

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

211810Orig1s000

OTHER REVIEW(S)

Department of Health and Human Science Public Health Services

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Gastroenterology and Inborn Errors

Consult Addendum

NDA	211810
Applicant	Daiichi Sankyo Inc
Drug	Pexidartinib (PLX3397; Turalio) from Daiichi Sankyo
Consulting Division	Division of Oncology Products 2 (DOP2)/ Office of Hematology and Oncology Products
Clinical Reviewer	Ruby Mehta, MD Medical Officer, Division of Gastroenterology & Inborn Errors Products (DGIEP)
Team Leader, DGIEP	Stephanie O. Omokaro, MD
Associate Director, Office of Pharmacovigilance & Epidemiology (OPE)	Mark Avigan, MD, CM
Date of Memo	July 28, 2019

This consult memorandum is a follow-up to the initial DGIEP & OPE consult addressing liver toxicity associated with pexidartinib and contains the histopathology findings reviewed by Dr. David Kleiner (Chief, Post-Mortem Section, NCI at NIH). Histopathology digital images for 8 subjects provided by the Applicant were sent for review of potential liver toxicity and its causal relationship to pexidartinib. The overall findings discussed by Dr. Kleiner in his report are consistent with our team's (DGIEP & OPE) findings of a range of cholestatic liver injuries associated with pexidartinib and progression to biliary ductopenia (Vanishing bile duct syndrome) in some of the patients. Both Dr. Kleiner and the consulting team share the concern that to observe so many cases of liver injury among the relatively few patients enrolled is evidence of a relatively high risk of DILI. Dr. Kleiner's histopathological findings and his impressions are summarized below:

The responses are limited as whole slides were not available for independent review. He stated, "the most that can be done with the photos is to see if features described in the reports are documented".

The pattern of injury is characterized using Drug Induced Liver Injury Network¹ for the histopathological classification of DILI.

Table 1: Patterns of Histological Injury

Study ID	Subject ID	Pattern
IST3397-001	(b) (6)	VBDS*, acute cholestatic
IST3397-006	(b) (6)	VBDS, chronic cholestatic
PLX108-10	(b) (6)	VBDS, chronic cholestatic
PLX108-01	(b) (6)	possibly chronic cholestatic
PLX108-07	(b) (6)	acute cholestatic
PLX108-09	(b) (6)	acute cholestatic
PLX108-14	(b) (6)	minimal changes
PLX108-14	(b) (6)	chronic hepatitic, immunoallergic features

Source: Copied and Electronically Reproduced from Dr Kleiner’s Consult Review.

VBDS*: Vanishing bile duct syndrome

The overall picture is consistent with cholestatic injury, with three cases demonstrating acute cholestasis (bile accumulation without significant inflammation) and three cases showing chronic cholestasis (ductular reaction and duct injury without much bile accumulation). One case showed a chronic hepatitis pattern with inflammatory infiltrates that suggest immunoallergic injury (eosinophils and granulomas).

Three cases that showed duct paucity (VBDS), one still showing acute cholestatic injury and two having progressed to chronic cholestatic changes. It may seem incongruous to not see changes of chronic cholestasis in a case in which there has been significant duct loss, but when duct loss happens suddenly, there may not be sufficient time to develop the changes of chronic cholestasis. The duct paucity is clearly severe in two cases. Of note, the histopathological findings of VBDS associated with Subject (b) (6) after progression of liver injury that culminated in liver transplantation have been documented in a recently published case report.²

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) do not present in this fashion and generally do not develop duct loss early in the disease course. The one exception is subject (b) (6), mostly because the histological findings are not distinctive and could be mimicked by many causes of chronic cholestatic injury, including chronic intermittent large duct obstruction, which is a difficult diagnosis to exclude. The chronic hepatitis case with immunoallergic features (subject (b) (6)) is also likely due to DILI.

¹ Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, Hayashi PH, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology* 2014; 59:661-670.

² Piawah S, Hyland C, Umetsu SE, Esserman LJ, Rugo HS, Chien AJ. A case report of vanishing bile duct syndrome after exposure to pexidartinib (PLX3397) and paclitaxel. *NPJ Breast Cancer* 2019; 5:17.

Table 2: Patterns of Injury with Dr. Kleiner’s Key Observations from Photomicrographs

Study ID	Subject ID	Pattern	Key Observations
IST3397-001	(b) (6)	VBDS, acute cholestatic	Minimal portal and parenchymal inflammation; no fibrosis, moderate cholestasis; duct loss documented; no ductular reaction
IST3397-006		VBDS, chronic cholestatic	Marked ductal loss in explant, steatosis present
PLX108-01		possibly chronic cholestatic	Mild portal inflammation, no parenchymal inflammation, periportal fibrosis present; ductular reaction present; mild steatosis
PLX108-07		acute cholestatic	Marked cholestasis; ductal injury present; steatosis is minimal; cholestatic rosettes, iron 2+
PLX108-09		acute cholestatic	mild portal inflammation with eosinophils, mild parenchymal inflammation; moderate cholestasis; no ductular reaction; mild steatosis
PLX108-10		VBDS, chronic cholestatic	mild portal inflammation; ductal injury present; duct loss documented; no ductular reaction
PLX108-14		minimal changes	mild portal and parenchymal inflammation; mild steatosis;
PLX108-14		chronic hepatitic, immunoallergic features	Moderate with interface hepatitis, eosinophils; granulomas present in parenchyma; duct injury is possible

Source: Adapted from a Pathology Summary Spreadsheet attached to Dr. Kleiner’s Report (not in the main memo)

Main Memo Submitted by Dr. Kleiner is Attached Below.



NATIONAL CANCER INSTITUTE
Center for Cancer Research

Date: July 22, 2019

From: David E. Kleiner, M.D., Ph.D.
Chief, Post-Mortem Section
Laboratory of Pathology, CCR, NCI

Subject: Evaluation of histological liver injury from clinical trials of pexidartinib

To: Christy Osgood, M.D., Medical Officer,
Division of Oncology Products 2 (DOP2)
Center for Drug Evaluation and Research
Food and Drug Administration

The Division of Oncology Products 2 has asked me to review pathology reports and photomicrographs relating to 8 instances of potential liver toxicity caused by pexidartinib in which liver biopsies were performed. For each biopsy, they ask that I comment on the histopathological changes, the severity of injury, the presence or absence of ductopenia and an assessment of the potential of the injury to be due to a drug. They also ask for comments on potential mechanisms of injury.

Unfortunately, my assessment is severely limited by the kind of information provided. No slides or whole slides scans are available for independent review. The pathology reports vary considerably in quality. A couple are very good (those for subject (b) (6) and (b) (6)) while the rest are very limited. The photomicrographs are generally of good quality but are few in number (except for subject (b) (6)) and naturally are skewed to show only what the local pathologist thought was important. Therefore, the most that can be done with the photos is to see if features described in the reports are documented. It is not possible to formulate an independent opinion of the pathology or to review the cases for overall similarities and differences that are not already included in the pathology reports.

With this limitation in mind, I have attempted place these cases within the same pattern of injury framework that was published by the Drug Induced Liver Injury Network for the histopathological classification of DILI(1). Further details, including the relative severity of findings, can be found in the attached spreadsheet (PathologySummary.xlsx).

Table. Patterns of Histological Injury

Study ID	Subject ID	Pattern
IST3397-001	(b) (6)	VBDS, acute cholestatic
IST3397-006	(b) (6)	VBDS, chronic cholestatic
PLX108-01	(b) (6)	possibly chronic cholestatic
PLX108-07	(b) (6)	acute cholestatic
PLX108-09	(b) (6)	acute cholestatic
PLX108-10	(b) (6)	VBDS, chronic cholestatic

PLX108-14	(b) (6)	minimal changes
PLX108-14	(b) (6)	chronic hepatitic, immunoallergic features

VBDS: Vanishing bile duct syndrome

There is a clear overall theme of cholestatic injury, with three cases showing acute cholestasis (bile accumulation without significant inflammation) and three cases showing chronic cholestasis (ductular reaction and duct injury without much bile accumulation). Of the two outliers, one case showed a chronic hepatitis pattern with inflammatory infiltrates that suggest immunoallergic injury (eosinophils and granulomas). In the report for this case, duct injury was noted, but the photos did not confirm the observation. It is possible that subtle changes of cholestasis (acute or chronic) could have been overlooked. The last case showed minimal changes, but again, subtle changes of cholestasis could have been missed by the local pathologist.

Three cases showed duct paucity, one still showing acute cholestatic injury and two having progressed to chronic cholestatic changes. It may seem incongruous to not see changes of chronic cholestasis in a case in which there has been significant duct loss, but when duct loss happens in suddenly there may not be sufficient time to develop the changes of chronic cholestasis. The duct paucity is clearly severe in two cases. The third case, subject (b) (6), did not clearly demonstrate VBDS on the initial biopsy, but the patient later progressed to require liver transplantation. This was documented in a case report(2). (I could confirm this because the photos that were submitted for review were the same as those in the publication).

With respect to the question of causality, assuming that the mundane causes of cholestasis have been excluded, five of the six of the cholestatic cases are likely due to drug injury. This is particularly true of the VBDS cases. Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) do not present in this fashion and generally do not develop duct loss early in the disease course. The one exception is subject (b) (6) mostly because the histological findings are not distinctive and could be mimicked by many causes of chronic cholestatic injury, including chronic intermittent large duct obstruction, which is a difficult diagnosis to exclude. The chronic hepatitis case with immunoallergic features (subject (b) (6)) is also likely due to DILI. The pattern is wrong for autoimmune hepatitis or chronic viral hepatitis and the latter can be excluded by serological tests. Histology is not helpful to determine causality in the case that only showed minimal changes.

As to the question of mechanism, the histology offers only a few clues. DILI related VBDS is often suggested to be the result of immunological injury—direct or indirect attack on the bile ducts. Unfortunately, none the cases with VBDS show significant portal inflammatory infiltrates. No history of steroid administration was included, but that could account for a minimal infiltrate. Induction of cholangiocyte apoptosis through alternate mechanisms might not require a substantial inflammatory infiltrate. Other possible mechanisms of duct loss include ischemic (as in the case of fluorodeoxyuridine infusion) or toxic. The latter could result from toxic metabolites excreted by hepatocytes into bile. Some papers on general mechanism of duct injury are included at the end of the document(3-6).

To see so many cases of liver injury among the relatively few patients enrolled is evidence of a relatively high risk of DILI compared to other agents, perhaps even higher than imatinib. I have looked into the literature to try and explore possible associations between the postulated effects of pexidartinib and liver injury. The aminotransferase elevations seen in 50% of patients have been associated with effects on Kupffer cells. I would speculate that this agent changes the predominant immunotolerant milieu of the liver, making it more sensitive to effects from microbial products coming from the gut. This may in turn sensitize the liver to other kinds of injury. However, it is hard to connect this kind of change to duct loss. I would be interested in reviewing whole slide images of the biopsies (and the explant in the case of subject (b) (6)). It would then be possible to provide a much more complete picture of the biopsy changes.

1. Kleiner DE, Chalasani NP, Lee WM, Fontana RJ, Bonkovsky HL, Watkins PB, Hayashi PH, et al. Hepatic histological findings in suspected drug-induced liver injury: systematic evaluation and clinical associations. *Hepatology* 2014;59:661-670.
2. Piawah S, Hyland C, Umetsu SE, Esserman LJ, Rugo HS, Chien AJ. A case report of vanishing bile duct syndrome after exposure to pexidartinib (PLX3397) and paclitaxel. *NPJ Breast Cancer* 2019;5:17.
3. Nakanishi Y, Saxena R. Pathophysiology and Diseases of the Proximal Pathways of the Biliary System. *Arch Pathol Lab Med* 2015;139:858-866.
4. Nakanuma Y, Tsuneyama K, Harada K. Pathology and pathogenesis of intrahepatic bile duct loss. *J Hepatobiliary Pancreat Surg* 2001;8:303-315.
5. Xia X, Demorrow S, Francis H, Glaser S, Alpini G, Marzioni M, Fava G, et al. Cholangiocyte injury and ductopenic syndromes. *Semin Liver Dis* 2007;27:401-412.
6. Yoo KS, Lim WT, Choi HS. Biology of Cholangiocytes: From Bench to Bedside. *Gut Liver* 2016;10:687-698.

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/s/

RUBY MEHTA
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Department of Health and Human Science Public Health Services

Food and Drug Administration

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NDA	211810
Applicant	Daiichi Sankyo Inc
Drug	Pexidartinib (PLX3397; Turalio) from Daiichi Sankyo
Consulting Division	Division of Oncology Products 2 (DOP2)/ Office of Hematology and Oncology Products
Clinical Reviewer	Ruby Mehta, MD Medical Officer, Division of Gastroenterology & Inborn Errors Products (DGIEP)
Team Leader, DGIEP	Stephanie O. Omokaro, MD
Acting Deputy Director, DGIEP	Bindi Nikhar, MD
Associate Director, Office of Pharmacovigilance & Epidemiology (OPE)	Mark Avigan, MD, CM
Date of Request	February 20, 2019
Date of Memo	June 21, 2019

Executive Summary

The Division of Oncology Products 2 (DOP2) consulted the Division of Gastroenterology and Inborn Error Products (DGIEP) and the Office of Pharmacovigilance and Epidemiology (OPE) to assess the risk of hepatotoxicity associated with pexidartinib. NDA 211810, for pexidartinib has been submitted for the indication of treatment of tenosynovial giant cell tumor (TGCT), which is a group of rare, benign tumors that involve the synovium, bursae and tendon sheath and are associated with a chronic yet debilitating course of disease secondary to growth and damage to the surrounding tissue and structures of the body. Surgery is the main treatment option; however, the tumor tends to recur resulting in significant damage and degeneration of the affected joint and surrounding tissues or structures.

Upon review of safety data from TGCT (N=140) and non-TGCT (data available for N=520) clinical trials, pexidartinib-induced hepatotoxicity and its association with a significant risk for serious outcomes was observed. The pattern of liver injury was often cholestatic, but both mixed and hepatocellular forms of injury were also identified in some patients. The spectrum of drug-induced liver injury (DILI) severity ranged from isolated and transient liver enzyme elevations to

ductopenia and liver failure. The time to liver injury onset after initiating pexidartinib varied between 2 weeks to 8 weeks in most cases.

Study PLX108-10 was a pivotal double-blind placebo-controlled phase 3 trial in subjects with TGCT, that randomized 61 subjects to the pexidartinib arm (1000 mg/day [administered as 500 mg BID] x 15-days followed by 800 mg/day [administered as 400 mg BID]) and 59 subjects to placebo.

The biochemical findings of hepatotoxicity observed during this trial in the sera of 61 subjects who received pexidartinib over a duration of 24-weeks were as follows: 66% of subjects experienced elevations in liver enzymes; 33% were found to have ALT \geq 3X ULN compared to none in placebo arm; 20% experienced ALT \geq 5X ULN and none in placebo arm; and 7% experienced ALT \geq 10X ULN and none in placebo arm. A total of 5% of subjects experienced both ALT \geq 3X ULN and TB \geq 2X ULN elevations suggestive of serious liver injury compared to none in the placebo arm. One subject in whom liver biopsy was performed secondary to continued rise in bilirubin was found to have severe ductopenic injury.

The criteria for dose modification for hepatotoxicity, i.e. discontinuation, interruption, and reduction, were based upon liver monitoring test results and assessed by Common Terminology Criteria for Adverse Events (CTCAE).

In the TGCT population, 22 patients had been treated for more than 18 months, 17 for more than 24 months, and one patient had been treated for more than 48 months at the time of data cut off.

Seven patients out of 91 were reported to experience significant liver injury in the TGCT trial, of which, four were attributed to pexidartinib use, one was considered possibly related, and two unrelated to pexidartinib use.

In the non-TGCT trials, a total of 768 unique subjects received pexidartinib with therapeutic intent and of these, data was available on 520 subjects for assessment of hepatotoxicity. The Applicant categorized the type of injury as cholestatic in 152 (29.1%), mixed in 18 (3.4%), hepatocellular in 4 (0.8%), and not applicable ¹ in 349 (66.7%) patients. However, an important limitation was that in the non-TGCT studies, complete data for liver toxicity in all subjects was not available to the Applicant, therefore, a comprehensive assessment of hepatotoxicity was not possible. Nonetheless, in the investigator-initiated trials, two subjects developed liver failure; one subject who was treated for breast cancer required liver transplant (Study IIS-SPY2-097517, Subject No. (b) (6)) and the other subject who was being treated for vaginal melanoma, died (Study PLX108-13, Subject No. (b) (6)).

¹ Subjects did experience elevations in liver enzymes, however, they did not meet the following criteria: i. ALT: \geq 3X to 5X ULN; >5X to 10X ULN; >10X ULN; ii. ALP: \geq 2X ULN; >3X to 5X ULN; >5X to 10X ULN; >10X ULN; iii. ALP or GGT \geq 2X ULN and TB \geq 2X ULN; iv. DB >0.5 mg/dL; v. ALT \geq 3X ULN and direct bilirubin (DB) \geq 0.5 mg/dL; vi. ALT \geq 3X ULN and ALP or GGT \geq 2X ULN and TB \geq 2X; ULN or DB >0.5 mg/dL were categorized in “not applicable” category

It is noteworthy that three subjects (PLX108-10 Subject No. (b) (6); IST3397-006 (Study IIS SPY2 097517) Subject No. (b) (6); IST3397-001 (Study IIS UCSF 12751) Subject No. (b) (6)) treated with pexidartinib across TGCT (N=140) and non-TGCT (N=523) trials developed clinically serious pexidartinib-induced hepatotoxicity, accompanied by **pronounced ductopenic injury** (or vanishing bile duct syndrome² [VBDS]) detected by liver biopsy. Severe ductopenia is defined as bile duct loss of $\geq 50\%$ and is an irreversible injury. Of greater concern is the irreversible nature of this type of liver injury, which may predispose a significant proportion of patients to eventually progress to cirrhosis and end stage liver disease requiring liver transplant. The extent, magnitude and progression of ductopenic injury occurring in subjects treated with pexidartinib is unknown, because liver biopsy was performed only in a total of 8 subjects; i.e., in seven subjects enrolled to the non-TGCT trials and in one subject enrolled to PLX108-10 (pivotal TGCT trial). Of the subjects enrolled in the non-TGCT investigator-initiated trials, out of 138 subjects dosed with pexidartinib, the subject who developed ductopenia, described above (Study IIS-SPY2-097517, Subject No. (b) (6)) with breast cancer developed subacute liver failure requiring liver transplant secondary to severe ductopenia. The proportion of subjects with ductopenia that would eventually progress to liver failure over an extended treatment period is not well characterized to date. Development of pexidartinib-induced cholestatic or mixed injury was not associated with dose or duration. Factors that may predispose to development of ductopenia could not be identified. Across both the TGCT and non-TGCT trials, out of the eight subjects who had a liver biopsy, a total of three subjects showed evidence of severe ductopenic liver injury that was assessed to have been caused by pexidartinib use, and a fourth and fifth (PLX108-14 Subject No. (b) (6) and PLX108-09 Subject No. (b) (6)) subjects with **liver biopsy findings were consistent with DILI** was also attributed to pexidartinib.

Across the pexidartinib development program (i.e., TGCT and non-TGCT trials), by-and-large, elevated liver enzymes returned back to baseline values after drug discontinuation (positive de-challenge) in days to weeks (~6-8 weeks), however, with mixed or cholestatic injury the recovery was much slower i.e., resolved over weeks to months upon pexidartinib interruption or discontinuation. The most prolonged cholestatic hepatotoxicity event in the TGCT population persisted for 7 months. In the non-TGCT population, there were two cases of cholestatic hepatotoxicity that had not resolved. There was evidence of recurrence of liver enzyme elevations upon restarting treatment with pexidartinib (positive re-challenge) in some patients (8 patients in TGCT 24-week DB, PC part of trial). The factors that predisposed patients to a positive rechallenge could not be characterized.

