse effect levels (NOAELs) in the rat and dog studies were 4 and 6 mg/kg, respectively; testicular alterations and emesis were the defining toxicities. PLX3397 was also noted to be teratogenic in the rat. Visceral malformations and skeletal variations (primarily related to decreased ossification) were observed in the rat at maternal doses of 40 mg/kg/day. In the preliminary embryofetal toxicity study in the rabbit, post-implantation loss, decreased litter size, decreased fetal weight, and fetal external malformations were observed at oral doses of 100-150 mg/kg/day.

Plexxikon's nonclinical development plan includes conducting the definitive embryofetal toxicology study in the rabbit in addition to 6- and 9-month chronic toxicology studies in the rat

and dog, a panel of in vitro of metabolism and transport studies, and a 14-C radiolabeled absorption, distribution, metabolism, and excretion (ADME) study in the rat.

Clinical experience with PLXX3397 as a single agent is derived from five clinical trials that have been completed or are ongoing in patients with refractory solid tumors, Hodgkin's lymphoma, and hematologic malignancies. Among 171 patients with advanced solid tumors or relapsed or refractory Hodgkin's lymphoma who received monotherapy with PLX3397, the most common (> 15%) treatment emergent adverse events were fatigue (54%), nausea (37%), decreased appetite (35%), hair depigmentation (27%), vomiting (23%), anemia (19%), diarrhea (19%), constipation (18%), and headache (16%).

One ongoing single arm clinical study (PLX108-01) and one randomized, placebo-controlled registration study (PLX108-10) are planned to support the efficacy and safety of PLX3397 in adult patients with symptomatic PVNS or GCT-TS where surgical resection may result in worsening functional limitation or severe morbidity.

Ongoing Study PLX108-01

Study PLX108-01 is an open-label two-part dose-escalation study with an expansion cohort. In the initial dose-escalation part of the study, patients with advanced solid tumors received PLX3397 daily at oral doses ranging from 200 to 1200 mg. At the conclusion of this part of the study, the identified RP2D was 1000 mg/day administered as a split dose. The objective of the ongoing extension cohort part of PLX108-01 is to evaluate the potential antitumor activity of PLX3397 in patients with selected tumor types including PVNS.

A total of 19 patients with PVNS have enrolled in the study. Among 17 patients who received PLX3397, 10 received 1000 mg/day as a split dose (600 mg every morning and 400 mg every evening), and 7 required a dose reduction. The median duration of treatment for the PVNS patients was 166 days and the mean duration of treatment was 155 days (range: 23–264 days). The effect of PLX3397 on PVNS was assessed by radiologic assessment of tumor burden by CT scan or MRI, and/or FDG uptake PET scanning. Tumor volume was scored using a semi-quantitative MRI scoring system, the Tumor Volume Score, which is an extension of the 4-point synovitis scale of the Whole Organ MRI Score (WORMS), originally developed for the evaluation of osteoarthritis. The change in Tumor Volume Score was calculated for each post-baseline MRI scan. Plexxikon stated that of 11 evaluable patients, 7 had partial responses (64%), 4 had stable disease, and none had a complete response or progressive disease. Evaluation using RECIST criteria in 9 evaluable patients demonstrated 1 complete response and 3 partial responses (44% overall response), while 4 patients had stable disease and one had progression.

Plexxikon reports that all 17 PVNS patients experienced at least one adverse event possibly or probably related to PLX3397. The most common AEs included fatigue, nausea, hair color changes, (all reported in at least 12 of 17 patients) in addition to diarrhea, decreased appetite and arthralgias. Two (11.8%) patients experienced 3 SAEs: one Grade 3 cholecystitis and Grade 4 hyponatremia, and another Grade 3 acute renal failure. Hyponatremia was assessed by the investigator to be related to PLX3397. No patients in the PVNS cohort died during the study.