Pexidartinib associated hepatotoxicity does not appear to be dose-dependent for the doses that were tested in the clinical trial subjects (1000 mg, 800 mg, 600 mg, and 400 mg). However,

² Bonkovsky HL, Kleiner DE, Gu J, Odin JA, Russo MW, Navarro VM, Fontana RJ, Ghabril MS, Barnhart H, Hoofnagle JH; U.S. Drug Induced Liver Injury Network Investigators. [Clinical presentations and outcomes of bile duct loss caused by drugs and herbal and dietary supplements](#). Hepatology. 2017 Apr;65(4):1267-1277

because of the lack of randomized comparisons at lower doses and differences in patient populations, definition of a threshold dose level below which hepatotoxicity does not occur is lacking.

While hepatocellular injury, as evidenced by isolated liver transaminase elevations occurs, is monitorable and maybe reversible; the cholestatic or mixed injury with onset of ductopenia is most likely irreversible. The time required for pexidartinib associated progression of ductopenia and subsequent liver failure is currently unknown, although 2 subjects progressed rapidly, the first of which progressed to liver failure over the course of 6 weeks (PLX108-13 Subject No. (b) (6)) while the second subject progressed to subacute liver failure and underwent liver transplant at month 20. Factors that could allow identification of subjects who are at risk of developing serious hepatotoxicity are currently not fully understood but the presence of underlying liver injury or concomitant medications that may exacerbate DILI should be further explored. In the event ductopenia/VBDS progresses to liver failure, liver transplant is likely the only treatment option.

Establishing a firm diagnosis of ductopenia requires performance of a liver biopsy, which is an invasive procedure. Therefore, the serial monitoring of patients for early progression to this stage of liver injury is inherently challenging. Moreover, the optimal time for performing a liver biopsy in patients treated with pexidartinib to reliably detect and better characterize ductopenic injury and its kinetic characteristics over time is currently not established. The anticipated time course of progression of ductopenic injury may be affected by whether the underlying hepatotoxicity with pexidartinib is subacute, chronic/indolent, progressive, or nonprogressive. Furthermore, a second hit or pathological event may hypothetically be required to precipitate liver failure. A second analysis of the histopathological progression was not performed in all except one aforementioned subject (Study IIS-SPY2-097517, Subject No. (b) (6)) with breast cancer who developed subacute liver failure, where the explant was available for repeat histology assessment. While overall biochemical enzymes improved in the majority of subjects' who developed liver enzyme elevations, the histological progression of ductopenia that occurred over time in the few subjects assessed for this outcome remains unknown at this time.

To understand the full scope of hepatotoxicity that occurred with pexidartinib, an information request (IR) was sent to the Applicant on March 19, 2019 requesting subject-level and population data to assess pexidartinib associated hepatotoxicity (across TGCT and non-TGCT programs), a hepatic adjudication committee assessment (HEAC) comprised of experts in the assessment of DILI, and a report of the DSMB's adjudication for hepatotoxicity. Findings of the HEAC regards causal association of the serious liver injury cases marked by cholestasis, or mixed injury and some with progression to ductopenia are generally in alignment with the analysis of the FDA review team.

With a demonstrated risk of serious hepatotoxicity associated with pexidartinib, as well as the significant gaps in our current knowledge surrounding assessment of risk for progression of

liver injury associated with long-term use of this product, the overall benefits of treating patients with TGCT, a non-malignant condition should be carefully weighed. It is self-evident that a high threshold of benefit for the intended treatment population must be exceeded in order to justify approval of the agent. Taking this concern into account, should DOP2 decide to “not approve” this drug, then we have no further comments. However, should DOP2 decide to approve the drug, it would be prudent for the Applicant to institute a stringent monitoring program with a REMS and ETASU that would enroll all patients prescribed pexidartinib in order to track pexidartinib exposure, the monitoring of liver enzymes, as well as outcomes of hepatotoxicity, including serious liver-related events. All patients with a serious hepatic adverse event associated with pexidartinib should be comprehensively evaluated both clinically and with appropriate diagnostic testing and reported in an expedited fashion to the FDA. In addition, a post-market clinical trial that would measure and analyze liver-related effects associated with both short-term and long-term pexidartinib treatment in TGCT patients is strongly advised. Follow-up of patients who have discontinued pexidartinib to rule out delayed hepatotoxicity effects is also advised. Reassessment of subjects exposed to pexidartinib should be undertaken on a yearly basis to assess for hepatotoxicity. Please see the Overall Conclusions and Recommendations sections below.

A. Background

The Division of Oncology Products 2 (DOP2) in the Office of Hematology and Oncology Products has requested a consult to evaluate the hepatotoxicity risk of pexidartinib, based on data that has been collected across the Tenosynovial giant cell tumor (TGCT) and non-TGCT clinical development programs (by Daiichi Sankyo). Currently, NDA 211810 is being reviewed by the FDA for tenosynovial giant cell tumor (TGCT), which is a group of rare, non-malignant tumors that involve the synovium, bursae and tendon sheath and are associated with a chronic and debilitating course of disease.

Pexidartinib is a small molecule tyrosine kinase inhibitor that targets colony stimulating factor-1 receptor (CSF1R). TGCT tumors consists of mononuclear and multi-nucleate giant cells and these non-neoplastic inflammatory cells do not express CSF-1 but are attracted to the tumor site because of its expression of CSF1R. Pexidartinib is a new molecular entity, that is administered orally.

The proposed indication is for the treatment of adult patients with symptomatic TGCT (b) (4) associated with significant morbidity and functional limitations, and not amenable to surgery. The recommended dose of Pexidartinib is 400 mg taken twice daily. In the double-blind, placebo-controlled, pivotal trial, ENLIVEN (PLX108-10, Phase 3), TGCT patients were randomized 1:1 to receive pexidartinib 1000 mg split BID for 2-weeks followed by 800 mg split BID (n=60) or matching placebo (n=59) for 24 weeks (Part 1). An open-label extension (OLE) study followed Part 1 and subjects continued taking pexidartinib until they experienced unacceptable toxicity, withdrawal of consent, or death occurred. The dose in the OLE was 800 mg split BID.

TGCT is a nonmalignant neoplasm involving the synovium and tendon sheath. It typically affects young and middle-aged adults of both sexes. TGCT that is localized is known as GCT-TS, which is monoarticular disease, most commonly occurring in the digits. The tumor mass grows very slowly; however, symptoms such as pain, stiffness, swelling, and reduced range of motion (ROM) can lead to functional limitation. The diffuse type of TGCT is also referred to as pigmented villonodular synovitis (PVNS). Diffuse TGCT is a locally aggressive, nonmalignant neoplasm. Diffuse TGCT most commonly occurs in large joints, particularly the knees, ankle and hip. Diffuse TGCT and localized TGCT have an estimated annual incidence of 1.8 cases per million and 9.2 cases per million, respectively, in the United States. The current standard of care for TGCT is surgical resection. Localized disease has a 6% recurrence rate, while diffuse disease carries up to 50% chance of recurrence after a surgical resection. Diffuse TGCT is rarely lethal and only rare cases of metastases have been described. No systemic anti-tumor agents are approved for treatment of TGCT.

A.1. Drug Metabolism and Use in Hepatic and Renal Impairment

CYP3A4 is the major enzyme responsible for the metabolism of pexidartinib. Uridine 5'-diphosphateglucuronyltransferase (UGT) 1A4, a glucuronosyltransferase, is the enzyme responsible for the formation of the major metabolite, ZAAD-1006a, an N-glucuronide metabolite of pexidartinib.

The Applicant has proposed no dose adjustments in subjects with hepatic or renal impairment. The levels of ZAAD-1006a were found to be increased in the setting of worsening renal function and impaired hepatic function. The Applicant states that the increased major metabolite levels are not clinically meaningful since ZAAD-1006a is considered pharmacologically minimally active.

Due to a safety signal of hepatotoxicity observed during the clinical trials, the Applicant proposes that pexidartinib be contraindicated in patients with hepatic impairment, which would include those with persistent elevation of serum transaminases or bilirubin, or active biliary tract disease.

The Applicant states that since most hepatic adverse events are observed during the first 8-weeks of initiation of the 1000 mg split BID dose that a starting dose of 800 mg split BID may provide a more acceptable hepatic safety profile based on their exposure-response analysis. The FDA Review team questions Applicant's approach, as this justification is not based on clinical data, rather it is Applicant's hypothesis. (Module 2.5 Clinical Overview Page 66).

Pexidartinib was granted orphan drug designation by the FDA on February 14, 2014 for the treatment of PVNS/GCT-TS. On October 28, 2015, pexidartinib was granted Breakthrough Therapy Designation for the treatment of patients with PVNS/GCT-TS where surgical resection was associated with potentially worsening functional limitation or severe morbidity.

Summary of Clinical Development Program

Study	Subjects Treated	Population
TGCT Indication		
PLX108-10 (Phase 3 ENLIVEN)	N=120 61 received pexidartinib during DB PC portion	TGCT
	30 during PBO cross- over	
PLX108-01 (Phase 1 Extension TGCT cohort)	39	TGCT
Total TGCT	159	
Non-TGCT Studies (Pexidartinib as Monotherapy)		
PLX108-01	93	Non-TGCT solid tumors
PLX108-03	20	Hodgkin's lymphoma
PLX108-04	38	Glioblastoma multiforme
PLX108-05	90	acute myeloid leukemia
PLX108-06	6	Prostate cancer
PLX108-13 (non-IND study)	6	KIT-mutant melanoma
PL3397-A-A103 (non-IND study)	11	Solid tumors, 1 TGCT subjects
Total	264	
Non-TGCT Studies (Pexidartinib in Combination with Other Chemotherapy Agent(s), or Radiotherapy)		
PLX108-07 (+ paclitaxel)	74	Solid tumors
PLX108-08 (+ temozolomide, radiotherapy)	65	Glioblastoma multiforme
PLX108-09 (+ vemurafenib)	13	BRAF mutant melanoma
PLX108-14 (+ pembrolizumab)	78	Solid tumors
PLX121-01 (+ PLX9486)	12	Solid tumors
Total	242	
Investigator Initiated Pexidartinib Studies		
Investigator-initiated studies (8 studies)	138	Solid and hematologic Tumors
Clinical Pharmacology Studies		
Clinical pharmacology studies (14 studies)	338	Healthy or special population subjects (not patients)
Total Subjects for All Studies		1141

Across the clinical studies, 630 subjects with cancer or TGCT received pexidartinib. In addition, 138 subjects received pexidartinib in investigator-initiated studies. **In total, 768 subjects received pexidartinib with therapeutic intent.**

A.2. Preclinical Toxicological Profile

In the repeat dose toxicity studies in rats adduces, 200 mg per kilogram for 28-days resulted in increased aminotransferases. In the 26-weeks rat toxicity study, biliary cysts and necrotizing inflammation was observed in female rats at a dose of ≥ 20 mg/kg/day and these changes were not reversible and remained persistent during the 16-week recovery.

In dogs, elevations in liver enzymes were also observed. The toxicology report states that hemosiderin pigment was observed in 2 at random males and females from group 5 selected for necropsy.

Transaminase and ALP elevations were also observed in monkeys in the repeat dose toxicology studies. It is not clear whether liver biopsies were performed in the monkey study.

A.3. Mechanistic Studies

Possible mechanisms for liver toxicity of pexidartinib and its *N*-glucuronide metabolite, ZAAD-1006a, were assessed by DILIsym[®] analysis based on *in vitro* hepatotoxicity data, the phase 3 study data (PLX108-10), simulations of chemical hepatic exposure, and simulations of hepatotoxicity mechanisms.

A.4. DILIsym Report

Submitted to Module 4.2.3.7.3 in EDR and reviewed.

DILIsym software was used to predict the possible risk of hepatotoxicity based on *in vitro* assay data, clinical data, simulations of hepatic exposure, and simulations of hepatotoxic mechanisms.

The Applicant states that the frequency of clinical aminotransferase (ALT) elevation was generally reproducible in DILIsym analyses. Mechanistic *in vitro* toxicity data for PLX3397 and ZAAD-1006a were translated into DILIsym toxicity parameter values including mitochondrial dysfunction, oxidative stress, and bile acid transporter inhibition, which contribute to the predicted hepatocellular injury including ALT elevations associated with PLX3397 treatment. In addition, effects from both the parent PLX3397 and the metabolite ZAAD-1006a were found to contribute to the predicted hepatotoxicity which is contrary to the Applicant's presumption that the metabolite is pharmacologically minimally active.

Hyperbilirubinemia was under-predicted with DILIsym in this study. The underprediction is in part due to, to the lack of an explicit representation of cholestasis and ductopenia in the current version of DILIsym. It is important to note that while a helpful perspective for hepatocellular injury, the DILIsym analysis is not yet established to predict cholestatic and mixed injuries.

A.5. Dose

It appears that pexidartinib-induced hepatotoxicity is not dose dependent in the dose range that was studied. Pexidartinib doses in TGCT program ranged from 600 to 1000 mg/day for

TGCT and hepatotoxicity was observed at all doses. In the non-TGCT program doses ranged from 200 to 5000 mg/day and hepatotoxicity was observed across all doses. However, there is some uncertainty because of the lack of randomized comparison, heterogeneity in the patient population, and a small number of events of cholestatic injury in the TGCT and non-TGCT populations. The duration of exposure did not appear associated with the occurrence of hepatotoxicity and no predisposing factors are apparent at this time.

A.7. Drug Modification/Stopping Rules for Hepatotoxicity

The pre-specified protocol treatment discontinuation criteria for pexidartinib included initiation of DILI evaluation with 1) grade 4 CTCAE hepatotoxicity 2) any grade ALT or AST elevation with increase in bilirubin or signs of hypersensitivity and 3) ALT or AST >5X ULN that did not resolve to Grade 1 in 14 days after pexidartinib interruption. If an alternate etiology for DILI was present and liver enzymes resolved to Grade 0-1 after interruption, then pexidartinib could be restarted at a lower dose (reduce by 200 mg capsule).

Notably, the Applicant does not appear to have established elevation of ALP alone for treatment interruption and discontinuation. Treatment interruption and discontinuation rules based on pre-specified ALP elevations were not present in the protocol. It appears that decisions about drug interruption and restart after ALP elevations for individual subjects were often left to the discretion of the investigator. See Table 1 for the pre-specified protocol treatment discontinuation criteria and DILI evaluation.

Using either the grade 4 CTCAE stopping criterion or an increase in bilirubin or signs of hypersensitivity, 11 (7.9%) subjects treated with pexidartinib in Study PLX108-10 (TGCT population) discontinued treatment secondary to abnormal liver test results.

At the time of data cut-off, the duration of treatment in the TGCT population was 18 months for 22 patients, more than 24 months for 17 patients, and more than 48 months for 1 patient.

Table 1: Dose Modification Guidelines for Liver Test Abnormalities

Toxicity Grade CTCAE v0.4	Initial Action	Outcome	Action
ALT or AST Grade 2 (> 3-5X ULN); No increase in bilirubin ^a	Re-check ALT and AST immediately Hold study drug Monitor weekly ^D Check for changes to medications and for symptoms	Resolution to Grade 0-1 or baseline (no bilirubin increase)	Restart on resolution Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Grade 3 ALT or AST increase (> 5-20X ULN);	Re-check ALT and AST immediately	Resolution to Grade 0-1 or baseline (no bilirubin increase) within 14 d	Restart on resolution to Grade 0- 1 or baseline at 1 dose lower (reduce by one 200 mg capsule)

No increase in bilirubin ^a	Hold study drug Monitor 2x/wk ^b Check for changes to medications and for symptoms	ALT and AST not decreasing within 14 d of holding study drug	Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule). For max AST or ALT > 8 \times ULN, consult with medical monitor prior to re-start
Grade 4 ALT or AST (> 20X ULN)	Discontinue treatment Monitor 2x/wk until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment. If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)
Any grade ALT or AST increase ^a with any bilirubin increase or signs of hypersensitivity	Discontinue treatment Monitor 2x/wk until resolution to Grade 2 Follow-up until resolution Grade 0-1 or baseline Check for changes to medications and for symptoms	All outcomes	Discontinue treatment. If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule)

Source: Electronically copied and reproduced from the Applicant's IR-16 response submitted on April 23-19

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

a. An increase in bilirubin is defined as all of the following: total bilirubin > ULN, total bilirubin > 20% above baseline, and direct bilirubin is > ULN. If all of these conditions are met, then bilirubin is considered increased and should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.

b. If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.

B. Liver Safety in the Pexidartinib Development Program

B.1. Type of liver injury

The Applicant has reported serious hepatotoxicity in the non-TGCT trials (2.3%, n=6 out of 258), DSI Sponsored studies (2.1%, n=5 out of 242), and investigator-initiated studies (1.4%, n=2 out of 138). In the double-blind, placebo-controlled, phase 3 part of the ENLIVEN trial (Part 1), 61 subjects received pexidartinib and 59 subjects were enrolled to placebo arm and treated for 24 weeks. In Part 2, placebo arm subjects (N=30) were rolled over to receive pexidartinib. When the placebo subjects were treated with pexidartinib, 30% of subjects experienced hepatic AEs.

Table 2: Overall Summary of Hepatic Adverse Reactions (Laboratory Data) in Part 1 (Randomized) of ENLIVEN

Liver Test Results	Placebo (N=59) n (%)	Pexidartinib (N=61) n (%)

Aminotransferase elevations (excluding concurrent TBIL $\geq 2 \times$ ULN)		
AST or ALT		
≥ 1 to $< 3 \times$ ULN	18 (31)	35 (57)
≥ 3 to $< 5 \times$ ULN	0	8 (13)
≥ 5 to $< 10 \times$ ULN	0	5 (8)
≥ 10 to $< 20 \times$ ULN	0	2 (3)
$\geq 20 \times$ ULN	0	2 (3)
Mixed or cholestatic hepatotoxicity		
ALT/AST $\geq 3 \times$, TBIL $\geq 2 \times$, and ALP $\leq 2 \times$ ULN (True Hy's Law)	0	0
ALT/AST $\geq \times$, TBIL $\geq 2 \times$, and ALP $> 2 \times$ ULN	0	3 (5)
TBIL $\geq 2 \times$ ULN (in absence of ALT $\geq 2 \times$ or ALP $> 2 \times$ ULN)	0	0

Source: Applicant Response to IR submission (submitted on 4-22-2019) page 22 of 325

A total of 5% subjects experienced serious liver injury with ALT/AST $\geq 3 \times$ ULN and TB $\geq 2 \times$ ULN compared to none in the placebo arm during Part 1 of PLX108-10 (ENLIVEN) study.

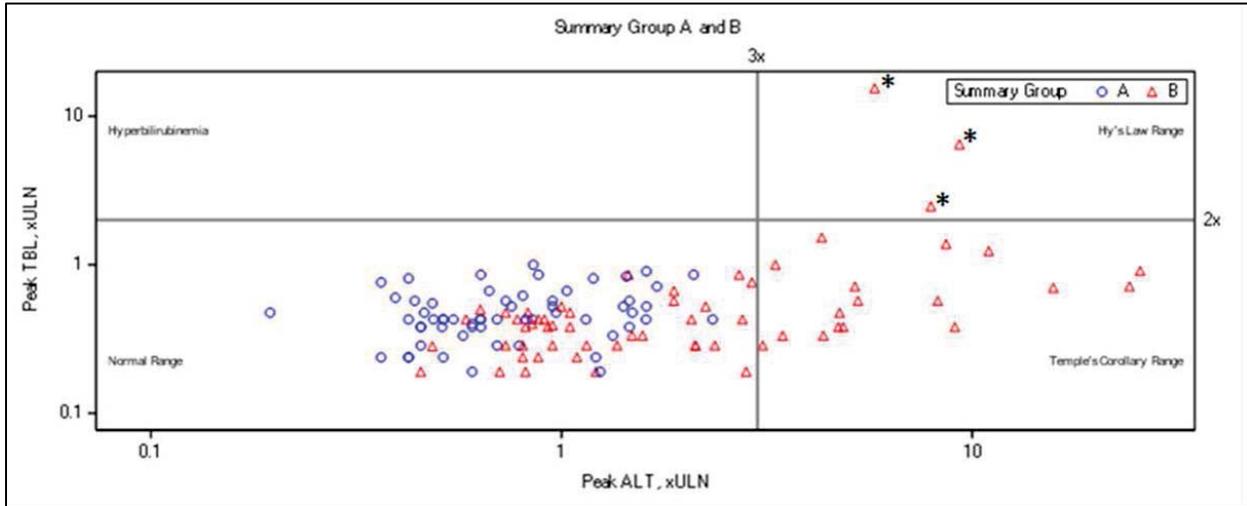
A total of 5% subjects experienced serious liver injury marked by a concomitant AST/ALT $\geq 3 \times$ ULN and TB $\geq 2 \times$ ULN in both Parts 1 & 2 (open label extension) of the ENLIVEN study.