Planned Study PLX108-10

One randomized, double-blind, placebo-controlled, registration study is planned for PLX3397 in patients with symptomatic PVNS or GCT-TS with recurrence or for whom planned surgery may result in worsening function limitation or severe morbidity. Study PLX108-10 is designed as a two-part study. Part 1 will test the hypothesis that PLX3397 is superior to placebo in patients with symptomatic PVNS or GCT-TS. Patients who complete Part 1 will be eligible for enrollment into Part 2, an open-label extension phase in which all patients will receive PLX3397.

Part 1 will randomize approximately 120 patients in a 1:1 ratio to receive either PLX3397 at a dose of 1000 mg/day (600 mg every morning and 400 mg every evening) or placebo for 24 weeks. The primary efficacy endpoint is the proportion of patients who achieve MRI (centrally read) responder criteria as defined by the Tumor Volume Score, i.e., $\geq 50\%$ reduction from baseline score, at the Week 25 visit. Assuming responder rates are 10% for placebo arm and 35% for experimental arm, 120 patients will provide 91% power at alpha of 0.05 (two-sided). The primary analysis is Pearson's chi-square test.

The secondary efficacy endpoints are: mean change from baseline in the BPI Worst Pain NRS Item at the Week 25 visit; mean change from baseline in the physical function domain of the WOMAC PVNS-GCTTS instrument at the Week 25 visit; and mean change from baseline in the stiffness domain of the WOMAC PVNS-GCTTS instrument at the Week 25 visit. The key secondary endpoints will be analyzed using linear mixed models for repeated measurements. A gatekeeping testing procedure is proposed to adjust alpha for these secondary endpoints. Plexxikon states that other endpoints will also be evaluated based on additional patient reported outcome (PRO) assessments, including the pain domain of the WOMAC, the WOMAC total score, and a physician global assessment.

After 24 weeks of randomized, double-blind study treatment (PLX3397 or placebo), patients will be eligible for enrollment into part 2 of the study. Patients enrolled in Part 2 will continue to receive PLX3397 until the last patient reaches at least the Week 49 extension phase visit (i.e., an additional 24 weeks on study treatment beyond the placebo-controlled phase). Depending upon the duration of enrollment, Plexxikon anticipates that some patients will receive PLX3397 for longer than one year.

On November 27, 2013, Plexxikon submitted a request for orphan drug designation to the Office of Orphan Products Development for PLX3397 in the treatment of patients with symptomatic PVNS or GCT-TS, where surgical resection is associated with potentially worsening functional limitation or severe morbidity. According to Plexxikon, on February 14, 2014, the FDA granted PLX3397 orphan drug designation for the "treatment of pigmented villonodular synovitis/giant cell tumor of the tendon sheath".

DISCUSSION

Clinical:

1. Does the US Food and Drug Administration (FDA) agree that the existing nonclinical program together with safety data from completed and ongoing clinical studies of PLX3397 support initiation of the planned phase 3 clinical study in patients with PVNS, PLX108-10?

FDA Response: FDA agrees that the safety data from ongoing clinical studies of PLX3397 in approximately 230 patients support initiation of the proposed clinical trial in patients with PVNS. Regarding the nonclinical program, include reports of the pivotal repeat-dose and the embryo-fetal toxicity studies in the original IND submission. The adequacy of these data to support the clinical plan will be determined following review of these reports.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

2. Does the FDA concur that the proposed study, PLX108-10, including design elements, methods and analyses meet the criteria for an adequate and well-controlled trial for the purpose of registration of PLS3397 in the indication for the treatment of PVNS/GCT-TS?

FDA Response: No, the trial design, methods and analyses for PLX108-10 are not adequate to support registration of PLX3397 for the proposed indication. FDA recommends modification of the protocol to address the following design issues:

- a. Durable objective response of sufficient magnitude supported by reliably detected effects on patient reported outcomes (PROs) which are clinically important may serve as a basis to support approval; however, the proposed trial design does not adequately measure durability of objective tumor responses which is essential to reliably interpret the meaningfulness of objective response.

Discussion During Meeting: Plexxikon stated that the current draft protocol is designed for 6-month placebo-controlled parallel dosing followed by at least 6-months of open-label PLS3397 treatment in both arms. All responders will have a minimum of 6 months of additional follow up with MRI-RECIST assessment every 3 months. Because enrollment is expected to take approximately 2 years, patients will have up to 3 years of exposure with regular ongoing MRI assessments. Plexxikon asked if this will constitute a sufficient period of time for assessing durability of response. FDA stated that this will be sufficient. Plexxikon confirmed that they will evaluate durability of response through the open-label portion of the trial.

- b. The proposed 25% absolute increase in objective response rate (ORR) in the treatment arm relative to placebo may not be of sufficient magnitude to support approval in this population. Please explain why a 25% increase in ORR constitutes a sufficient level of benefit (or predicts benefit) to justify the risk of the drug.

Discussion During Meeting: Plexxikon noted that the ORR for placebo is estimated to be 5-10%. Plexxikon also noted that a 25% absolute increase represents at least a 2.5-fold increase over placebo and that experts regard this as a meaningful clinical outcome. Patient-reported outcomes (PRO) data will support the clinical meaningfulness of tumor response by RECIST 1.1. Plexxikon believes this is a conservative treatment difference in response rate which was used for the sample size justification, and stated that based on results of the Phase 1 PVNS extension cohort in PLX108-01, the safety profile for PLX3397 thus far appears acceptable for this serious and debilitating disease for which no alternative systemic therapy exists. Plexxikon believes an absolute improvement of 25% in ORR by RECIST is an underestimate of what will be seen in the proposed trial.

FDA stated that a 20% response rate is the minimal amount of activity to continue development in most solid tumors, so 25% is relatively modest, but is a reasonable starting point. FDA will also need to see durability of response and additional supportive information to show that the observed response rate provides clinically benefit. Plexxikon stated that they believe they will see higher absolute difference in response rate than 25%, and agrees that supportive information will be important.

- c. FDA acknowledges that linear measurement of tumor burden may not be optimal for diffuse PVNS; however, there is insufficient experience with the proposed Tumor Volume Score to justify utilization for evaluation of the primary efficacy endpoint in a trial with registration intent. FDA has extensive experience with use of RECIST criteria to define measurability and assess response in oncology settings. FDA therefore encourages Plexxikon to incorporate a volumetric assessment using the modified WORMs as a secondary endpoint to provide supportive clinical information. The primary assessment of both RECIST and WORMs should be based on an independent review masked to treatment assignment. Additional information should be provided on the reliability and reproducibility of the WORMs assessment in a marketing application.

Discussion During Meeting: Plexxikon stated that objective response rate according to RECIST 1.1 will be the primary endpoint and the modified WORMs will be a secondary endpoint. The assessment by RECIST and modified WORMs in the primary and secondary endpoint analyses will be based upon an independent review masked to treatment assignment. Plexxikon also noted that evaluation of inter-reader reproducibility will be based upon the intra-class correlation coefficient of two independent readers (as was done for Tumor Volume Score in the Phase 1 study, Protocol PLX108-01).

With regard to the proposed supportive analyses of efficacy, Plexxikon will focus on mass effect as the driver of clinical outcome. Due to the asymmetrical growth behavior of diffuse PVNS, Plexxikon speculated that longest linear dimension might not be the most accurate way to monitor disease progression as it relates to mass effect. Therefore, Plexxikon obtained information on PVNS lesions in which the linear shortest dimension and tumor volume directly (scoring) were also measured. All three measurements showed treatment activity (decrease in PVNS lesions size), but the longest linear dimension was least sensitive to changes in volume. Plexxikon believes that with a larger number of patients and a placebo arm in the proposed trial, it will be possible to detect a treatment effect with the longest linear measurement, but requested FDA input on whether the longest or shortest dimension would be the most appropriate primary endpoint.