During Part 1, 66% of subjects developed any ALT elevation with pexidartinib treatment, of which the following were considered significant:

- 33% experienced ALT $\geq 3 \times$ ULN compared to none in the placebo arm
- 20% experienced ALT $\geq 5 \times$ ULN compared to none in the placebo arm
- 7% experienced ALT $\geq 10 \times$ ULN compared to none in the placebo arm

The implications of isolated elevations in ALP that would guide dose modification of pexidartinib to mitigate against progression to ductopenia are not easily discernable during the trial. Of note, significant ALP elevations were observed in some subjects, including in subjects who experienced serious liver injury. Impact of elevations in ALP with long term treatment is not fully defined and remains a significant concern.

Table 3: eDISH Plot of Maximum Postbaseline Total Bilirubin versus Maximum Postbaseline Alanine Aminotransferase in Part 1 (Randomized) of ENLIVEN Trial



Source: Electronically copied and reproduced from the Applicant's IR -16 response submission (submitted on 4-22-2019) page 22 of 325. The placebo patients are represented in blue circles & the pexidartinib treated patients in red triangles (Trial PLX108-10/ENLIVEN Trial).

For each subject, the type of liver injury was characterized by the type of hepatotoxicity (hepatocellular, cholestatic, or mixed) observed. The R value assessment was based on a calculation using a ratio of the maximum (times(X)ULN) post baseline ALT and ALP (times(X)ULN) post baseline:

1. If the R value was ≤ 2 , injury was categorized as Cholestatic Injury
2. If the R values was >2 , to ≤ 5 injury was categorized as Mixed Injury
3. If the R value was ≥ 5 , the injury as categorized as Hepatocellular injury.

Type of Liver Injury	All- TGCT Studies N=140	Non-TGCT Studies N=523	All N=663
Cholestatic	33 (23.6%)	152 (29.1%)	185 (27.9%)
Hepatocellular	1 (0.7)	4 (0.8%)	5 (0.8%)
Mixed	8 (5.7%)	18 (3.4%)	26 (3.9%)
Not Applicable ^(1*)	98 (70%)	349 (66.7%)	447 (67.4%)

Source- Applicant response to IR submitted on 4-22-2019

Liver Biochemistries	All- TGCT Studies N=140	Non-TGCT Studies N=523	All N=663
ALT:			
$\geq 3X$ to $5X$ ULN	13 (9.3%)	35 (6.7%)	48 (7.2%)
$>5X$ to $10X$ ULN	13 (9.3%)	25 (4.8%)	38 (5.7%)
$>10X$ ULN to $20X$ ULN	6 (4.3%)	20 (3.8%)	26 (3.9%)
$>20X$ ULN	2 (1.4%)	4 (0.8%)	6 (0.9%)
ALP:			

≥2X ULN	14 (10.0%)	119 (22.8%)	133 (20.1%)
>3X to 5X ULN	3 (2.1%)	50 (9.6%)	53 (8.0%)
>5X to 10X ULN	6 (4.3%)	22 (4.2%)	28 (4.2%)
>10X	0	3 (0.6%)	3 (0.5%)
(ALP or GGT ≥2X ULN) and (TB ≥2X ULN)	5 (3.6%)	22 (4.2%)	27 (4.1%)
DB >0.5 mg/dL	11 (7.9%)	58 (11.1%)	69 (10.4%)
(ALT ≥3X ULN) and (DB ≥ 0.5 mg/dL)	6 (4.3%)	27 (5.2%)	33 (5.0%)
(ALT ≥3X ULN) and (ALP or GGT ≥2X ULN) and (TB ≥2X ULN or DB >0.5 mg/dL)	7 (5.0%)	21 (4.0%)	28 (4.2%)

Source – Copied and electronically reproduced from the Applicant’s Response to IR-16, submitted by the Applicant on 4-22-2019

In pooled analyses of non-TGCT solid tumor subjects treated with any dose of pexidartinib (200 mg, 600 mg, 900 mg, and 1200 mg split BID), a total of 32 (19%) subjects experienced treatment related hepatic adverse events; of these, 20 (11.9%) experienced hepatic adverse events of equal or greater than Grade 3 Common Terminology Criteria for Adverse Events (CTCAE). The Applicant reports that there were no subjects meeting Grade 5 CTCAE.

B.2. Drug Discontinuation

A total of 8% (11 of 140) of subjects discontinued treatment with pexidartinib due to hepatotoxicity in the TGCT trial. The Applicant states in the clinical study report that AEs of hepatotoxicity (based on ALT/AST and/or TB elevation) leading to pexidartinib discontinuation were assessed as treatment related. Criteria to restart pexidartinib at a reduced dose was pre-specified in the protocol; however, these were not instituted uniformly across different sites, both for the dose reduction(s) and number of times the rechallenge was allowed.

The following subjects experienced hepatotoxicity leading to treatment discontinuation and in the parentheses are the reasons for the treatment discontinuation not as provided by the Applicant is noted. (Source-line listing 16.2.7.5, Adverse Events Leading to Dose Reduction-Safety Analysis Set).

1. Subject No. (b) (6) (reason for D/C ↑ transaminases, hair discoloration and photophobia)

2. Subject No. (b) (6) (reason for D/C ↑ transaminases)
3. Subject No. (b) (6) (reason for D/C ↑ bilirubin)
4. Subject No. (b) (6) (reason for D/C ↑ transaminases)
5. Subject No. (b) (6) (reason for D/C ↑ abnormal liver enzymes)
6. Subject No. (b) (6) (reason for D/C ↑ hepatotoxicity)
7. Subject No. (b) (6) (reason for D/C ↑ liver dysfunction)
8. Subject No. (b) (6) (reason for D/C ↑ transaminases)

Among the non-TGCT population, 3 (1.2%) of 257 subjects receiving pexidartinib monotherapy and 11 (4.8%) of 227 subjects in the other non-TGCT studies discontinued pexidartinib due to hepatotoxicity. The Applicant did not submit predisposition for N=768 subjects who were enrolled across the non-TGCT programs. The Applicant provided information on only 484 patients.

B.3. Dose reductions during the PLX108-10 trial

8 of 91 (9%) subjects receiving pexidartinib had 1 or more treatment emergent adverse events (TEAEs) leading to a dose reduction during Part 1. In 5 of these subjects, TEAEs were attributed to treatment with pexidartinib:

1. **Subject No.** (b) (6)
 - a. Transaminases increased on Day 22 resulting in a dose reduction.
 - b. Transaminases increased on Day 57 resulting in a second dose reduction.
 - c. The subject continued to receive pexidartinib at 400 mg/day and entered Part 2 of the trial. Subject continued to have Grade 1 CTCAE liver enzyme elevations and/ or fluctuation but remained within the Grade 1 CTCAE.
2. **Subject No.** (b) (6)
 - a. ALT increased on Day 43 resulting in a dose reduction.
 - b. The subject continued to receive pexidartinib 600 mg/day and entered of the Part 2 trial. Aminotransferase increase (Grade 1) was ongoing at the time of the last available report.
3. **Subject No.** (b) (6)
 - a. Blood ALP, ALT, and AST increased on Day 71 resulting in a dose reduction.
 - b. The subject continued to receive pexidartinib 600 mg/day and entered Part 2 of the trial. Aminotransferase increase (Grade 1) was ongoing at the time of the last available report.
4. **Subject No.** (b) (6)
 - a. ALT increased on Day 170 resulting in a dose reduction (600 mg and then to 400 mg).
 - b. Subject withdrew from the trial on Day 297, his liver enzymes normalized after discontinuing pexidartinib.
5. **Subject No.** (b) (6)
 - a. Hepatic enzymes increased on Day 56 resulting in a dose reduction.
 - b. The subject continued (Day 170) to receive pexidartinib 400 mg/day and entered Part 2 of the trial.

6. **Subject No.** (b) (6)
- a. Elevation of ALT/AST on Day 44 leading to treatment interruption secondary to positive IgM antibodies for hepatitis A and E. Pexidartinib 800 mg restarted once liver enzymes normalized on day 183.
 - b. Elevations of ALT/AST on Day 189 leading to dose reduction (pexidartinib 400 mg on Day 206 but increased on 600 mg on Day 233 but subject developed skin hypopigmentation).
 - c. Elevation of ALT/AST on Day 197 leading to dose reduction (pexidartinib 400 mg).
 - d. Pexidartinib was discontinued on Day 360, cause was skin hypopigmentation; however, liver enzymes remained elevated (Grade 1) and the liver tests normalized on pexidartinib discontinuation.
7. **Subject No.** (b) (6)
- a. ALT/AST elevation on Day 211 pexidartinib reduced to 600 mg.
 - b. Aminotransferase elevation (Grade 1) ongoing at the time of the last available report.

Source- Line listing 16.2.7.6 (Adverse Events Leading to Dose Reduction) and Applicant's IR response. Information on only 7 subjects could be found and information on 8th subject was not available in IR response or Line Listing.

Once the liver enzymes reached Grade I CTCAE, pexidartinib could be restarted at a reduced dose. However, in two subjects who continued to experience grade 1 CTCAE liver enzyme elevations after pexidartinib dose was reduced, once pexidartinib was discontinued the liver enzymes returned to normal values, indicating a positive dechallenge.

Positive Re-challenge

In the IR response (submitted on 4-22-2019), the Applicant provided information on four (3 in TGCT trial and one in non-TGCT trial) subjects who experienced positive rechallenge and subsequent discontinuation for hepatic AEs:

1. PLX108-10 (TGCT) Subject ID: (b) (6)
2. PLX108-10 (TGCT) Subject ID: (b) (6)
3. PLX108-01 (TGCT) Subject ID (b) (6)

Non-TGCT Population

4. PLX108-14 (Non-TGCT) Subject ID: (b) (6)

Dose Interruption due to elevation of liver enzymes/hepatotoxicity occurred in the following subjects: (b) (6) (Day 211), (b) (6) (Day 190), (b) (6) (Day 43), (b) (6) (Day 36), (b) (6) (Day 15), (b) (6) (Day 44), (b) (6) (Day 51), (b) (6) (Day 22), (b) (6) (Day 15), (b) (6) (Day 22), and (b) (6) (Day 29). Some subjects who had treatment interruption also were dose reduced, while some subjects had pexidartinib discontinued after treatment interruption.

B.4. Treatment of Hepatotoxicity

5 subjects received steroids for treatment of hepatotoxicity associated with pexidartinib. This information in the following table suggests varying practices in management of hepatotoxicity including with the use of immunosuppressive agents.

Subject	Indication	Adverse Event	Steroid Treatment	Comment (e.g., chemotherapy regimen and disease stage)
PLX108-08- (b) (6) (b) (6)	Glioblastoma	Cholestasis	Prednisone	Temozolomide combination
IST3397-001 (UCSF12751)	Breast cancer	Cholestatic jaundice	Prednisone	Eribulin combination. Progressive liver metastases
IST3397-006 (ISPY2)- (b) (6)	Breast Cancer	Hepatobiliary disease Cholecystitis	Prednisone Dexamethasone ursodiol	Paclitaxel combination Liver transplant
PLX108-14- (b) (6) (b) (6)	Breast cancer	Liver function test increased	Prednisone	Pembrolizumab combination
PLX108-14- (b) (6)	Breast Cancer	Drug-induced liver injury Increased ALP, ALT, AST, GGT, TBil	Prednisone Dexamethasone	Pembrolizumab ALP Grade 2 at baseline abdominal ultrasound, innumerable hepatic metastases; died on Day 37 due to progressive disease

Source – Applicant’s response to IR (SN 0034, submitted on 4-22-2019)

With the input from their hepatic event adjudication committee (HEAC) comprised of 3 DILI experts (see below), the Applicant submitted a response to the IR on 4-22-2019 that “pexidartinib is associated with two clinically distinct types of hepatotoxicity. First and the more common is isolated aminotransaminases elevations. This is dose dependent and related to CSF1R inhibition mechanism of pexidartinib. The dose response relationship with ALT or AST was assessed by exposure-response modeling. This injury was responsive to dose interruption and reduction. The second type of injury observed was mixed or cholestatic hepatotoxicity, which is idiosyncratic. This type of hepatic adverse reaction did not show dose dependence in exposure-response modelling. Severe cases of mixed or cholestatic hepatotoxicity were observed across pexidartinib dose levels and the TGCT and non-TGCT population. As noted by hepatic safety experts, the lack of dose-dependency is expected for mixed and cholestatic hepatotoxicity.”

FDA Review Team Comment:

Whether the early cholestatic and hepatocellular biochemical signatures observed in the study population exposed to pexidartinib necessarily represent distinct pathological effects of the drug or might be associated with a spectrum of elevated risk for hepatotoxicity is not yet fully determined.

The IND 117,332 for pexidartinib was placed on partial clinical hold (PCH) because of concern surrounding two serious adverse events (SAE) of hyperbilirubinemia and concurrent increase in transaminases. The PCH was then removed on April 10, 2017 when the Applicant proposed a risk mitigation plan (increased frequency of monitoring and a proposal to characterize the risk of liver injury). In addition, treatment interruptions were mandated when subjects met CTCAE Grade 3 liver enzyme elevations, instead of CTCAE Grade 4 elevations. FDA placed the clinical program on again on PCH on November 24, 2017 to implement the risk mitigation strategies for hepatotoxicity across the entire pexidartinib program. The second PCH was lifted on January 12, 2018, once the Applicant had implemented these changes across all pexidartinib programs.

C. Case Narrative Summarized- Case Adjudication

Notably, all subjects enrolled in the TGCT trial had normal hepatic enzymes at baseline. The Applicant provided the hepatic event adjudication committee (HEAC) report. Three hepatologists with expertise in evaluating drug-induced liver injury comprised the committee:



Pexidartinib Hepatic Event Adjudication Form (by Committee and Individual Expert Review) are attached in Appendix B. Both the HEAC (combined) and individual expert assessments and adjudication are attached.

Applicant Cases were analyzed for the Applicant by the DILI experts for casual association with pexidartinib using a categorical scale previously used by the FDA and the NIH drug-induced liver injury network (DILIN) **(See Appendix D)**.

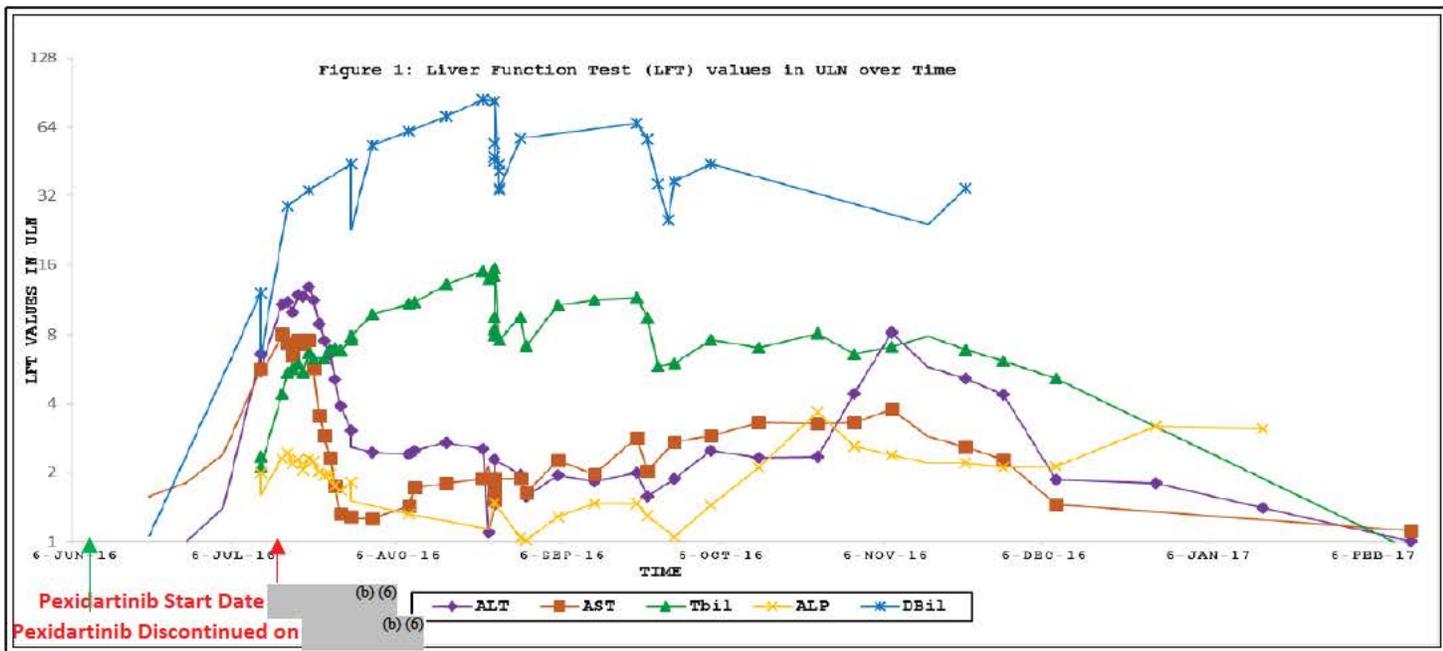
- Appendix A - Information Request sent to the Applicant
- Appendix B - HEAC Report
- Appendix C – Adjudicated Case Narratives by the Individual DILI Experts
- Appendix D – DILIN/FDA Causality Scale

C.1. TGCT Population

Among the 140 TGCT subjects treated with pexidartinib, there were more than 5 subjects who experienced serious hepatotoxicity that are described below. Our case level assessment of these TGCT cases is followed by evaluation of cases of interest in the Non-TGCT trials.

PLX108-10 Subject No. (b) (6) **(Phase 3)** [Cholestatic Hepatotoxicity lasting about 7-months]

A 75-year-old white female, weighing 60 kg initiated pexidartinib at 1000 mg split BID with dose reduction to 800 mg split BID on Day 15 per protocol. At study entry, hepatic laboratory values were within normal limits. On Day 1, subject was diagnosed with hypercholesterolemia and started on atorvastatin 50 mg/day. On Day 29, hepatic values were elevated with ALT 5.7X ULN, AST 5.3X ULN, ALP 1.6X ULN, TB 2.1X ULN, and DB 6.4X ULN. Pexidartinib was interrupted and permanently discontinued on Day 31. On Day 34, the subject was hospitalized due to deteriorating liver function. On Day 37, atorvastatin was discontinued. Bilirubin levels continued to rise, and a liver biopsy was performed on Day 72, **findings were notable for fatty liver and cholestasis with ductopenia**. The subject was treated with 2 courses of bilirubin dialysis. On Day 217, transaminases were almost resolved, and TB was 1.1 mg/dL.



Source: Clinical Study Report page 2634 of 3809; Study PLX108-10- Subject: (b) (6)

FDA Reviewer Comments:

Impression: Cholestatic Ductopenic Injury or VBDS

Pexidartinib was discontinued on Day 31; despite pexidartinib discontinuation the hepatic injury continued to progress and maximal increase in total bilirubin was observed on Day 100. A liver biopsy collected on Day 72 demonstrated severe ductopenia, with only 2 ducts observed in 10 portal tracts. The subject had a long and protracted course prior to complete resolution of biochemical elevations. However, due to lack of a repeat liver biopsy, the histological progression is unknown. The subject met the criteria of vanishing bile duct syndrome (VBDS). This is a very concerning case, following the long-term clinical course of this subject is very important, and if possible, a repeat liver biopsy should be obtained. On the liver biopsy subject was found to have mild fatty liver (~10% fatty degeneration).