FDA stated that it is understood that RECIST might not be optimal for evaluating PVNS, but FDA has far more experience with RECIST in the solid tumor setting. FDA noted that the best measurement tool versus whether a drug is working are two different questions, so it is preferable to anchor the measurement with a tool that can provide reliable results. FDA would like Plexxikon to use RECIST in the traditional manner with focus on the longest linear measurement, but encouraged Plexxikon to take as many additional measurements as they wish, as the totality of the evidence will be considered. Plexxikon agreed with this approach.

- d. In addition to the proposed PRO measures, assessment of the treatment effects on physical functioning would be greatly strengthened by a focused physical examination at specified timepoints during the trial. The examination should be performed by a third party such as an orthopedic clinician or a physical therapist blinded to treatment assignment to mitigate potential sources of bias in this open-label trial. Please be aware that lack of blinding will be a major issue limiting interpretation of PRO data obtained in this trial.

Discussion During Meeting: Plexxikon asked FDA to provide guidance on specific and suitable physical exam instrument(s) that might be appropriate for use in this study.

FDA considers an objective range of motion exam to be one example of an objective physical finding. FDA noted that assessment of physical signs and symptoms in the open-label portion of the study may be difficult to interpret due to the potential for bias, so using as much objective criteria as possible is important. If there are standard measurements in clinical practice that are already being used, it is best to use those established measurements. Plexxikon stated that orthopedic practice has established standardized exam measurements that can be used. Plexxikon asked if it would be adequate to have the measure as a secondary measurement. FDA stated that all measurements will need to be reviewed and a determination will need to be made regarding the key supportive measurements versus exploratory measurements. Plexxikon should identify the measurements they consider important and that they would like to use to make labeling claims.

Plexxikon asked if FDA has any bias regarding the third party physical exam versus PRO endpoints. FDA stated their preference for third party independent exam over PROs which are not validated in this population.

- e. Refer to FDA responses 7 and 8 for discussion of the proposed secondary endpoints. Refer to FDA response 13 for general information regarding adequacy of this single trial to serve as the primary data in support of an NDA.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

- 3. Does the FDA agree that the proposed inclusion and exclusion criteria in protocol PLX-108-10 support the PVNS population covered by the planned indication?

FDA Response: The inclusion of patients with PVNS or GCT-TS with recurrent disease or with disease that is not amenable to surgical resection is appropriate for the study population. Inclusion criterion #3 requires “Measurable disease [REDACTED]”^{(b) (4)} The presence of measurable disease at baseline is essential; however, FDA prefers use of RECIST criteria for determination of measurable disease based on greater familiarity and common use of this criteria in oncology (see FDA response 2). Revise this inclusion criterion to add a linear baseline tumor measurement requirement. The requirement of a baseline measurable limitation in a PRO is appropriate; however, the proposed scoring algorithm will be reviewed in detail by FDA Study Endpoints and Label Development staff and comments will be provided in a separate communication (see responses to questions 7 and 8). The other eligibility criteria are reasonable.

Discussion During Meeting: Plexxikon will revise inclusion criteria #3 to add a linear baseline tumor measurement.

- 4. Does the FDA agree with PLX3397 dose selection and duration of treatment for Study PLX108-10?

FDA Response: The proposed dose of 1000 mg daily (600 mg in the morning and 400 mg in the evening), appears to be reasonably safe but may not be tolerable over time. If the product is intended for chronic use, a safe and biologically effective dose may be lower than the MTD established from one treatment cycle on PLX108-01. Provide justification for the chosen dose given that 41% of PVNS patients required dose reductions in the expansion cohort of PLX108-01. If the chosen dose is effective but not tolerable, a post marketing study could be required to identify an optimal biological dose.

Discussion During Meeting: Plexxikon agreed that the 1000 mg per day dose may not be tolerated by all patients, but approximately half were able to continue dosing long-term at this dose. The ongoing Phase 1 study PLX108-01 is using this dose, and current

safety and efficacy data from this study indicate that the proposed dose reduction algorithm can be implemented clinically.

FDA agreed that this seems reasonable, but emphasized that if the product is to be administered chronically, a post-marketing study might be required to establish an optimal dose. Plexxikon stated that they are amenable to this. Plexxikon asked if a dose reduction algorithm is implemented would that be okay, or would FDA prefer starting at a lower dose. FDA stated that it is important that the labeling recommend a dose that is tolerable to the majority of patients. If the majority of patients cannot tolerate the initial starting dose for more than a few weeks, one might question the value of exposing patients to that level of toxicity for several weeks.

FDA has the following additional recommendations regarding dosing:

- a. Explore the exposure-response (E-R) relationships for PLX3397 with the pharmacokinetics data obtained in the proposed trial for measures of effectiveness, pharmacodynamics biomarkers, and toxicity. The goals of the analyses are to provide supportive evidence of acceptable effectiveness and safety profile and to support the dosing recommendations. Refer to the FDA Guidance for Industry entitled “*Exposure-Response Relationships – Trial Design, Data Analysis, and Regulatory Applications*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf>.

Discussion During Meeting: Plexxikon stated that an exposure-response relationship will be explored in Protocol PLX108-10.

- b. Conduct the planned food effect trial to determine whether PLX3397 should be administered under the fasted state or under the fed state in the proposed Phase 3 trial as the food effect on the absorption of PLX3397 has not been adequately evaluated.

Discussion During Meeting: Plexxikon intends to conduct a food effect study prior to the start of PLX108-10.

5. A dose reduction algorithm was used in PLX108-01, the dose-escalation study. This same algorithm is proposed for the planned phase 3 study, PLX108-10.

Does the FDA agree with the proposed dose reduction algorithms in 200 mg increments (b) (4) (see Protocol PLX108-10 Section 12.3[Appendix 6.1])?

FDA Response: FDA agrees that the dose reduction algorithm is reasonable; however, the algorithm for re-escalation is not adequately described. In the protocol submitted with the IND, provide the algorithm for dose re-escalation.

Discussion During Meeting: Plexxikon stated that a dose re-escalation algorithm will be provided. Once a toxicity resolves to \leq Grade 1, the dose will be re-escalated to the drug level administered prior to development of toxicity. If toxicity re-occurs at this dose, the patient will continue treatment only at the lower dose. FDA stated that this is reasonable.

6. The proposed primary efficacy endpoint in Study PLX108-10 (see Protocol PLX108-10 Section 9.1 [REDACTED] (b) (4)

[REDACTED] The rationale for the proposed primary efficacy endpoint is given in Section 4.3.3.4. Does the FDA agree with the proposed primary efficacy endpoint?

FDA Response: FDA agrees that objective response is an appropriate primary efficacy endpoint in this population; however, the trial will need to demonstrate durability to allow for a reliable interpretation of the clinical meaningfulness of response. FDA does not agree [REDACTED] (b) (4) RECIST criteria is preferred with utilization of WORMS to provide additional supportive information. See FDA response to question 2.

Discussion During Meeting: Plexxikon stated that they will change the primary endpoint to overall response rate according to RECIST 1.1, assessed at the end of the blinded treatment period and will use the modified WORMS as a secondary endpoint. FDA stated that this is acceptable.

7. The secondary efficacy endpoints selected for Study PLX108-10 are:

- Mean change from baseline in the BPI Worst Pain NRS item at the Week 25 visit
- Mean change from baseline in the physical function domain of the WOMAC PVNS-GCTTS instrument at the Week 25 visit
- Mean change from baseline in the stiffness domain of the WOMAC PVNS-GCTTS instrument at the Week 25 visit.

The secondary efficacy endpoints proposed in protocol PLX108-10 were chosen to capture clinically meaningful outcomes in PVNS. Does the FDA agree with the proposed secondary efficacy endpoints?