Steatosis was reported on pathology report in few patients. Given the limited number of biopsies obtained, it is difficult to attribute causality of steatosis to pexidartinib with certainty at this time. While it is possible steatosis may be a concomitant injury with pexidartinib, it is not clear whether steatosis and cholestatic injury are a simultaneous finding. These findings should be kept in mind as additional biopsy data becomes available.

We adjudicated this case as “**probable**” in its causal association with pexidartinib (>50% likelihood).

The HEAC members combined and individual expert opinion was that this patient experienced cholestatic injury, with a latency period of 17 days and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. **In alignment with our assessment,**

there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B and C- See Appendix B -Page 149 of 325).

PLX108-10 Subject No. (b) (6) (Phase 3) Cholestatic Hepatotoxicity:

A 52-year-old white male, weighing 68.4 kg initiated pexidartinib at 1000 mg split dose BID with dose reduction to 800 mg split BID on Day 15 per protocol. Hepatic laboratory values were within normal limits at baseline. On Day 29, hepatic parameters were elevated with ALT 3.4X ULN, AST 3.8X ULN, and ALP 1.1X ULN; TB and DB within normal limits. Pexidartinib was interrupted on Day 36. On Day 38, the subject presented with jaundice with subsequent bilirubin increase. On Day 43, hepatic values worsened with elevations of ALP 2.3X ULN, AST 4.8X ULN, ALT 9.3X ULN, DB 18.8X ULN, and TB 6.5X ULN. On Day 45, a computed tomography (CT) scan of the abdomen noted a contracted gallbladder with mild enhancement of the gallbladder wall without definite intra- or extrahepatic ductal dilation. On Day 58, significant improvement was seen in hepatic function with TB 1X ULN and DB 2.6X ULN.

FDA Reviewer Comments:

Impression: Mixed Hepatocellular/Cholestatic Hepatotoxicity

Study PLX108-10 Subject (b) (6) had elevations in liver enzymes including TB, DB, and ALP indicating cholestatic injury. Pexidartinib was discontinued on day 36. Two positive de-challenge were observed, liver enzymes normalized after discontinuing pexidartinib. On day 78 biochemical injury resolution was documented. The reviewer assessment is that Pexidartinib was the causative agent for patients DILI.

We adjudicated this case as “probable” in its causal association with pexidartinib (>50% likelihood).

*The HEAC members combined and individual expert opinion was that this patient experienced mixed type injury, with a latency period of 4 weeks and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. **In alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B and C- see Appendix B- page 151 of 325).***

PLX108-10 Subject No. (b) (6) (Phase 3) Cholestatic Hepatotoxicity:

A 67-year-old white female, weighing 84 kg initiated pexidartinib at 1000 mg split BID with dose reduction to 800 mg split BID on Day 15 per protocol. At screening, hepatic laboratory values were within normal limits. On Day 43, an increase in transaminases was noted with AST 2.6X ULN, ALT 4.2X ULN, and ALP 1.4X ULN. A further increase was noted on Day 56 with AST 4.7X ULN, ALT 7.9X ULN, GGT 18X ULN, and ALP 2.1X ULN. Pexidartinib 800 mg split BID was permanently discontinued on Day 56 due to hepatotoxicity (Grade 3). On Day 57, the hepatic laboratory values were AST 4.5X ULN and ALT 6.7X ULN. On Day 64, the subject experienced chills, nausea, and abdominal pain with subsequent choluria on Day 68. On Day 71, the subject was hospitalized due to the events with elevated transaminases. An abdominal ultrasound and echography showed increased signal intensity meaning hepatic steatosis without pathological images; no dilatation of the bile duct; gallbladder of normal size and liquid content without stones or other findings. Antimicrobial therapy was provided for cholangitis and hepatotoxicity. On Day 76, the subject was without pain and had improved dietary tolerance. On Day 89, the cholangitis resolved with subsequent resolution of transaminitis on Day 118.

FDA Reviewer Comments:

Impression: Mixed Hepatocellular/Cholestatic Hepatotoxicity

Pexidartinib was discontinued on Day 56. The FDA medical reviewer's assessment is that pexidartinib seems to be the cause of the liver injury, no concomitant medication confounders apparent, time to onset was 6 weeks from starting pexidartinib, and imaging did not reveal evaluation consistent with cholecystitis. Steatosis has been observed in patients who are treated with pexidartinib, however, the steatotic injury to date is not well characterized. A positive de-challenge was observed, liver enzymes normalized after discontinuing pexidartinib. Investigator attributed the liver injury secondary to pexidartinib.

*We adjudicated this case as “**probable**” in its causal association with pexidartinib (>50% likelihood).*

*The HEAC members combined and individual expert opinion was that this patient experienced mixed type injury, with a latency period of 6 weeks and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. There was documented positive dechallenge in this patient. **In alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B and C- see Appendix B- page 153 of 325).***

PLX108-10 Subject No. (b) (6) (Phase 3) Positive Re-challenge:

A 39-year-old white female with a weight of 77 kg initiated pexidartinib at 1000 mg split BID. At baseline, the hepatic laboratory values were within normal values. On Day 15, hepatic values were elevated with ALP 1.9X ULN, ALT 8.3X ULN, and AST 7.6X ULN. Pexidartinib was interrupted the same day. On Day 27, hepatic laboratory elevations were resolved. On Day 29, pexidartinib was reintroduced at 800 mg split BID. On Day 35, hepatic abnormalities were noted, including AST 3.3X ULN, ALT 8.6X ULN, and ALP 6.2X ULN. Pexidartinib was interrupted on Day 36, and the events subsequently resolved. On Day 50, pexidartinib was reintroduced at 600 mg split BID. After taking the evening dose of 400 mg, the subject experienced nausea, vomiting, hot and cold flashes, and abdominal pain. On Day 51, hepatic values were elevated with ALT 2.5X ULN, AST 3.5X ULN, ALP 2X ULN, and GGT 4.1X ULN, at which time pexidartinib was interrupted. Hepatic elevations were resolved on Day 64. On Day 68, pexidartinib was reintroduced at 400 mg split BID, and on Day 70, hepatic enzymes were elevated with ALP 2.9X ULN, ALT 7.9X ULN, AST 6.7X ULN, TB 1.4X ULN, and GGT 6.4X ULN. Pexidartinib was discontinued with the last dose on Day 69. Abnormal liver function tests were resolved on Day 98.

FDA Reviewer Comments:

Impression: Mixed Hepatotoxicity

Pexidartinib was discontinued on Day 69. Time to onset of liver injury was 2 weeks. The subject had 4 positive dechallenges and 3 positive rechallenges. The dose was lowered from 800 mg to 600 mg to 400 mg and each time with repeat pexidartinib introduction the subject had elevations of liver enzymes. Pexidartinib was permanently discontinued on Day 69 and liver enzymes normalized on day 98. The medical reviewer attributes the cause of injury to pexidartinib.

In addition, the investigator attributed liver injury secondary to pexidartinib use.

*We adjudicated this case as “**probable**” in its causal association with pexidartinib (>50% likelihood). The HEAC did not adjudicate this case.*

PLX108-10 Subject No. (b) (6)

54-year-old AA female started on pexidartinib 1000 mg split BID on (b) (6) with dose reduction to 800 mg split BID on Day 15. At baseline, liver enzymes were normal. On Day 44, AST 15.9X ULN, ALT 12.5X ULN, ALP 2.3X ULN and TB was normal. On Day 45 pexidartinib was interrupted due to further increase in transaminases and ALP. On Day 50 ALT 24.2X ULN, the ALP 5X ULN and AST 15.9X ULN and DB 1.4X ULN. The subject tested positive for both Hepatitis A and hepatitis E IgM antibodies. Pexidartinib treatment was interrupted. On Day 182, ALT/AST normalized and pexidartinib was restarted at 800 mg split BID. On Day 183 ALT increased to 1.2X ULN. On Day 189 ALT was 6.2X ULN, AST was 5.1X ULN and ALP was 3.1X ULN and the enzymes remained elevated, therefore, on Day 204 pexidartinib was reduced to 400 mg split BID. On Day 233 pexidartinib dose was increased, however, was reduced again on Day 234, but the liver enzymes did not return to baseline. The subject developed skin hypopigmentation and pexidartinib was discontinued on Day 360. On Day 387 the liver enzymes returned to normal range; however, ALP was 1.4X ULN (previously 2.4X ULN on Day 274).

FDA Reviewer Comments:

Impression: Possible Mixed (Hepatocellular/Cholestatic) Hepatotoxicity

The Applicant states that the liver enzyme elevation in PLX108-10 Subject (b) (6) was secondary to Hepatitis A and E infection and not related to pexidartinib. The Applicant did not provide information on whether this subject received Hepatitis A or whether the patient definitely had concurrent Hepatitis A and E infection. On Day 182, liver enzymes normalized, and a reasonable assumption was made by the medical reviewer that hepatitis A and/or Hepatitis E infection resolved. It is known that Hepatitis E infection once resolved typically does not have features of chronicity. Pexidartinib was restarted after the liver enzymes normalized; however, liver enzyme elevations reoccurred after pexidartinib was restarted and remained elevated until pexidartinib was finally discontinued, indicating a positive dechallenge. The Applicant states that these elevations were not related to pexidartinib; however, there appears to be a strong causal association with pexidartinib given the positive dechallenge. Additionally, viral serologies were not evaluated to assess whether the recurrence of liver enzymes elevation was related to recurrence/relapse of viral hepatitis.

We adjudicated this case as “possible” in its causal association with pexidartinib (25-49% likelihood).

Among the HEAC members opinions differed. HEAC experts concluded that this event was unrelated to pexidartinib and related to Acute Hepatitis A and E. was a possible causal association with pexidartinib (see Appendix B and C see Appendix B- page 298 of 325).

Other Cases of Interest

PLX108-10 Subject No. (b) (6)

60-year-old female with PVNS started on pexidartinib 1000 mg split BID on (b) (6) On Day 22 subjects ALT 25.6X ULN, AST 10.6X ULN. She experienced abdominal pain, nausea and headache. On Day 24, ALT 16.5X ULN, AST 7.5X ULN and DB 2X ULN; fatigue and vomiting were also reported. On (Day 29), the subject’s hepatic parameters revealed a decrease to ALT 21X ULN, AST 7.1X ULN, ALP 1.1X ULN, and DB was 1.2X ULN and all medications were held with exception of omeprazole. On Day 50 liver enzymes normalized and symptoms resolved. On day 50 pexidartinib was restarted at a reduced dose of 600 mg split BID, on the same day the subject

complained of nausea. On day 57, transaminases increased again to ALT 11.2X ULN, AST 6.1X ULN and pexidartinib was interrupted. On Day 71 pexidartinib was restarted at 400 mg split BID and AST 26 U/L but ALT 2.4X ULN. Thereafter, ALT continued to fluctuate between normal and mild elevations throughout.

FDA Reviewer Comments: *Impression: hepatocellular toxicity caused by pexidartinib followed by partial liver adaptation*

Study PLX108-10 Subject (b) (6) demonstrates partial adaptation. Adaptation to a drug refers to resolution of increased serum aminotransferase levels attributed to a drug while continuing its use at the same dose. However, this patient did not achieve complete adaptation as the transaminases continued to show fluctuating increases; once the liver adapts to a drug, transaminases should stabilize or normalize and should not continue to fluctuate.

We adjudicated this case as “probable” in its causal association with pexidartinib (>50% likelihood).

The HEAC members combined and individual expert opinion was that this patient experienced a hepatocellular injury, no confounders; the final determination was “probably” related to pexidartinib. In alignment with our assessment, there was a consensus among the HEAC experts that the event was probably related to pexidartinib (See Appendix B- page 240 of 325).

PLX-108-01 Subject No. (b) (6) (Transaminase Elevation with Biopsy Evaluation):

A 42-year-old white female initiated pexidartinib at 1000 mg split BID. Baseline hepatic values were within normal limits, and TB was within normal limits until Day 602, and DB was within normal limits throughout the study. On Day 15, hepatic evaluation revealed AST/ALT Grade 1 elevation. On Day 70, hepatic evaluations were ALT 1.6X ULN and AST 3.5X ULN that were attributed to the start of atorvastatin 14 days prior to elevations, which was discontinued that same day. On Day 92, the subject experienced vomiting and pexidartinib was interrupted then restarted on Day 93 at the same dose. On Day 112, pexidartinib was interrupted again due to increased AST/ALT and restarted on Day 126 at 400 mg split BID. Pexidartinib continued with periodic, temporary interruptions due to elevated liver enzymes until Day 538 when the last dose of pexidartinib was administered; pexidartinib was permanently discontinued on Day 539 due to transaminitis (ALT 4.6X ULN; AST 8.9X ULN; ALP 1.4X ULN) at which time the dose was 600 mg split BID. At the end of study (Day 551), AST/ALT improved to Grade 1, but subsequent elevations were noted (Day 574). On Day 575, a hepatologist recommended an ultrasound of the liver and a liver biopsy. On Day 602, transaminitis Grade 3 was noted, and on Day 649, a liver biopsy showed bile duct injury with portal acute and chronic inflammation and reaction, portal fibrosis with areas of bridging, and mild macrovesicular steatosis (5%). The findings were thought to be due to drug toxicities (multiple positive de-challenges in the absence of other etiologies); however, there was well-developed fibrosis that was suggestive of a chronic process. On Day 791, a hematologic evaluation showed antimitochondrial antibodies indicating primary biliary cholangitis Grade 1. Throughout the time of transaminase elevations, bilirubin was elevated on only one occasion, which was just after the liver biopsy. On Day 1170, the subject was under the supervision of a hepatologist for continued fluctuations of transaminases of unclear etiology, at which time no new signs or symptoms indicative of hepatic encephalopathy were noted.

FDA Reviewer Comments:

Impression: Cholestatic Hepatotoxicity

PLX-108-01 Subject No. (b) (6) was diagnosed with PBC (positive AMA value not provided and liver biopsy suggestive of PBC), although the pathologist did not report the number of bile duct present in 10 portal tracts, there is evidence that ductopenia was present. There are two confounders in this case, one is PBC diagnosis, and the second was presence of hypothyroidism which can cause elevated liver enzymes. In this case, more than likely liver injury was secondary to underlying PBC and unlikely to be due to pexidartinib.

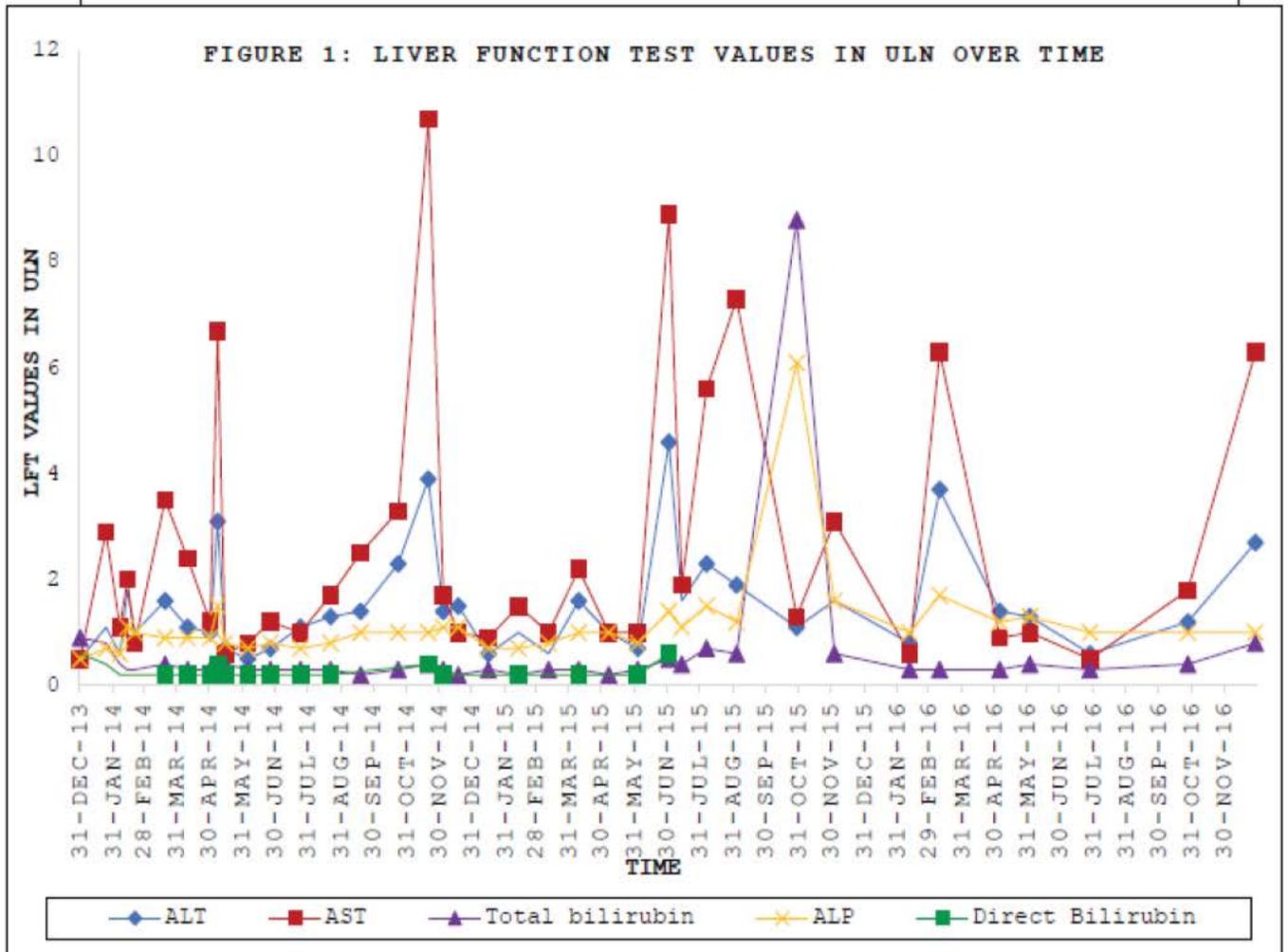


Figure 1: Graphical presentation of LFT values for the subject (b) (6)

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We adjudicated this case as “not related” in its causal association with pexidartinib. The HEAC members combined and individual expert opinion was that this patient experienced a cholestatic type of injury with a latency period of 6-weeks, with elevated AMA and biopsy consistent with PBC as notable confounders; the final determination was unlikely to be related to pexidartinib. In alignment with our assessment, there was a consensus among the HEAC experts that the event was of an unlikely to be related to pexidartinib. See Appendix B- page 148 of 325.

C.2. Non-TGCT Population

Among the 258 non-TGCT subjects (168 non-TGCT solid tumors + 90 AML) treated with pexidartinib, the Applicant presented the most notable hepatic events, which are summarized below:

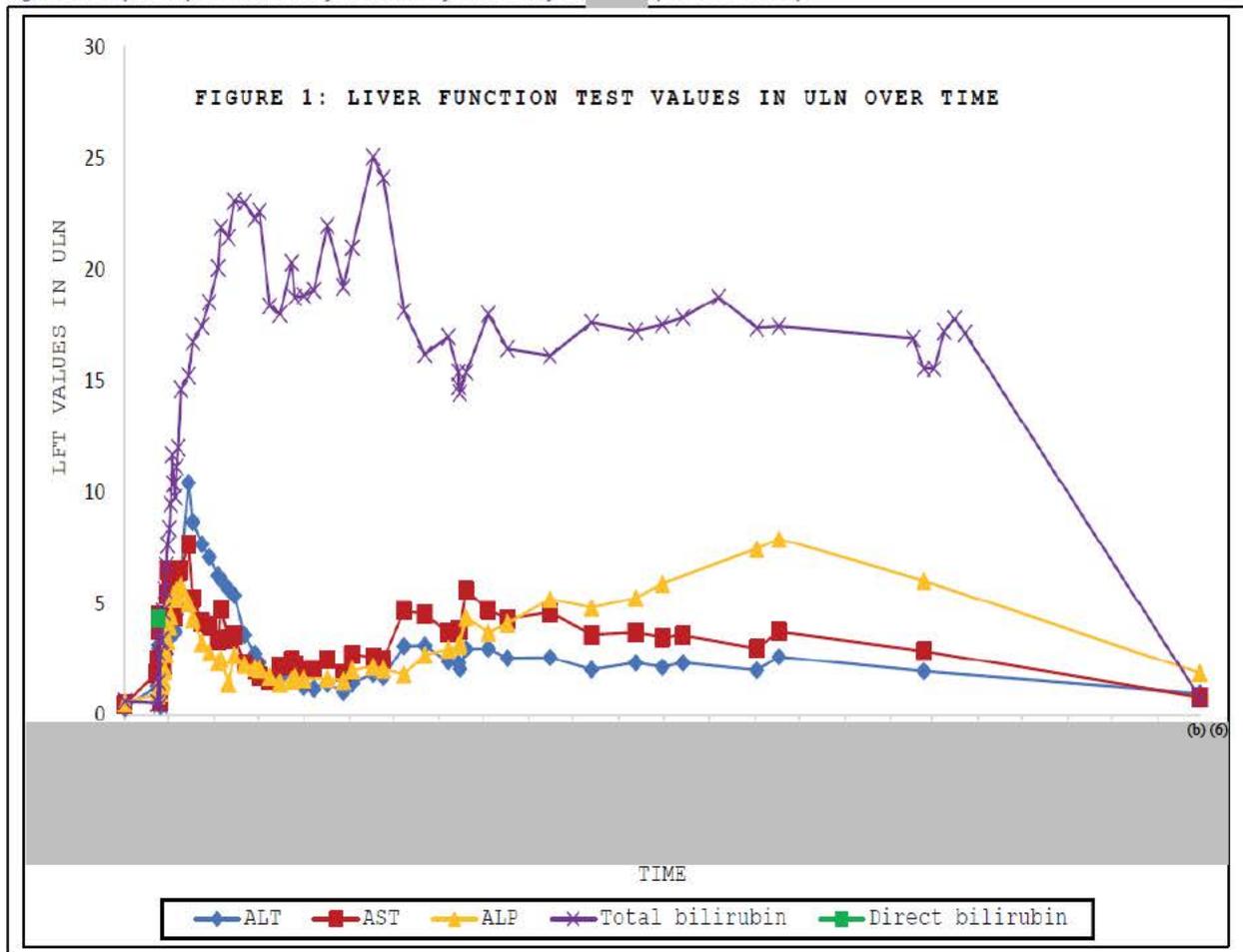
Investigator-Initiated Studies

Study IST3397-006, Subject No. (b) (6) (IIS-SPY2-097517)- 60-year-old Caucasian female was diagnosed with breast cancer. On (b) (6) the subject received first dose was started on pexidartinib and paclitaxel. The liver enzymes were normal at baseline (i.e. prior to initiation of the pexidartinib). On (b) (6), 2015, the subject presented with fever and chills and was hospitalized with. Subjects ALT was 65, AST was 105, ALP was 85 U/L and total bilirubin 0.7 mg/dl. Screening for hepatitis B antigen, hepatitis C, HIV, alpha-1 antitrypsin were negative. Abdominal ultrasound revealed thickened gallbladder with pericholecystic fluid, there was no evidence of cholelithiasis or biliary duct or dilation or fatty infiltration of liver or masses in the liver. A CT of the abdomen revealed gallbladder wall thickening with pericholecystic inflammatory fat stranding and pericholecystic fluid and hyperenhancements of the gallbladder wall, cystic duct and common bile duct. The subject had a cholecystectomy on (b) (6) intraoperative findings revealed an edematous purulent gallbladder. The pathology report stated gallbladder was unevenly thin with focal erythema, the overlying serosa was roughened by scattered filamentous adhesions. The cystic duct was 0.4 cm and patent and no lymph nodes identified, the final diagnosis was reported as acute cholecystitis.

Laboratory evaluations were performed frequently, the subject continued to have elevated liver enzymes in particular concerning was the gradual rise of TB. Hepatology was consulted was done due to this the continued enzyme elevation, an endoscopic retrograde cholangiopancreatography (ERCP) was performed on 21 October 21, 2015, which revealed no evidence of biliary obstruction or dilation or stones, the cause of cholestasis was thought to be drug toxicity, and TB was 10.9 mg/dL. A liver biopsy was performed on (b) (6) which revealed five complete portal tracts available for evaluation instead of nine portal tracts. The bile ducts were small and attenuated, the biopsy revealed cholestasis and severe steatosis (grade 3), with minimal lymphocytic inflammation in the portal tract. Trichrome stain showed no fibrosis. The overall findings are suggestive of cholestasis duct damage and duct loss. (b) (6) the AST was 206, ALT was 181, ALP was 494 U/L, and TB 15.2 mg/dL. The subject was started on ursodiol and prednisone 40 mg once a day. The liver enzymes continued to be elevated increase and on (b) (6) the total bilirubin was TB 19 mg/dL, ALT 327, AST 273, ALP 547 U/L. Treatment with pexidartinib and paclitaxel were temporarily interrupted. In (b) (6) the TB increased from 22.7 mg/dL to 24.1 mg/dL and finally to 30 mg/dL on (b) (6) The subject underwent bilateral mastectomy on (b) (6) The liver enzymes continued to increase be elevated until (b) (6) when the subject underwent liver transplantation.

Review of Explanted/Native Liver Histopathology Report: Only 4 ducts were observed in 9 portal tracts. No ductular reaction was seen, lobular cholestasis and severe steatosis were present. Patch hepatocyte atrophy was observed. In addition, insufficient number of portal tracts were available to establish a firm diagnosis. Absence of ductular reaction and fibrosis.

Figure 1 Graphical presentation of LFT values for the subject (b) (6) (Breast Cancer)



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FDA Reviewer Comments:

Study IST3397-006, Subject (b) (6) The reviewer considers this injury to be related to pexidartinib use. The subject developed cholestatic hepatotoxicity that presented with elevation of liver enzymes about 2 weeks after starting pexidartinib. The liver enzyme elevation was confounded by presence of acute acalculous cholecystitis, for which cholecystectomy was performed. However, despite cholecystectomy the subject's liver enzymes continued to worsen, especially concerning was the rise in TB. A liver biopsy was performed 4 weeks after starting pexidartinib and 2 weeks after the cholecystectomy. The liver biopsy demonstrated ductopenia and an ERCP did not demonstrate biliary obstruction or stones. The subject developed liver failure 1 month after starting pexidartinib and at month 20 she underwent liver transplantation. This subject experienced cholestatic injury, and once injury occurred it continued to progression until to liver failure, (i.e., the injury was not reversible with drug discontinuation (pexidartinib discontinued at month 2)).

We adjudicated this case as "**probable**" in its causal association with pexidartinib (>50% likelihood).

The HEAC experts unanimously agreed that the injury was probably related to pexidartinib use leading to vanishing bile duct syndrome and subsequently required liver transplant. In addition, one of the experts speculated that acalculous cholecystitis could also have been caused by pexidartinib. Thus, **in alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B and C).**

IST3397-001 (Study IIS UCSF 12751) Subject No. (b) (6) / DSU-2015-123981

A 58-year-old female with triple negative/basal-like breast cancer with metastases to lymph nodes, liver, and bone initiated started pexidartinib at 1000 mg split BID/day orally for 5 days (off 2 days) and eribulin 1.4 mg/m² intravenously on Day 1 and Day 8 for a 21-day cycle. At baseline, a hepatic evaluation of Grade 1 AST increased (42 U/L) was noted. On Day 29, the subject presented with hepatic enzyme abnormalities and was diagnosed with 'jaundice cholestatic of severe intensity', which required hospitalization. The subject was treated with anti-emetics, and study medications were interrupted that same day. On Day 43, a CT scan of the abdomen revealed diffusely scattered hypoattenuating hepatic lesions with peripheral enhancement that were more conspicuous in appearance than in an earlier CT scan as well as mild fatty infiltration of the liver. Study medications were permanently discontinued that same day. On Day 44, an MRI of the abdomen showed 4 enhancing lesions consistent with disease progression and not the cholestatic event. On Day 72, a transjugular liver biopsy was performed and the pathology report was consistent with ductopenia with cholestasis, no specific etiology was identified. No significant lobular inflammation, steatosis, or infiltrative carcinoma was identified. Prednisolone was initiated on Day 73. Bilirubin returned to normal approximately 5 months after onset of the event. Testing for viral hepatitis (HBV, HCV, EBV) were negative. IgM, IgG were normal. ANA, SMA and AMA were performed; however, results were not reported in the narrative.

Review of Biopsy Report reviewed: In 15 portal tracts, rare duct (2 ducts in 15 portal tracts) observed, there is no ductular reaction, and; lobular parenchymal cholestasis and is observed. Focal area of hepatic atrophy was as observed. Many biopsy stains were done performed to rule out other etiologies for VBDS.

FDA Reviewer Comments:

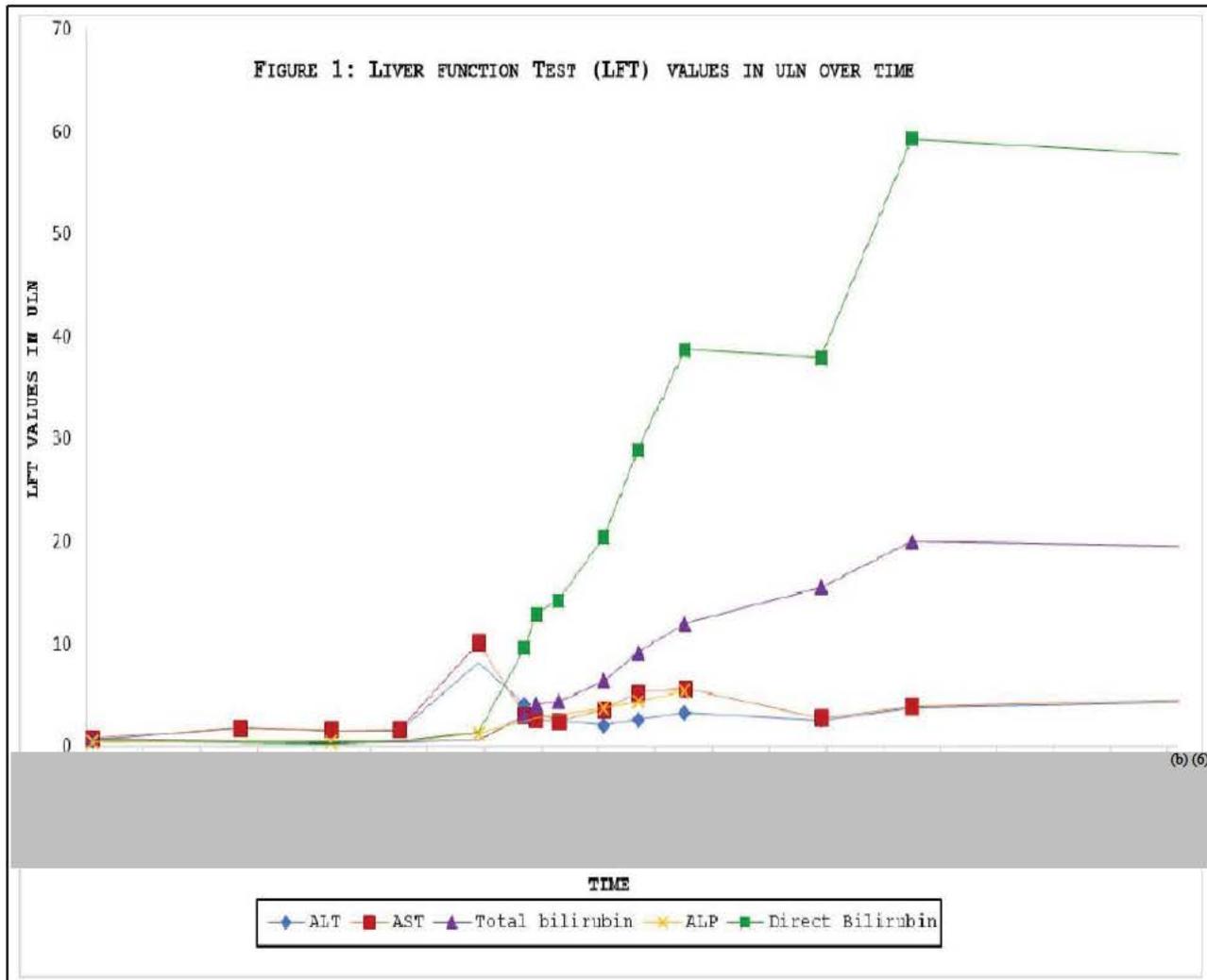
*Cholestatic injury most likely secondary to pexidartinib use. Time to onset of liver injury was about 1 month after pexidartinib initiation. Biopsy consistent with ductopenic injury. Alternative etiologies for liver disease were ruled out. Patient was also on concomitant eribulin treatment, which rarely causes liver injury. Bone and liver metastasis were identified, however, the that does not explain the observed ductopenic injury to liver. We adjudicated this case as “**probable**” in its causal association with pexidartinib (>50% likelihood).*

*The HEAC members combined and individual expert opinion was that this patient experienced cholestatic injury, with a latency period of 17 days and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. **In alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B -page 145 of 325).***

Study PLX108-13, Subject No. (b) (6) 66-year old Chinese female who was initially diagnosed with Stage IIIC vaginal mucosal melanoma. The subject started pexidartinib 1000 mg split BID on (b) (6). Subject previously had surgical resection of tumor and underwent chemotherapy with cisplatin, recombinant human endostatin, temozolomide. At screening the, ALT was 74 IU/L, AST 79 IU/L, TB 0.55 mg/dL, DB 0.13 mg/dL, GGT 14 IU/L. On (b) (6) the subject experienced fatigue, abdominal distension and loss of appetite and liver biochemical indices were elevated AST 451, ALT 324, GGT 216, ALP 199 IU/L, TB 0.73 mg/dL and DB 0.4mg/dL. Pexidartinib was discontinued secondary to AST/ALT elevation and concerning, not due to DB elevation and clinical symptoms. On (b) (6) the total serum bile acids increased to 226.2 μ mol/L and TB was 3.45 mg/dL and DB was 3.33 mg/dL. Subject received Silbyum marianum (milk thistle; plant-based supplement) for liver injury in addition to ursodeoxycholic acid, ademetionine 1,4-butanedisulfonate, and some other unspecified herbal and traditional medications on Day 25, after the increased liver enzymes were reported.

The TB and DB continued to increase and on (b) (6) the TB was 5 mg/dL and DB 4.98 mg/dL, AST 132, AST 117 and GGT was 451 and ALP 444 IU/L, and pexidartinib was permanently discontinued due to drug- induced liver injury. On (b) (6) the, TB was 10.7 mg/dL and DB 10.1 mg/dL, ALP 695 and subject was started on prednisone 10 mg once daily. The subject had continued with deterioration of the liver synthetic function and TB increased to 13.9 mg/dL, / DB of 13.56 mg/dL and ALP of 863 U/L. On (b) (6) metastasis of tumor was reported and her TB 18.6 mg/dL, and DB 15.07 mg/dL and continued to increase and on (b) (6) with TB was 23 mg/dL and DB of 20.8 mg/dL on (b) (6). The subject underwent bilirubin adsorption twice, however, the subject's hematuria secondary to metastasis worsened. The synthetic function of liver continued to deteriorate and on (b) (6), the TB was 28 mg/dL and prothrombin time was 42% of normal, INR was not reported. The subject died secondary to disease progression on (b) (6) the subject died. The death certificate stated that the reason for death was melanoma cachexia; however, the subject also had liver failure. Liver function declined significantly and rapidly, and the causality of the DILI was attributed to pexidartinib associated DILI by the investigator.

Figure 2 Graphical presentation of LFT values for the subject (b) (6) in Study PLX108-13.



Source: - Electronically Copied and Reproduced from Applicant Clinical Study Report (Section 14)

FDA Reviewer Comments:

Study PLX108-13, Subject (b) (6) Subject developed biochemical abnormalities on Day 20, pexidartinib was interrupted on day 20, and later discontinued. The liver injury continued, and the subjects eventually developed liver failure by day 47 (~6 weeks), the TB 28 mg/dL, DB 14.05 mg/dL, albumin 2.4 mg/dL; GGT was 729 and ALP 444 U/L, a pattern consistent with cholestatic injury was observed. The liver enzymes obtained on Day 25, prior to starting the treatment for hepatotoxicity with silbyum marianum, ursodeoxycholic acid, bicyclol and magnesium isoglycyrrhizinate, were total serum bile acids 226.2 $\mu\text{mol/L}$ (reference range 4-10 $\mu\text{mol/L}$), TB 59.1 $\mu\text{mol/L}$ (3.5 mg/dL) and DB 57 $\mu\text{mol/L}$ (3.3 mg/dL), AST 136 and ALT 162. On day 26 the subject was started on an unknown Chinese herbal medication, after significant liver injury was already observed. It may be possible that the liver failure progressed rapidly due to other hepatoprotective agents, but the subject had already had sustained severe cholestatic liver injury prior to start of any hepato-protective agents, including the Chinese herbal products. This case indicates a rapid progression of liver injury culminating in death, despite discontinuing

pexidartinib on day 20. Although potential DILI evaluation was not fully performed, based on the time to onset of liver injury is very proximal to pexidartinib use, and its association of positive dechallenge the reviewer has assessed this event of DILI as related to pexidartinib. Although the cause of death seems related to progression of cancer or use of other drug/herbal products.

The HEAC committee stated that there was insufficient data to assess causality (See Appendix B Page 156 of 325).

Other Non-TGCT Studies Cases

PLX3397-A-A103 Subject No. (b) (6) (Monotherapy):

A 74-year-old Asian male with Stage IV renal cell carcinoma initiated pexidartinib at 600 mg split BID. At screening, hepatic evaluations were within normal limits. On Day 8, the subject presented with Grade 1 AST, with subsequent increases on Days 15, 22, 29, and 43 (these increases all remained at Grade 1). On Day 57, multiple hepatic enzymes were elevated including AST 6X ULN, ALT 3.1X ULN, ALP 6.2X ULN, TB 2.6X ULN, and DB 8.5X ULN. Pexidartinib was interrupted on Day 58. The subject had no exposure to alcohol or to any environmental chemical agent. On Day 69, a liver ultrasound showed no liver metastasis or fatty liver. Hepatitis B and C viral tests were negative. Hepatic enzymes were improving and pexidartinib was restarted on Day 70 at a reduced dose of 400 mg split BID. On Day 79, hepatic enzymes and bilirubin were within normal range; however, AST/ALT were mildly elevated. On Day 85, the subject withdrew consent and received the last dose. On Day 113, hepatic enzymes and bilirubin were within normal limits.