FDA Response: The proposed secondary efficacy endpoints seem reasonable and may provide supportive information regarding the clinical benefits derived from treatment with PLX3397. The FDA Study Endpoints and Labeling Development (SEALD) staff will review the meeting package to evaluate the adequacy of the proposed conceptual framework, scoring algorithm and documentation of content validity for the chosen BPI Worst pain NRS and WOMAC instruments for use in the PVNS population. A letter of advice from SEALD to Plexxikon will be forthcoming. FDA reminds Plexxikon of the following general principles relevant to PRO endpoints in clinical trials:

- a. Pain assessment should be specific to the medical condition of interest and should not assess other pain the patient may be experiencing (e.i., headache) to the extent possible. FDA acknowledges that Plexxikon modified the BPI item accordingly.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

- b. Prespecified methods of quantifying analgesic use for each patient at time points of interest should be described in the protocol to ensure that any improvement in pain or physical function is not due to concomitant medication use. .

Discussion During Meeting: Plexxikon proposed to use a paper-based diary of analgesic use. FDA will provide additional advice at a later date, once input from SEALD colleagues has been received.

- c. Efforts should be made to retain blinding whenever possible. A reliable interpretation of PRO endpoints is difficult in the setting of inadvertent unblinding due to treatment-related toxicity and may not support labeling claims.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

- d. Prespecified methods for minimizing and handling missing PRO data should be included in the trial design and analytic plan.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

8. The secondary efficacy analyses are:

- Mean change from baseline in the BPI Worst Pain NRS Item at the Week 25 visit in the intent-to-treat (ITT) population
- Mean change from baseline in the physical function domain of the WOMAC PVNS–GCTTS instrument at the Week 25 visit in the lower extremity (LE) subset of the ITT population
- 3a. Mean change from baseline in the stiffness domain of the WOMAC PVNS–GCTTS instrument at the Week 25 visit in the LE subset of the ITT population
- 3b. Mean change from baseline in the stiffness domain of the WOMAC PVNS–GCTTS instrument at the Week 25 visit in the ITT population

Does the FDA agree that the secondary efficacy endpoints can be included in the clinical studies section of the product labeling if these endpoints are found to be statistically significant using the gatekeeping testing procedure?

FDA Response: The chosen PRO endpoints could provide useful supportive data if it can be shown that they reliably measure an improvement in pain or function in the PVNS

population enrolled on the trial. The FDA will review the PRO instrument development and testing in conjunction with clinical trial results to determine whether a labeling claim is substantiated. Please refer to the following guidance for additional information regarding use of PRO instruments to support labeling claims: *Draft Guidance for Industry. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* at <http://www.fda.gov/downloads/Drugs/Guidances/UCM193282.pdf>

Regarding the proposed analysis plan for handling missing data, section 14.3 of the draft protocol states: “If there are any patients who do not have a baseline value of such a quantitative endpoint, the baseline value will be imputed by the average baseline value for all randomized patients”. This is not acceptable since validity of the model assumption is difficult to verify.

Discussion During Meeting: Plexxikon will revise Protocol PLX108-10 to address the FDA comment on handling of missing data (PROs).

9. Physical examinations, vital signs, 12-lead electrocardiograms (ECGs), cardiac echocardiograms, AEs, chemistry, hematology, hormonal levels, coagulation tests, and urinalysis will be used to assess the safety and tolerability of PLX3397 in the phase 3 study, PLX108-10.

Does the FDA agree with the other important components of the proposed study, PLX108-10, such as the frequency of safety and laboratory assessments?

FDA Response: No, FDA does not agree with the schedule of physical examinations and laboratory assessments. Physical examinations should be performed more frequently (b) (4) after starting the investigational agent given the risk for certain treatment-related toxicities such as skin rashes, and periorbital and/or peripheral edema. Hematology and chemistry labs should be obtained at the cycle 1, day 15 (C1D15) visit when the patient has PK sampling and an ECG performed. The schedule of assessments is otherwise reasonable.

Discussion During Meeting: Plexxikon will revise the protocol to require physical examinations at C2D1, C4D1 and every 3 cycles thereafter. FDA stated that this is acceptable. Plexxikon is in agreement with the frequency of the hematology and chemistry lab monitoring as suggested by FDA.

10. Does the FDA agree that the planned number of patients and planned duration of exposure to be included in the safety database is adequate to support submission of the marketing application for PVNS?