Figure 3: Graphical profile of Liver Enzyme Elevations

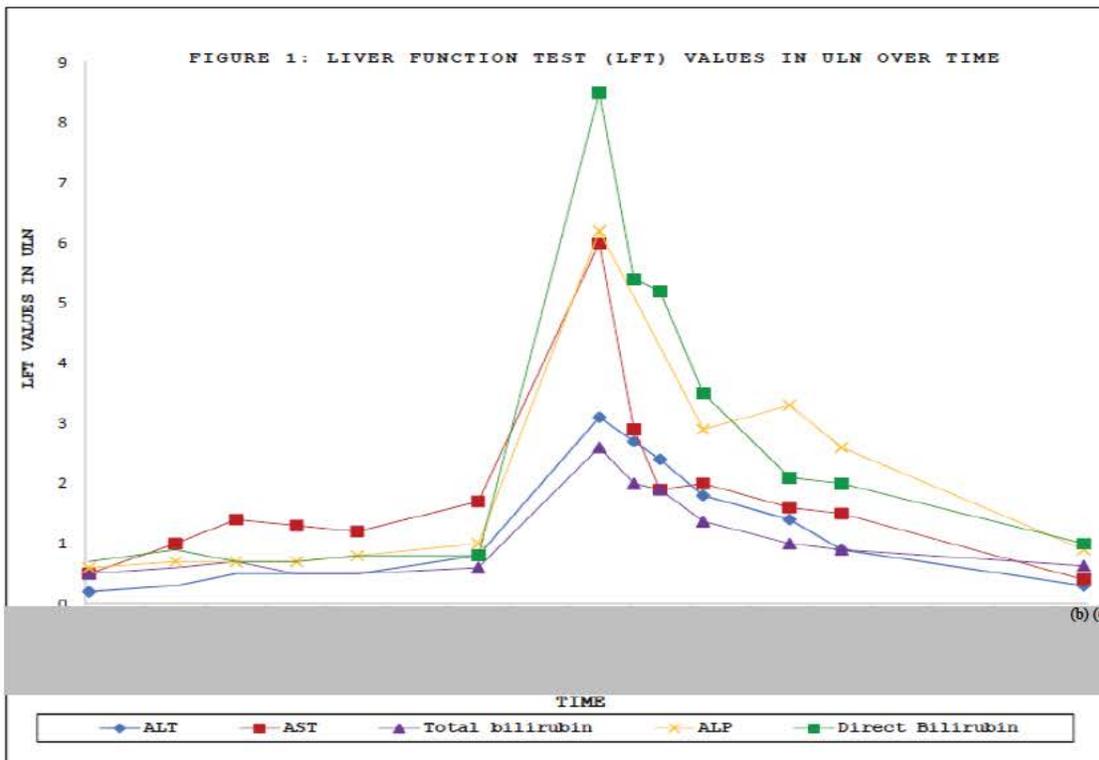


Figure 1: Graphical presentation of LFT values for the subject (b) (6)

Source- Electronically Copied and Reproduced from Applicant's Clinical Study Report (Section 14)

FDA Reviewer Comments:

When pexidartinib was discontinued, a positive dechallenge response was observed, the liver enzymes started trending down as seen on the above graph. On Day 70 pexidartinib was restarted, even though the liver enzymes had not completely normalized, but were still trending down. On Day 79, the liver enzymes remained elevated and did not normalize (AST 71 U/L, ALT 56 U/L, ALP 306 U/L, TB 1 mg/dL, DB 0.39 mg/dL). TB returned to baseline; however, on Day 85 the subject withdrew consent and discontinued pexidartinib therapy. On Day 113, AST, ALP, TB and DB all returned to baseline (AST 19 U/L, ALP 83U/L, TB 0.63 mg/dL and DB 0.19 mg/dL). A positive dechallenge was observed again at this time in this subject. In total, there were two positive dechallenges for this patient.

We adjudicated this case as “probable” in its causal association with pexidartinib (>50% likelihood).

The HEAC members combined and individual expert opinion was that this patient experienced mixed type injury, with a latency period of 7 weeks and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. There were two positive dechallenges and one positive

rechallenge. In alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B -See page 139 of 325).

PLX108-04 Subject No. (b) (6) (ALT or AST ≥ 3 x ULN with TBIL ≥ 2 x ULN):

A 58-year-old white female with glioblastoma started on pexidartinib at 1000 mg split BID. Baseline hepatic abnormalities included **ALT 6X ULN**. Concurrent warfarin was noted. On Day 8, INR was 5.1 (CTCAE Grade 3) with blood in stool. Warfarin was interrupted, and the subject was treated with vitamin K. On Day 9, the INR improved to Grade 1. On Day 17, pexidartinib was interrupted due to Grade 3 AST elevation (5.7X ULN) with normal DB and TB. On Day 23, ALT was 518 U/L and AST 25.36X ULN. On Day 31, ALP was 416 U/L, TB was 1.7 mg/dL and DB 1.3 mg/dL. On Day 29 TB 3.9 mg/dL and DB was 3 mg/dL, and on Day 31 TB was 3.8 mg/dl and DB was 2.9 mg/dL. On Day 45, the subject was discontinued from pexidartinib due to disease progression; improvement of hepatic values was noted ALT 18 U/L, AST 93 U/L, ALP 176 and DB was 0.3 mg/dL. The last dose of pexidartinib was on Day 16.

FDA Reviewer Comments:

The baseline liver enzymes were normal, there is a typographical error in ALT value noted as abnormal in the CSR, highlighted in bold. Time to onset of liver injury was 2-3 weeks. However, the narrative stated subject had ALT of 6 U/L at baseline (reference range 7 to 52 U/L). Once injury occurred on Day 17, the enzymes continue to increase despite interruption of treatment with pexidartinib. INR elevations were secondary to Warfarin use; however, liver enzyme elevations including TB/DB seemed to be secondary to pexidartinib use, and there was a positive de-challenge response. There is a lag between pexidartinib discontinuation and resolution of enzymes, in this case the liver enzymes normalized by Day 45.

*We adjudicated this case as “**probable**” in its causal association with pexidartinib (>50% likelihood).*

*One HEAC individual expert’s opinion was that this patient experienced mixed type injury and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. **In alignment with our assessment, one HEAC experts noted this as a probable association with pexidartinib (see Appendix B- page 286 of 325.***

PLX108-05 Subject No. (b) (6) (ALT or AST ≥ 3 x ULN with TBIL ≥ 2 x ULN):

A 59-year-old white female with AML started on pexidartinib at 3000 mg split BID. At baseline, hepatic values were within normal range. On Day 2, the subject experienced Grade 4 platelet count decrease and required transfusions with subsequent transfusion support as needed. On Day 61, pexidartinib was discontinued due to disease progression with the last dose administered that same day. On Day 64, ALT 1.9X ULN, AST 3.8X ULN, ALP 4.52X ULN and normal TB at 1.0 mg/dL. On Day 65, the subject presented to the hospital with history of fatigue, nausea, worsening leukocytosis, poor appetite (since 3 to 7 days), and occasional blood in mouth upon waking up; the subject was reported with Grade 3 lung infection after a physical examination and chest x-ray were performed. The subjects LDH was 6.8X ULN. The subject was treated with antimicrobial therapy. On Day 69, ALT 86 U/L, AST 102 U/L, ALP 363 U/L, TB 3 mg/dL, and DB 1.5 mg/dL. On Day 71, the subject was discharged from the hospital. On Day 121, the subject died secondary to disease progression.

FDA Reviewer Comments:

It is likely that liver enzyme elevations in this patient could be secondary to infection. There is “insufficient information” to adjudicate this case.

- a. PLX108-05 Subject No. (b) (6) (ALT or AST \geq 3X ULN and TB \geq 2X ULN)
- b. PLX108-05 Subject No. (b) (6) (ALT or AST \geq 3X ULN and TB \geq 2X ULN)
- c. PLX108-05 Subject No. (b) (6) (ALT or AST \geq 3X ULN and TB \geq 2X ULN):

The above 3 cases were summarized by the Applicant as meeting the criteria for DILI and were reviewed and adjudicated. However, the reviewer assessed that these cases were not likely due to pexidartinib. *Subjects a & b above had sepsis at the time of liver enzyme elevations. Sepsis can cause liver enzyme elevations and interpretation is therefore confounded. Subject c had multiple confounders including alcohol associated cirrhosis at baseline, was diagnosed with pneumonia, had dyspnea & pyrexia and was treated with antimicrobial therapy. Since concurrent presence of sepsis and infections can confound interpretation of DILI, these cases could not be appropriately adjudicated. Pexidartinib was discontinued after onset of liver enzyme elevations. No follow-up information was provided on these patients as they were not restarted on pexidartinib.*

DSI-Sponsored Studies

PLX108-07 Subject No. (b) (6) (Biopsy-Confirmed Hepatic Injury):

A 61-year-old Caucasian female with epithelial ovarian cancer (Stage IIIC recurrent platinum-resistant high-grade serious carcinoma) initiated oral pexidartinib (600 mg split BID) and intravenous paclitaxel (150 mg/m² weekly) on (b) (6) (Day 1). At screening, bilirubin, transaminases, and ALP were normal. On Day 14, the subject presented to the hospital with fever, nausea, vomiting, and increased liver tests: ALT 3X ULN, AST 7X ULN, and ALP 1.1X ULN; albumin and TB were within normal limits. The last dose of pexidartinib was on Day 14 and paclitaxel was on Day 7. Three days after the last dose of pexidartinib, the subject was admitted to the hospital with elevated liver tests and kidney injury; ALT 3X ULN, AST 5X ULN, ALP 1.4X ULN, and TB 2.6X ULN; additional laboratory results included creatinine at 3X ULN. On Day 50, 37 days after the last dose of pexidartinib, hepatic laboratory elevations continued with TB 19X ULN and ALP 8X ULN. A liver biopsy revealed no liver metastasis and severe drug-induced liver injury attributed by timing/exposure to clinical trial medications. There was no evidence of obstruction, but there was severe cholestasis with severe bile duct injury with no inflammatory component. The subject was discontinued from the study on Day 41 due to mixed hepatocellular/cholestatic liver injury. Hepatic enzymes remained elevated and the subject entered hospice care and died due to disease progression on (b) (6) (Day 121).

FDA Reviewer Comments:

The medical reviewer has assessed that this case was related to pexidartinib use. Although the patient died secondary to malignancy progression. The type of injury is cholestatic, and liver biopsy reveals injury to bile ducts and evidence of cholestasis.

We adjudicated this case as “probable” in its causal association with pexidartinib (>50% likelihood).

The HEAC members combined and individual expert opinion was that this patient experienced mixed type injury, with a latency period of 2 weeks, severity score of 3 and no concomitant drug suspected as a confounder; the final determination was probably (>50% likelihood) related to pexidartinib. **In alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B- page 154 of 325).**

PLX108-14 Subject No. (b) (6) (Biopsy-evaluated hepatic event):

A 54-year-old white female with Stage IV TXNXM1 ductal breast carcinoma with lymph node, liver, and lung involvement initiated started pexidartinib at 600 mg daily split BID and pembrolizumab 200 mg once every 3 weeks. At baseline, hepatic abnormalities included Grade 1 ALT (96 U/L), Grade 2 AST (120 U/L), and Grade 2 ALP (318 U/L). On (b) (6), 6 days after the first dose of study medication, the subject experienced Grade 3 DILI, Grade 2 ALP increased (461 U/L), Grade 3 AST increased (238 U/L), and Grade 1 ALT increased (138 U/L). The subject was treated with prednisone and dexamethasone, and study medication was interrupted due to the events of drug-induced liver injury DILI and AST increased. On Day 11, an ultrasound of the liver revealed innumerable hepatic metastases, no intrahepatic or extrahepatic biliary duct dilation, and a gallstone of 1 cm in the gallbladder. On Day 13, a CT scan of the chest, abdomen, and pelvis with contrast showed tiny lung nodules and increased tumor nodule of chest wall; increased hepatic metastases, lymphadenopathy was noted in the thorax, and suspicion of peritoneal carcinomatosis. On Day 22, a liver biopsy revealed mild apoptotic hepatocellular injury with minimal inflammation and no fibrosis; mild macrovascular steatosis and acidophilic bodies with minimal inflammation were noted. On Day 32, transaminases were resolving, but Grade 3 TBIL increased was noted. A CT scan of the chest, abdomen, and pelvis with contrast revealed significant progression of extensive hepatic metastases with associated increased hepatomegaly; increased pelvic ascites and pleural effusion; and metastatic progression of cutaneous/subcutaneous nodules were noted along the right chest wall near the mastectomy scar. Increased mild adenopathy was seen in the superior retroperitoneum, inferior right axilla, and left supraclavicular regions. That same day, an abdominal ultrasound noted an enlarged liver with hypoechoic metastases consistent with disease progression. Study medications were not reintroduced following interruption on Day 7; treatment was discontinued due to progressive disease with the last dose administered on (b) (6) for pembrolizumab and on (b) (6) for PLX3397pexidartinib. On Day 37, the subject died due secondary to progressive disease. An autopsy was not performed.

FDA Reviewer Comments:

Unlikely to be related to pexidartinib, hepatic metastasis present on imaging and injury on liver biopsy was not cholestatic, rather more hepatocellular, possibly related to pembrolizumab use.

*The HEAC members combined and individual expert opinion was that this patient experienced Cholestatic injury, , severity score of 5 and no concomitant drug suspected as a confounder; the final determination was unrelated to pexidartinib. **In alignment with our assessment, there was a consensus among the HEAC experts of a unrelated association with pexidartinib (see Appendix B- page 154 of 325).***

PLX108-14 Subject No. (b) (6) (Biopsy-Confirmed Hepatic Event):

A 75-year-old white female with Stage IIIC T3cN1M0 fallopian tube cancer with ovary involvement started on pexidartinib at 600 mg daily split BID and pembrolizumab 200 mg once every 3 weeks. Hepatic enzymes and bilirubin were all within normal limits at baseline. On Day 29, the subject experienced Grade 1 AST increased (89 U/L), ALT increased (135 U/L), and ALP (211 U/L) with normal DBIL and TBIL. On Day 30, a liver biopsy revealed hepatic parenchyma with moderate portal inflammation containing moderate numbers of eosinophils with focal

granuloma formation and bile duct inflammation. On Day 50, the subject experienced increased GGT (Grade 2; 193 U/L). No action was taken with the study medications. On Day 57, the events of ALT increased, and AST increased worsened to Grade 2, and GGT worsened to Grade 3; pexidartinib was interrupted due to these events and was never restarted. On Day 64, the event of AST increased improved to Grade 1 (91 U/L), with ALT at 180 U/L (Grade 2), ALP at 302 U/L (Grade 1), and GGT at 264 U/L (unspecified grade). The TBIL and DB IL remained normal throughout the event. On Day 85, the subject's hepatic evaluations revealed ALT at 21 U/L, AST at 19 U/L, ALP at 107 U/L, and GGT at 71 U/L; and the event of 'ALT increased' was considered resolved and the severity of 'GGT increased' improved to Grade 1. The treatment with pembrolizumab and PLX3397 pexidartinib was discontinued due secondary to progressive disease with the last dose administered on (b) (6) and (b) (6), respectively. Liver biopsy report provided by sponsor states "Cholestasis with moderate portal inflammation containing moderate numbers of eosinophils with focal granuloma formation and bile duct inflammation".

FDA Reviewer Comments:

Type of Injury- Cholestatic hepatotoxicity

Liver enzymes started to trend down with pexidartinib interruption, i.e., positive dechallenge. The patient's underlying disease progressed, which ultimately led to pexidartinib discontinuation. We adjudicated this case as "probable" in its causal association with pexidartinib (>50% likelihood).

In alignment with our assessment, there was a consensus among the HEAC experts of a probable association with pexidartinib (see Appendix B – page 270 of 325).

DDI Study 126

Detailed information on this subject is not available. Provided information includes 43-year-old female (Subject # (b) (6)) was dosed with 800 mg of pexidartinib and on Day 21 she presented with mixed hepatotoxicity with hyperbilirubinemia. Her recovery period was 2 months. Details about how many doses of pexidartinib, or concomitant drugs were not provided.

FDA Reviewer Comment

Enough data to adjudicate was not presented, however, if pexidartinib was the only drug with hepatotoxic potential that the patient was administered, it indicates that hepatotoxic injury occurred across various trials.

C.3. Review of Liver Biopsy Reports (n=8, biopsy reports and digital images were submitted for all 8 patients):

The following 8 subjects had hepatic AEs and liver biopsy performed. Pathology reports were available for the following 4 subjects:

1. **PLX108-10 Subject No.** (b) (6)
 - a. Significant ductopenia (2 bile ducts in 10 portal tracts observed), canalicular and hepatic cholestasis observed
2. **IST3397-001 (Study IIS UCSF 12751) Subject** (b) (6)
 - a. Severe ductopenia with cholestasis

3. IST3397-006 (Study IIS SPY2 097517) Subject No. (b) (6)
- a. Severe ductopenia with cholestasis, outcome liver transplant
4. PLX108-01 Subject No. (b) (6)
- a. Portal acute and chronic inflammation with bile duct injury and reaction, portal fibrosis with areas of bridging. Mild macrovesicular steatosis observed. No inflammation or fibrosis observed.
- b. Severe parenchymal cholestasis observed, however, only 2 portal tracts were available for review. Cholestasis was associated with feathery degeneration and necrosis of hepatocytes. Mild apoptotic hepatocellular injury with minimal inflammation and no fibrosis. Mild macrovesicular steatosis observed.
- FDA Reviewer Comments:**
- This subject had a positive AMA and biopsy findings are consistent with diagnosis of PBC.*
5. PLX108-14 Subject No. (b) (6)
- a. Eosinophilic injury and granuloma formation likely drug-induced liver injury related to pexidartinib.
6. PLX108-09 Subject No. (b) (6)
- a. Prominent cholestasis³ and mild portal and lobular inflammation with milk prominence of eosinophils, most consistent with drug-induced liver injury, negative for malignancy.
7. PLX108-14 Subject No. (b) (6)
- a. Mild apoptotic hepatocellular injury with minimal inflammation and no fibrosis. Mild macrovesicular steatosis.
8. PLX108-07 Subject No. (b) (6) - biopsy report could not be located.

Of these 8 subjects, 7 subjects had a liver pathology report submitted to the EDR. Of the 7 subjects, **3 subjects** (PLX108-10 Subject No. (b) (6); IST3397-006 (Study IIS SPY2 097517) Subject No. (b) (6); IST3397-001 (Study IIS UCSF 12751) Subject No. (b) (6)) developed **severe ductopenia secondary to pexidartinib use**, fourth patient had ductopenia related to development of PBC, **fifth and sixth subject** (PLX108-14 Subject No. (b) (6) and PLX108-09 Subject No. (b) (6)) **had a liver biopsy findings consistent with drug-induced liver injury.**

³ The inflammatory infiltrate contains lymphocytes, plasma cells, and with scattered eosinophil portal inflammation is relatively mild compared to the degree of lobular inflammation and the 2 and 3 cholestasis. Overall, the findings are most in keeping with drug-induced liver injury. There is no evidence of metastatic melanoma. A trichrome stain shows no significant injury.

D. Overall Conclusions

Preclinical findings support the hepatotoxic potential of pexidartinib. Elevations of liver enzymes, development of biliary cysts and necroinflammation of liver were observed in rat toxicology studies. Elevations of liver enzymes were also observed in dog and monkey toxicology studies.

The Applicant explored potential mechanisms for liver toxicity of pexidartinib and its N-glucuronide metabolite, ZAAD-1006a. These were assessed by DILIsym[®] analysis based on in vitro hepatotoxicity data, phase 3 clinical data (PLX108-10), simulations of chemical hepatic exposure, and simulations of hepatotoxicity mechanism. Based on the findings of DILIsym analyses, the Applicant concluded that pexidartinib has a potential for hepatocellular toxicity; however, DILIsym analysis is not yet able to predict cholestatic injury.

The types of pexidartinib associated hepatotoxicity observed in the clinical development program included predominantly cholestatic, mixed, (hepatocellular/cholestatic), and hepatocellular forms of injury which were observed both in the TGCT and non-TGCT trials. The severity of hepatotoxicity ranged from biochemical enzyme elevations to ductopenia and liver failure. Liver biopsy was performed only in 8 subjects, out of which a pathology report was submitted for 6 subjects. **Of these 6 subjects severe ductopenic injury was observed in 3 subjects.** Of the 3 subjects who developed ductopenia, 2 subjects developed liver failure with one who underwent liver transplant and the other who died. The third subject is still alive; however, the long-term outcome is unknown. Two subjects had liver biopsy findings consistent with drug-induced liver injury. In addition, steatosis was also observed on liver biopsy in many subjects; steatosis with pexidartinib needs to be further characterized.

During the pivotal (PLX108-10, ENLIVEN) clinical trial for TGCT, only 61 subjects were exposed to pexidartinib for a short duration trial of 24 weeks (~6 months). This population will eventually require long-term therapy with pexidartinib, and currently long-term effects of treatment with pexidartinib are unknown. Even with 6 months exposure to pexidartinib, a high proportion (66%) of subjects in the TGCT clinical trial had elevations of transaminases, and 5 (5%) subjects developed significant liver injury with concomitant ALT \geq 3x ULN and TB \geq 2 x ULN elevations. Liver biopsy was only performed in one subject (PLX108-10 Subject No. (b) (6)), who was found to have ductopenic injury and had severe cholestatic injury with a prolonged and protracted course.

Notably, of the 140 subjects enrolled in the TGCT trial 23 (16.4%) subjects experienced ALP \geq 2X ULN and 5 (3.6%) subjects experienced concomitant ALP \geq 2X ULN or GGT \geq 2X ULN and TB \geq 2X ULN. The Applicant did not have pre-specified dose modification, interruption or discontinuation criteria for ALP elevations, which is an important marker of cholestatic injury.

During the pivotal ENLIVEN trial, 4 out of 61 subjects required discontinuation of pexidartinib due to transaminase or total bilirubin elevation. Even with the protocol specified stopping and monitoring rules, subjects developed clinically consequential injury during the ENLIVEN trial. All

acute cases of liver injury occurred within 8 weeks of pexidartinib initiation. In the TGCT trial, out of 7 subjects, 4 subjects experienced severe drug-induced cholestatic liver injury that can be attributed to pexidartinib. Of these 4 subjects who developed severe DILI, one developed significant ductopenia.

In the non-TGCT population, a similar pattern of injury was observed. Serial liver biopsies were not collected in any subject; therefore, we cannot comment whether there is histological progression of ductopenic injury overtime. In the non-TGCT trial, three subjects developed severe ductopenic liver injury, of which two subjects developed liver failure and one subject underwent liver transplant.

Currently, there are uncertainties with long-term treatment using pexidartinib. One concern that remains with long-term treatment beyond 6 months is whether mild liver enzymes elevations that are below the threshold criteria of protocol specified discontinuation of pexidartinib may still lead to chronic or subacute liver injury. Ductopenia has the clinical and biological underpinnings for long-term poor outcomes and this is quite concerning. Ductopenic injury can be progressive, despite discontinuing pexidartinib early after the onset of liver injury, as observed in 2 subjects who continued to progress to liver failure.

However, key challenges include obtaining a liver biopsy, which is invasive, but is crucial for establishing a diagnosis of ductopenia. Optimal time at which liver biopsy should be performed after a cholestatic injury is observed is currently not established.

E. Recommendations

In considering the benefits and risks of long-term treatment with pexidartinib for TGCT (a non-lethal but debilitating disease) the treatment related risk of life-threatening hepatotoxicity with ductopenia must be carefully weighed. Based on the benefit of treating a non-malignant TGCT with long-term pexidartinib maintenance therapy and from the clinical and laboratory data that has been gathered in study subjects, it is self-evident that a high threshold of benefit for the intended treatment population must be exceeded in order to justify approval of the agent. What has yet to be fully elucidated is whether extended periods of treatment beyond the duration of pexidartinib exposure tested in the pivotal PLX108-10 study using protocol-specified liver test monitoring and stopping rules in place would (or would not) be associated with progression of smoldering forms of liver injury not marked by ALT or ALP levels (that would trigger protocol-based treatment discontinuation) to more severe forms of hepatotoxicity in an even higher percentage of treated patients than what was observed in the trial. This would require a longer duration study of pexidartinib treatment of the same or an equivalent cohort of patients together with a follow-up evaluation of liver parameters, ideally including biopsy assessments.

Taking these concerns into account, should DOP2 decide to “not approve” this drug, then we have no further comments. However, should DOP2 decide to approve the drug, we believe that it would be appropriate to institute a stringent monitoring program with a REMS and ETASU, as

the Applicant has proposed, in order to enroll all patients prescribed pexidartinib in a registry to accurately track product use and regularly monitor them on a regular schedule for the development of liver injury. Any patient with a serious hepatic adverse event associated with pexidartinib should be comprehensively evaluated both clinically and with appropriate diagnostic testing and reported in an expedited manner to the FDA. In addition, we recommend that the product be contraindicated or limited in use for patients with metastatic disease as well as those with pre-existing liver disease. Education of investigators and patients will be critical, for example, knowing to immediately discontinue pexidartinib in any patient with significant elevations of serum liver biochemistries or signs and symptoms of clinical hepatitis (i.e., fatigue, abdominal pain, nausea, etc.) in the presence of any elevation of liver enzymes. In addition, a post-marketing requirement to conduct a clinical trial to follow up both the short-term and long-term outcomes in all subjects who are treated with pexidartinib is strongly advised. Long-term follow-up of patients in the study who have discontinued pexidartinib to rule out delayed hepatotoxicity effects is also recommended. Reassessment of subjects exposed to pexidartinib should be undertaken in regular intervals to assess both short-term and long-term effects of treatment related hepatotoxicity.

Appendix A

An IR was sent out on 3-18-19 to the Applicant for submitting the following information to expedite our review of hepatotoxicity.

Please provide the following information and data to better characterize the drug-induced liver injury (DILI) risk associated with Pexidartinib. Please submit your complete response no later than April 20, 2019.

1. Provide complete data for all study subjects in Pexidartinib phase 2 and 3 trials in an e-DISH format, with narratives compiled by a professional with expertise in the diagnosis of DILI. See attached documents "Format of Standard Narrative Data" and "e-Dish data requirements" for submission of the e-DISH data.

The subject-specific information you provide should be included in the appended narratives. For subject-level narrative content and formatting, provide all cases of interest with:

- i. ALT \geq 5X ULN
- ii. ALT \geq 3X ULN **and** total bilirubin (TB) \geq 2X ULN
- iii. ALP \geq 2X ULN
- iv. ALT \geq 3X ULN **and** direct bilirubin (DB) \geq 0.5 mg/dL
- v. ALT \geq 3X ULN **and** ALP or GGT \geq 2X ULN **and** TB \geq 2X ULN or DB > 0.5 mg/dL

Please refer to Tabs "Narrative SAS Data" and "Narrative PDF file" in the eDISH Data Specifications.

2. Provide narratives, timeline graphs and long-term follow-up for subjects DSU-2018-^{(b) (6)} and DSU-2018-^{(b) (6)} who received pexidartinib at a starting dose of 800 mg/day and developed cholestatic hepatotoxicity.
3. Provide the following information on the degree and type of injury experienced by subjects treated with Pexidartinib across clinical trials that have been conducted for various indications (TGCT and non-TGCT populations):
 - a. Number (and %) of subjects who experienced elevations in liver tests (ALT, AST, TB, DB, GGT, ALP and INR), tabulate separately for TGCT population, non-TGCT population, all populations combined)
 - b. Type of injury for each subject (i.e., hepatocellular, mixed, cholestatic)
 - c. Number (and %) of subjects who met Hy's Law criteria
 - d. Number (and %) of subjects who met the following thresholds
 - i. ALT: $\geq 3X$ to $5X$ ULN; $>5X$ to $10X$ ULN; $>10X$ ULN etc.
 - ii. ALP: $\geq 2X$ ULN; $>3X$ to $5X$ ULN; $>5X$ to $10X$ ULN; $>10X$ ULN etc.
 - iii. ALP or GGT $\geq 2X$ ULN **and** TB $\geq 2X$ ULN
 - iv. DB >0.5 mg/dL
 - v. ALT $\geq 3X$ ULN **and** direct bilirubin (DB) ≥ 0.5 mg/dL
 - vi. ALT $\geq 3X$ ULN **and** ALP or GGT $\geq 2X$ ULN **and** TB $\geq 2X$ ULN or DB >0.5 mg/dL
4. Summarize the following elements for each subject who experienced pexidartinib-associated liver injury marked by elevation of liver biochemical enzymes (as outlined in comment #3d) and/or concomitant clinical symptoms who were enrolled in TGCT and non-TGCT trials (subject level data). Please provide the case narratives as well as summarize the cases in a separate table (see comment 4h for table outline):
 - a. Time to onset of hepatotoxicity relative to Pexidartinib administration (including granular information on time to each of the following: biochemical injury, clinical symptoms, liver biopsy, liver failure, liver transplant or death, Pexidartinib interruption, discontinuation or re-challenge)
 - b. Response to re-challenge (i.e., if treatment was interrupted and then resumed), re-challenge dose, and time between discontinuation and re-challenge
 - c. Time to recovery after Pexidartinib discontinuation (including trajectory/graphical profiles of liver biochemical indices status/clinical status in subjects with suspected DILI [include biochemical changes, clinical symptoms and/or clinical outcomes])
 - d. Reversibility of injury
 - e. Submit pathology report(s) and digitalized histopathology images for all subjects in whom liver biopsy was performed. Also provide the following:
 - i. For Subject who underwent liver transplant, include pathology report and digitalized histopathology images of the explanted liver

- ii. For Subject who died, submit the liver pathology report and digitalized histopathology images
- f. List which other causes of liver injury were excluded and what assessments were performed to rule out them out
- g. Number (and %) of subjects that required Pexidartinib discontinuation secondary to hepatotoxicity
- h. Complete the following Table for subjects suspected for DILI who experienced liver-related clinical outcomes or elevations of ALT/AST, ALP/GGT, TB/DB alone or in combination:

Study number / Phase of Trial / Subject number / Age/Sex	Pexidartinib Dose	Baseline liver enzymes	Date of liver enzyme elevation/ Day number from start of treatment	Liver test abnormality (by date, including peak elevations and return to baseline)	Clinical Symptoms	Pexidartinib Treatment Interrupted/ Discontinued/ Rechallenge	Type of injury	Concomitant drugs with hepatotoxic potential (Provide correlation to Pexidartinib dosing and onset of liver injury)	Resolution of the injury (Date/Correlation to Pexidartinib dosing)	Clinical Outcomes (Date/Relationship to Pexidartinib dosing)

- 5. Summarize the following for TGCT and non-TGCT populations:
 - a. Relationship between Pexidartinib doses and incidence of hepatotoxicity occurrence
 - b. Serum drug levels and its major metabolites obtained in any subject who developed an adverse event of hepatic injury or decompensation
 - c. Protocol specified Pexidartinib discontinuation criteria for liver injury
 - d. Perform an analysis of hepatic related signs and symptoms by:
 - i. Symptoms of abdominal pain, worsening or new fatigue, anorexia, nausea, rash, vomiting or diarrhea with and without presence of biochemical elevations. Please note that even vague symptoms of “just not feeling well” have been associated with drug induced hepatotoxicity and should be similarly analyzed in all subjects with liver biochemical elevations above baseline
 - ii. Evidence of worsening renal function or dehydration
 - iii. Intercurrent illness, such as gastroenteritis
 - iv. Fasting conditions
 - v. History of NAFLD or other underlying liver disease at baseline
 - vi. Reversibility of injury
- 5. Summarize the safety monitoring plan for hepatotoxicity proposed in the protocol and protocol amendments. Additionally, provide a summary of compliance with

protocol safety monitoring plan for hepatotoxicity and individual discontinuation criteria for all the completed and ongoing programs.

6. We are aware that a DSMB was convened during the clinical trial; provide a copy of the DSMB's adjudication report for subjects who experienced hepatic adverse events.
7. Provide long-term follow-up information on the use of corticosteroids or other therapy(ies) used to treat hepatotoxicity for all patients that experience hepatotoxicity across the development program for pexidartinib.
8. Convene a hepatic advisory committee (HEAC) (separate from the DSMB) with one or more individuals who have recognized clinical expertise in the assessment of DILI risk to evaluate all pertinent clinical characteristics, and diagnostic data to determine the severity and adjudicate causality of each case of liver injury as outlined in the FDA guidance on drug-induced liver injury: premarketing evaluation (2009) in Pexidartinib treated subjects both in studies that provide the primary safety data in NDA 211810 and for all Pexidartinib clinical studies. Cases of interest typically include those marked by acute elevations of the following during exposure to the study drug or in the follow-up period:
 - i. ALT: $\geq 3X$ to $5X$ ULN; $>5X$ to $10X$ ULN; $>10X$ ULN etc.
 - ii. ALP: $\geq 2X$ ULN; $>3X$ to $5X$ ULN; $>5X$ to $10X$ ULN; $>10X$ ULN etc.
 - iii. ALP or GGT $\geq 2X$ ULN **and** TB $\geq 2X$ ULN
 - iv. DB >0.5 mg/dL
 - v. ALT $\geq 3X$ ULN **and** direct bilirubin (DB) ≥ 0.5 mg/dL
 - vi. ALT $\geq 3X$ ULN **and** ALP or GGT $\geq 2X$ ULN **and** TB $\geq 2X$ ULN or DB >0.5 mg/dL

Using graphic tools, such as eDISH, the HEAC should provide FDA with a comprehensive report of the study drug's hepatotoxic risk profile that includes a comprehensive clinical and laboratory assessment of individual case-level data supported by timeline graphs of biochemical test and diagnostic results, study drug dosing schedules and all pertinent clinical and diagnostic findings.

In addition, analysis of study population-level data including an assessment of dose and duration of treatment related imbalances in liver test abnormalities between pexidartinib and randomized comparators should be performed by the HEAC. Analysis of the powering of each of the relevant clinical trials and duration of treatment along with monitoring protocols should be included in the report to gauge potential for hepatotoxicity at the population level.

An analysis of drug-host, drug-disease and drug-drug interactions that impact risk of the liver injury should also be provided.

Finally, assessment of pertinent hepatic pharmaco-toxicological data obtained from pre-clinical models, as well as pexidartinib dose & exposure-related liver toxicity findings in human studies should be included in the HEAC report.

FDA recommends that Daiichi Sankyo bring a member of the HEAC to present key findings and conclusions regarding Pexidartinib's risk for hepatotoxicity at the upcoming Advisory Committee Meeting.

9. Based on the PK data obtained from phase 1, 2, and 3 of your completed and ongoing trials in which adequate liver monitoring was performed, provide a treatment population-based analyses in graphic and/or tabular format demonstrating the relationship between Pexidartinib PK/AUC and subjects experiencing elevations in liver enzymes or a decline in liver function, for the following:
 - a. ALT \geq 3X ULN
 - b. ALT \geq 3X ULN **and** TB \geq 2x ULN
 - c. ALP \geq 2X ULN **and** TB \geq 2x ULN
 - d. ALT \geq 3X ULN and ALP or GGT \geq 2X ULN and TB \geq 2X ULN or DB >0.5 mg/dL

10. Summarize annualized rates in patient-years for hepatic adverse events. Provide cumulative incidence plots for the following:

For Completed trials (pool data from all completed trials):

- Treatment (pool all dose levels) vs. placebo
- Dose (1000 mg split BID, 800 mg split BID)
- Severity (by Grade of each liver biochemical elevation, by symptom severity, etc.)
- Indication

Ongoing trials – (pool data from all ongoing trials)

- Overall event rates
- Trial (note doses studied)
- Severity
- Indication

Use the same y-axis across all of the plots. Include the number at risk under the x-axis. For each plot, provide inferential statistics to assess differences between the curves.

11. Summarize the regulatory history of the development program including reasons for placement on partial clinical hold (PCH) and your response addressing the PCH.

Appendix B -- HEAC Committee Case Adjudication Forms

Appendix C – Adjudicated Case Narratives by the Individual DILI Experts

Appendix D – DILIN/FDA Causality Scale

Pexidartinib HEAC (b)(4)
Group 1 Case Review Meeting Minutes
Teleconference
Friday, October 13th 2017
2:00-3:00 PM EDT

HEAC Attendees:

(b)(4) (Chair)
[Redacted]

(b)(6)

Attendees:

(b)(4)
[Redacted]

Summary Notes:

The HEAC met and reviewed each of the 18 Group 1 cases and arrived at HEAC consensus decisions on liver injury pattern, severity score, relationship to study drug, and hepatic adaptation (yes/no) during their discussion. Specific case assessments are described within the case review forms. With respect to the case review form itself, the HEAC would like to share with DSI that in designating the liver injury pattern and the severity, genuine disagreements can occur depending on the timing within the case. Severity, in some cases, was due to underlying disease and may not be related to the study drug. Comments were included in the confounding factors and comments by individual reviewer columns based on discussion during the teleconference as applicable, and were extensions of comments provided in the review forms completed by each HEAC member individually.

The attached By Committee case reviews have been adjudicated by the HEAC.

(b)(4)
[Redacted]

HEAC Chair

10/18/17
Date

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSJ-2016-130232/ (b) (6) /PL3397-A-A103/TAIWAN, PROVINCE OF CHINA/Male/74 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	tumor type not specified; many surgeries	+ rechallenge; + dechallenge R = 2.2, so mixed. May have initially been pure cholestasis, but by the time of first lab tests, was mixed. AST/ALT/bili back to normal in 26 days (if stop date was 01SEP), but alk phos lagged. Next alk phos not provided until 1 month later.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (\text{ALT/ULN})/(\text{Alk Phos/ULN})$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2014-129906(2012 PLX04022)/(b)(6)/PLX-108-04/UNITED STATES/Female/58 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	on temoz. since 2/12	+ dechallenge; AST>ALT; absence of baseline values and limited workup; Probable DILI

Liver Injury pattern:

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
- Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
- Mixed: R 2-5

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also $TB > 2X$ ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2014-131378/ (b) (6) /PLX-108-09/UNITED STATES/Male/62 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	melanoma; on vemurafenib; cannot determine which drug (or both) contributes	-severity score impacted by additional SAEs -hospitalized for infection on hand, not for liver event

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2015-115224/ (b) (6) /PLX-108-08/UNITED STATES/Male/74 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	taking temozolomide	-Equally likely not the study drug -Cholestatic hepatitis pattern

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-117700/ (b) (6) /PLX-108-08/UNITED STATES/Male/53 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	-bactrim, dilantin and temozolomide -apparent Stevens-Johnson syndrome -negative dechallenge for study drug	Negative dechallenge

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-123981/ (b) (6) /IIS-UCSF-12751/UNITED STATES/Female/58 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	bone mets; also on eribulin; liver massess ductopenia on liver biopsy	-probably related to PLX for initial rise in ATs and bili with ductopenia and cholestasis on liver biopsy but progressive bone disease likely explains progressive rise in alk phos (which was not fractionated)

Liver Injury pattern:

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
- Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
- Mixed: $R 2-5$

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB $> 2X$ ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-133092(DSU-2015-135086)/(b) (6)/IIS-SPY2-097517/UNITED STATES/Female/60 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 due to transplant	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Updated information was provided for this subject. -vanishing bile duct -required liver transplant

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (\text{ALT/ULN})/(\text{Alk Phos/ULN})$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-134908/ (b) (6) /IIS-UCSF-12751/UNITED STATES/Female/59 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	-sepsis -Also on eribulin along with PLX -Reaction possible related to other drug -diffuse liver mets	PLX is possibly related; however, as noted in liver tox, use of eribulin has been associated with changes in bilirubin and aminotransferases and there have been cases of apparent drug related hepatitis ascribed to the drug.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (\text{ALT/ULN})/(\text{Alk Phos/ULN})$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-106629/ (b) (6) /PLX-108-07/UNITED STATES/Female/50 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Limited evaluation but possible dechallenge; ultrasound showed no liver mets or dilated ducts; increased INR on xarelto

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-112210/ (b) (6) /PLX-108-01/UNITED STATES/Female/44 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	PBC; elevated AMA	We thought it was due to PBC and not the drug

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-125207/ (b) (6) /PLX-108-10 (Blinded)/GERMANY/Female/75 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 hospitalization with dialysis	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	no other suspect drugs	ductopenia on liver biopsy

Liver Injury pattern:

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
- Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
- Mixed: R 2-5

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB $> 2X$ ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-128875/DSU-2016-131117//PLX-108-14/UNITED STATES/Female/60 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	combination therapy with pembrolizumab	either or both drugs may be related