FDA Response: Given the rarity of the disease, the estimated safety database of a maximum of 60 patients who will have been treated for at least 48 weeks and a maximum of 120 patients who will have been treated for at least 24 weeks with the intended PLX3397 total daily dose of 1000 mg as a split dose, in conjunction with the safety

database accumulated in clinical trials of PLX3397 in other patient populations, may be sufficient to support a marketing application provided that no unusual toxicities are identified. This question should be revisited at the time of the pre-NDA meeting.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

Clinical Pharmacology:

11. Clinical pharmacokinetics (PK) of PLX3397 are described in Section 4.5. The following additional clinical pharmacology studies are planned to support the registration of PLX3397:

- Fed versus fasted PK single-dose study
- ¹⁴C-radiolabel mass balance study
- Thorough QT study

Will the clinical pharmacology program as proposed be adequate to support filing of a marketing application for this indication?

FDA Response: No. As recommended in the response to question 4, Plexxikon should conduct exploratory E-R analyses and include the report of the results in the NDA submission. In addition, Plexxikon should provide plans to address the following:

- As PLX3397 is metabolized mainly by CYP3A4 *in vitro*, clinical studies to assess the effect of strong CYP3A4 inhibitors and inducers on the pharmacokinetics of PLX3397 are warranted if the contribution of this enzyme to the overall elimination of the drug is either substantial ($\geq 25\%$ of the clearance pathway) or unknown.
- Determine the need for *in vivo* drug interaction studies based on the results from *in vitro* assessment. Refer to the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.
- Depending on the results from the planned mass balance study, further studies to evaluate the effect of hepatic and/or renal impairment on PLX3397 exposure may be warranted.
- Conduct a study to assess the effect of pH-elevating agents [e.g., proton pump inhibitors (PPIs), H₂ antagonists and antacids] on the absorption of PLX3397 if PLX3397 demonstrates pH dependent solubility and becomes poorly soluble as gastrointestinal pH increases. The study may be conducted to first assess the effect of a PPI on the exposure of PLX3397. In the event that concomitant administration of a PPI has a large impact on PLX3397 exposure, an H₂ antagonist and an antacid should be subsequently evaluated.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

Non-Clinical:

12. Does the FDA agree that the nonclinical studies conducted and proposed with PLX3397 would support registration for the PVNS indication?

FDA Response: No, FDA does not agree. Because patients with PVNS have long life-expectancies, an assessment of the carcinogenic potential of PLX3375 will be required. In addition, an assessment of fertility and peri-postnatal toxicity will be required for approval in this indication. The full package of reproductive toxicology and carcinogenicity studies should be included in the NDA.

Also, in addition to the endpoints listed in the briefing document FDA recommends that Plexxikon assess fetal plasma exposure and maternal reproductive histopathology (as well as gross lesions and known target organs) in the definitive rabbit embryofetal study.

Discussion During Meeting: Plexxikon asked if, in regards to the requested carcinogenicity and rabbit embryofetal development studies, they can submit additional specific questions to the pre-IND file in order to initiate these studies as soon as possible. Plexxikon will include outlines of the proposed studies together with their questions. FDA stated that a special protocol assessment (SPA) will be requested for the carcinogenicity study. The SPA will be presented to ECAC, who will provide feedback on the design. Plexxikon noted that FDA-requested evaluation of the fetal plasma exposure; FDA noted that a point estimate from fetuses is sufficient, and that the collection should occur at the time of sacrifice for main study dams. Fetal plasma samples can be pooled by litter due to limited fetal blood volume.

FDA recommended that Plexxikon submit SPAs for carcinogenicity studies. Plexxikon asked if an SPA can be submitted under the pre-IND. FDA stated that an SPA may not be submitted under a pre-IND; however, an SPA could be submitted under another PLX3397 oncology IND if Plexxikon wished to submit before an IND was established for the PVNS indication.

A guidance document detailing the timing, format, and procedures for special protocol assessments for carcinogenicity can be found on FDA's website:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm078924.pdf>

Regulatory:

13. Does the FDA agree that a single randomized, placebo-controlled study of PLX3397 in PVNS patients would be sufficient to demonstrate efficacy in this rare disease?

FDA Response: In general, FDA will accept a single trial to support an application for registration if results show a highly statistically significant effect on a measure of clinical

benefit or a surrogate for clinical benefit that is internally consistent across relevant subgroups. The results of the single trial must be sufficiently robust and so compelling that it would be unethical to repeat the study. For further information please refer to the FDA document “Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products” at <http://www.fda.gov/cder/guidance/index.htm>.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

14. Based on the seriousness of this disease as well as the clinical data collected to date for PVNS patients treated with PLX3397 in Study PLX108-01, does the FDA agree that there is sufficient evidence to meet the preliminary clinical evidence criteria for Breakthrough Designation?

FDA Response: Based on the information provided in the meeting package, it does not appear at this time that there are sufficient early clinical data demonstrating that PLX3397 has potential to provide a substantial improvement over available therapy. FDA agrees that unresectable PVNS is a serious condition with limited existing therapies; however, it would be preferable to demonstrate effect in a larger sample size and collect extended duration of response data prior to requesting Breakthrough Designation.

Discussion During Meeting: Plexxikon stated that an updated, larger dataset from PVNS patients participating in the ongoing Phase 1 study PLX108-01 will be analyzed in April 2014. At that time, efficacy and safety results for approximately 24 patients treated for periods of up to 65 weeks is expected to be available. Plexxikon asked if these results could potentially provide sufficient early clinical data to demonstrate substantial improvement over available therapy.

FDA asked if they will all be response-evaluable patients. Plexxikon stated that there will be 20-24 evaluable patients. FDA stated it will also depend on the number of patients with durable responses. Plexxikon stated there will be approximately eight patients with one year of exposure. FDA stated that 20 patients would be the low-end of the number of patients to be considered for Breakthrough Designation. FDA stated that Plexxikon can submit the available data to the pre-IND, and FDA will review and provide informal feedback. However, Breakthrough Designation cannot be requested under a pre-IND.

15. Plexxikon has three ongoing INDs with PLX3397 and is utilizing the Development Safety Update Report (DSUR) format and International Development Birth Date of 28 August 2009 for submission of a combined IND Annual Report. Does FDA agree with this approach for the subject IND?

FDA Response: This is acceptable.

Discussion During Meeting: Plexxikon acknowledged the response and requested no further discussion.

ADDITIONAL COMMENTS

Clinical:

16. Provide rationale for the (b) (4) interval between MRI evaluations after C13D1. A shorter interval may be more reliable for demonstration of sustained response.

Discussion During Meeting: Plexxikon stated that the interval between MRIs will be shortened to 3 months throughout the study.

17. Perform subgroup analyses to assess objective response rate, duration of response and changes in PRO assessment parameters by location of disease (large or small joints) and specific type of tenosynovial GCT (GCT-TS vs. PVNS).

Discussion During Meeting: Plexxikon stated that the suggested subgroup analyses will be performed.

18. Clarify if the eligible patient population will include or exclude patients who have had prior external beam radiation or radioisotope treatments.

Discussion During Meeting: Plexxikon stated that the study will allow patients who have had prior external beam radiation or radioisotope treatments.

19. An MRI acquisition protocol will need to be provided to all investigators and submitted to the original IND.

Discussion During Meeting: Plexxikon stated that the MRI acquisition protocol will be standardized and quality controlled, including site training on the image acquisition technique. The MRI acquisition protocol will be included in the original IND.

20. Submit the radiographic imaging charter to the original IND.

Discussion During Meeting: Plexxikon stated that the imaging charter will be included in the original IND.

Additional Discussion During the Meeting:

FDA inquired into the reported 5-10% response rate in the placebo arm. Plexxikon stated that they believe this is an overestimation, and that it is not something seen radiographically.

PREA Requirements

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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. 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

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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, see [CDER/CBER Position on Use of SI Units for Lab Tests](#).

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/s/

DEANNE R VARNEY
03/10/2014