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-129240/ (b) (6) /PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Exact dates of treatment uncertain; no con meds	positive dechallenge after consistent latency and negative serology

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-130954/ (b) (6) /PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Positive rechallenges (2) on different doses

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-133478/ (b) (6) /PLX-108-10 (Blinded)/SPAIN/Female/67 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		-severity of 2 because of jaundice; positive dechallenge

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-142567(2016PLX000087)/ (b) (6) /PLX108-07/UNITED STATES/Female/61 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	episode of acute kidney injury portal vein thrombosis	-Severity is not a 5 because subject died due to underlying cancer disease progression

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2017-110948/ (b) (6) /PLX108-13/China/Female/61 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		positive dechallenge after PLX interrupted with negative rechallenge for ALT but positive rechallenge for alk phos

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Reviewed and Approved by: HEAC Date: 13Oct2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2017-118366/ (b) (6) /PLX108-13/China/Female/66 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 subject died	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input checked="" type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Updated information was provided for this subject; negative dechallenge with no work ups; billirubin continued to rise; death was not due to liver failure (may have been due to underlying malignancy); not enough data to determine relationship

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (\text{ALT/ULN})/(\text{Alk Phos/ULN})$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 8/31//2017 Reviewer: Laurie DeLeve



Case Control #/Subject ID/Study#/Country/Gender/Age		DSJ-2016-130232/ (b) (6) PL3397-A-A103/TAIWAN, PROVINCE OF CHINA/Male/74 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Daily dose of drug from (b) (6) through (b) (6) (report lists both dates as last dose). Liver test abnormalities noted on day 57, (b) (6) tbili 2.6, AST 185, ALT 128, alk phos 647. All tests back to normal by (b) (6) (alk phos normalized one month after other tests). R=2.2, so mixed. May have initially been pure cholestasis, but by the time of first lab tests, this was a mixed picture. AST/ALT/bili back to normal in 26 days (if stop date was 01 Sep) but alk phos lagged. Next alk phos not provided until 1 month later

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

(b) (4)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 8/31/2017



Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2014-129906(2012 PLX04022), (b) (6) PLX-108-04/UNITED STATES/Female/58 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug from (b) (6) (b) (6) AST 172, drug held. (b) (6) AST 1268, ALT 518, alk phos 416, bili 1.7, dbili 1.3, Liver tests near-normal by 24-Jan. No CK available, with AST>>ALT but with conjugated bili elevations. Negative U/S and viral serology

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/1/2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2014-131378/ (b) (6) PLX-108-09/UNITED STATES/Male/62 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Vemurafenib, but this is described as hepatocellular	Therapy (b) (6) Baseline liver tests normal and remained normal through (b) (6) On (b) (6) ALT 346 (8.65 x ULN), AST 241, t bili normal range initially and then max of 1.4 (dbili 0.7), alk phos 325 (2.95 x ULN). R=2.95, mixed picture. Blood tests normalized by (b) (6) but note that AST/ALT went up and down and peaked (b) (6), alk phos went up and down and peaked (b) (6). Negative HBV, HCV, CMV, EBV, ANA, anti-mito. (b) (6) liver biopsy: prominent cholestasis and mild portal and lobular inflammation with mild prominence of eosinophils, most consistent with drug-induced injury;

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)

(b) (4)

2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Page 5

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/12/17__

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2015-115224/ (b) (6) PLX-108-08/UNITED STATES/Male/74 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Temozolomide	Drug from (b) (6) Temozolomide (b) (6) Urine dark since (b) (6) ALT, bili and alk phos elevated (b) (6) peak a little later and near-normal (b) (6) peak bili 28.7 on 11 May with elevated dbili, initial R 5.5. Negative viral serology. Negative US.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/12/17 _____

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-117700, (b) (6) PLX-108-08/UNITED STATES/Male/53 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Negative dechallenge for study drug	(b) (6) on drug; 20 Feb-04 Mar and 10 Mar onwards on temozolomide. Elevated AST/ALT/alk phos starting (b) (6) (normal bili), R 8.5, (b) (6) single bili-2.3, no dblii tested. (b) (6) temozolomide restarted (b) (6) AST/ALT & alk phos go up again and alk phos continue to climb through last value on 01 Apr.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date:9/12/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2015-123981, (b) (6) IIS-UCSF-12751/UNITED STATES/Female/58 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		(b) (6) on study drug. Drug stopped but progressive hyperbilirubinemia, elevations of alk phos, liver bx ductopenia Bili peak (b) (6) normal by (b) (6) ALT normal by (b) (6) Alk phos peak (b) (6) and remained elevated last lab (b) (6) (b) (6) Neg w/u for AIH and viral, neg CT for other cause cholestasis

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/12/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2015-133092(DSU-2015-135086)/ (b) (6) IIS-SPY2-097517/UNITED STATES/Female/60 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug (b) (6) Very limited info. Pt altered MS and weak, T 101.4, negative US (b) (6) On unknown date CT reported as cholecystitis. HIDA scan no viz of GB and no excretion out of common bile duct. 14-Oct bili 2.7, ALT 158, no alk phos provided. Lap chole: purulent gallbladder. Dx acute cholecystitis. Liver tests continued to rise after cholecystectomy. Neg MRCP. Liver biopsy: cholestasis zone 1/2 and duct damage and duct loss, no fibrosis, review of path: acute dili and <u>vanishing bile duct</u> . Bili remained in mid-20s. Liver transplant (b) (6)

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

(b) (4)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/12/2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-134908/ (b) (6) / IIS-UCSF-12751/UNITED STATES/Female/59 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Eribulin (b) (6) can give same picture	Study drug (b) (6) restart (b) (6) AST 206, alk phos 402. (b) (6) admitted with T 102.8, HR 142, WBC 14, lactate 3.4, nl CXR and UA, neg BC, AST 562,, ALT131. Alk phos 392, bili 1. Blood cx negative. Ultrasound negative, rapid drop transaminases, slower drop alk phos by (b) (6) D/c'd home on antibiotics

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/12/17_

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-106629/ (b) (6) PLX-108-07/UNITED STATES/Female/50 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug (b) (6) (on rivaroxoban for 2 years). ALT 05 Feb 302, progressively climbed to 747 5 days after d/c drug and then slow decline over 5 weeks to 141 on (b) (6) (b) (6) Alk phos also rose in first week after dechallenge and stayed stably elevated until last value (b) (6) (2 months). Bili 5.5 or (b) (6) peak after 2 weeks and slow decline, normal at 2 months. Initial R4.3, c/w cholestasis. Negative U/S. INR 1.4. Should get follow up on alk phos after (b) (6) and needs liver bx if alk phos never normalized (if still alive)

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction

(b) (4)

4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017__

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-112210/ (b) (6) PLX-108-01/UNITED STATES/Female/44 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Elevated AMA c/w PBC	Study drug (b) (6) ALT elevation (b) (6) and (b) (6) fluctuating elevations through (b) (6) (b) (6) AST similar. Alk Phos elevation (b) (6) and remain elevated through (b) (6). Bili normal (except after liver bx). Liver biopsy portal inflammation, bridging fibrosis. AMA positive but no value given. Probably PBC

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction.
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4) _____ Page 14

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017_

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-125207/ (b) (6) PLX-108-10 (Blinded)/GERMANY/Female/75 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug or placebo: (b) (6) (b) (6) Initial presentation (b) (6) elevated transaminases (ALT 200-400), alk phos 200, and bili 2.8. Hospitalized briefly (b) (6) Liver bx (b) (6) ductopenia, severe cholestasis, near normal transaminases, nl alk phos (fluctuating to 2x ULN), bili 8.6 with elevated dbili. Symptoms pruritus. Bili and ALT normal (b) (6) Diagnosis drug-induced ductopenia

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-128875/DSU-2016-131117//PLX-108-14/UNITED STATES/Female/60 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Pembrolizumab	Study drug (b) (6) Pembrolizumab (b) (6) ongoing (Pembrolizumab is given q 3 weeks). (b) (6) ALT elevation up to 5x ULN, AST 10 x ULN, minimal change alk phos, bili normal, lasting 10 days (b) (6). No follow up given after (b) (6) (b) (6) but presumably it would have been reported if liver test abnl recurred with pembrolizumab

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-129240/ (b) (6) PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Placebo or study drug: (b) (6) (b) (6) then lower dose until (b) (6) (b) (6) Emer Dept bili 4.0; (b) (6) hospitalized for N/V, jaundice and pruritus; tbili 74. Dbili 5.6, ALT 371, AST 174. Only 3 alk phos values: nl (b) (6) 2x ULN (b) (6) nl (b) (6) All liver tests nl (b) (6) Imaging: (b) (6) U/S GB wall thickening , some sludge; U/S and CT: no dilated ducts; neg serology. No reported fever or leukocytosis

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017__

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-130954/ (b) (6)/PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Placebo or drug: (b) (6) (b) (6) ALT 315; Alk phos 189. Restart lower dose (b) (6) and on 24 Aug alk phos 666, ALT 332. Restart (b) (6) (b) (6) and on (b) (6) abd pain, N/V, ALT138, AST 192, alk phos 220, bili nl, GGT 4 x ULN; held drug. Restart (b) (6) (b) (6) drug x 1 day and recurrent crampy abd pain. (b) (6) alk phos 314, ALT 433, bili 1.5 x ULN. Two positive rechallenges.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-133478/ (b) (6) PLX-108-10 (Blinded)/SPAIN/Female/67 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Drug or placebo: (b) (6) then lower dose (b) (6) (b) (6) ALT 244, alk phos 228, but alk phos peaked 2 w later 472 (peak bili 1.3x ULN. Liver tests nl by (b) (6) Presented (b) (6) with 1 week of abd pain N, dark urine, hospitalized, negative U/S

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-142567(2016PLX000087), (b) (6)/PLX108-07/UNITED STATES/Female/61 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug (b) (6) (b) (6) aclitaxel (b) (6) On (b) (6) T103.9, N/V, ALT 169, AST 273, alk phos 127, bili 0.8; not hosp. 07 Dec CK 300's (b) (6), AST 345, ALT 250, bili 1.2. Adm for kidney injury, worsening CK, AST and ALT, bili 3.4; hospitalized. (b) (6). RUQ U/S normal. Last values (b) (6) provided: ALT 230 (4xULN), AST333 (9ULN), alk phos 1279 (11xULN), bili 26.7 (20xULN). Liver bx severe, bland cholestasis with duct injury but no inflammatory cells. No date for liver bx. Was patient bone marrow suppressed at time of bx?? (lack of inflammatory cells?). "Viral and autoimmune lab results WNL" Died of underlying cancer progression.

Liver Injury pattern:

(b) (4)

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
 - Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
 - Mixed: $R 2-5$
- $R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB $> 2X$ ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2017-110948, (b) (6)/PLX108-13/China/Female/61 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug (b) (6) (b) (6)ALT569 (14xULN), AST390 (8.7xULN), alk phos 311 (2xULN), tbili just above ULN, dbili 2.2xULN. 11 days later liver tests near normal. Serology: HBsAB+, HBeAb+, all other serology negative.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/14/2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2017-118366/ (b) (6)/PLX108-13/China/Female/66 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input checked="" type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug (b) (6) (b) (6) lower dose.: (b) (6) ALT 324 (8X), declines by (b) (6) to 2.5x, AST : 10x on (b) (6), decline to 2.6x, bump up to 6x (last value 19Jun). (b) (6) alk phos 199, steady climb through (b) (6) when 863 (5.4x). Bili climbs from (b) (6) 4xULN to 19Jun 12xULN. Hospitalized. U/S liver cysts and ??chronic cholecystitis (GB wall thickening) (b) (6) discharged home with continued jaundice. No liver biopsy, AMA, ANA. No evidence of liver mets on CT. Death likely due to underlying malignancy.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)

(b) (4)

3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSJ-2016-130232, (b) (6)/PL3397-A-A103/TAIWAN, PROVINCE OF CHINA/Male/74 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Asian male with advanced solid tumor; latency 7 weeks but no liver tests between start of Tx and when S.D is interrupted; narrative says positive Rechallenge; then positive dechallenge after pt withdraws consent

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2014-129906(2012 PLX04022)/ (b) (6)/PLX-108-04/UNITED STATES/Female/58 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		female with recurrent glioblastoma; latency 2-3 weeks ; no baseline LFTs but positive dechallenge; limited workup

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2014-131378/ (b) (6)/PLX-108-09/UNITED STATES/Male/62 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		male with metatstic melanoma; latency about 3 weeks ; probably related to PLX for initial increase in LFTs with positive dechallenge ; antibiotics likely responsible for the 2nd rise when admitted for cellulitis

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-115224/ (b) (6)/PLX-108-08/UNITED STATES/Male/74 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	could also be due to temozolamide	male with glioblastoma; latency about 4 weeks; either or both drugs could be responsible as they were started together [Temo associated with mixed/cholestatic injury in 12% of cases]

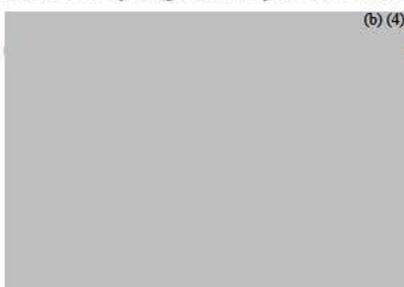
Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2, Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 June 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-117700/ (b) (6) PLX-108-08/UNITED STATES/Male/53 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	bactrim and dilantin as well as temozolomide	male with glioblastoma; latency about 2 weeks after receiving temozolomide; unlikely related to PLX but more likely due to Temozolomide given the positive rechallenge for that agent; confounded by two potentially hepatotoxic agents (bactrim and dilantin)

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-123981/ (b) (6)/IIS-UCSF-12751/UNITED STATES/Female/58 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	bone mets	female with metatstic breast Cancer ; latency about 1 month; probably related to PLX for initial rise in ATs and bili with ductopenia and cholestasis on liver biopsy but progressive bone disease likely explains progressive rise in alk phos (which was not fractionated)

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10-2-17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2015-133092(DSU-2015-135086), (b) (6) IIS-SPY2-097517/UNITED STATES/Female/60 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed R= 2-5	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 required liver transplant	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	secondary sclerosing cholangitis from acalculous cholecystitis? ?	60. y.o. female with breast Ca starts IP with paclitaxel in (b) (6) with last dose about 3 weeks later when she develops acalculous cholecystitis and undergoes lap chole with no CBD stones. Her LFTs continue to rise with liver Bx 10 days after last IP dose and 5 days after surgery showing cholestasis and bile duct loss. Despite Tx with urso, steroids she progresses over the course of the next 2 years and undergoes liver transplant in (b) (6) (with breast Ca in remission on letrozole). There is no pathology report of the explanted liver but VBDS seems likely as the cause of the progressive liver injury despite cholecystectomy (making me wonder whether the IP could have been responsible for the acalculous cholecystitis).

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction

(b) (6) kidney failure due to liver injury
 (b) (6) failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-134908/ (b) (6) IIS-UCSF-12751/UNITED STATES/Female/59 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	diffuse liver mets ; sepsis	female with metastatic breast cancer; latency about 3 months; PLX is possibly related; unlikely to be caused by eribulin (which rarely causes liver injury); the pt has progressive metatstatic disease

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-106629/ (b) (6)/PLX-108-07/UNITED STATES/Female/50 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		female with advanced solid tumor; latency about 3 weeks; limited evaluation but possible dechallenge; US showed no liver mets or dilated ducts; increased INR on xarelto

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-112210/ (b) (6) PLX-108-01/UNITED STATES/Female/44 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		female with giant cell tumor; complicated case; atypical for DILI and unlikely given marked increased LFTs 4 and 9 months after S.D had been discontinued; PLX was able to be restarted without a positive rechallenge for 6 months

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2, Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-125207/ (b) (6) PLX-108-10 (Blinded)/GERMANY/Female/75 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	statin	German female with giant cell tumor; latency 17 days from a normal baseline; liver Bx showed ductopenia and cholestasis 2 months after start of S.D.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/22/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-128875/DSU-2016-131117//PLX-108-14/UNITED STATES/Female/60 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	pembrolizumab	breast cancer; latency 2 weeks after first dose pembrolizumab which is the likely cause rather than PLX or eribulin since the ALT rose after pembro and responded to prednisone and there was a positive rechallenge with pembro.

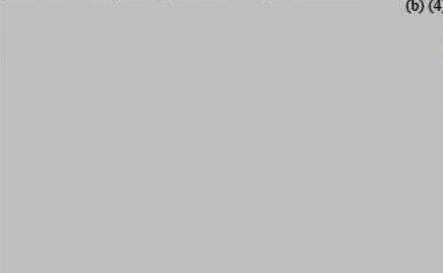
Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



9/22/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-129240/ (b) (6) PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	no con meds	giant cell tumor; latency about 4 weeks with symptoms jaundice, pruritus, nausea, vomiting; positive dechallenge after consistent latency and negative serology

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-130954/ (b) (6)/PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		female with giant cell tumor; latency about 6 weeks with symptoms ; 3 peaks in 75 days; positive dechallenge and positive rechallenge with eventual recovery

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-133478/ (b) (6)/PLX-108-10 (Blinded)/SPAIN/Female/67 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		giant cell tumor; latency 6 weeks; positive dechallenge

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-142567(2016PLX000087), (b) (6) /PLX108-07/UNITED STATES/Female/61 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	paclitaxel	latency 2 weeks with fever, nausea, vomiting; liver Bx 1 month after start of event showing severe cholestasis and ductopenia ; pt had disease progression resulting in hospice and eventual death about 4 months after start of S.D.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

9/23/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 23 Sept 2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2017-110948/ (b) (6)/PLX108-13/China/Female/61 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		female with metastatic melanoma; latency 5 weeks; positive dechallenge after PLX interrupted with negative rechallenge for ALT but positive rechallenge for alk phos

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



9/22/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10-2-17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2017-118366/ (b) (6)/PLX108-13/China/Female/66 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed R=3.3 for first event R=2.1 for 2nd flare	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 pt died	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	cholecystitis several weeks after IP discontinued	66 y.o female with vaginal melanoma has pre-existing mild elevations in AST and ALT with an acute rise (acute on chronic?) on the last day of the IP (latency 18 days) . There is then a positive dechallenge back to baseline ALT/AST until a 2nd flare occurs about 5 weeks later with progressive rise in AP and Bili likely due to cholecystitis. (or possibly VBDS from the initial reaction or progression of her underlying liver disease - but no liver biopsy). She dies 2 months later (no autopsy). The initial event is considered probably due to the IP but the 2nd event is considered unlikely for the reasons above.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSJ-2016-130232/ (b)(6)/PL3397-A-A103/TAIWAN, PROVINCE OF CHINA/Male/74 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Tumor type not specified many surgeries	On drug (b)(6) AP 64 ALT 128 AP 647 TB 2.64 R - 2.2 (Mixed)

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2014-129906(2012 PLX04022)/ (b) (6)/PLX-108-04/UNITED STATES/Female/58 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	On lemoz. since (b) (6)	Probable DILI on drug (b) (6) - (b) (6) (16 day) Clearance of baseline lab (b) (6) ALT 312 AST 924 PT 22.8 seconds (b) (6) ALT 137; AST 411 Prothrombin 3.7 (3.0 direct) AP 426 Definite Cholestatic features. Many features of severe injury.

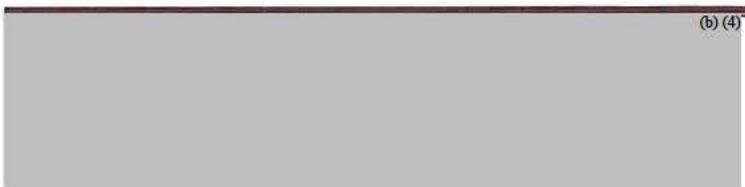
Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2014-131378/ (b) (6)/PLX-108-09/UNITED STATES/Male/62 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Melanoma Also on Vemurafenib (both started same time) Cannot determine which drug (or both) Contributed	Therapy (b) (6) Normal baseline Peak abnormalities (b) (6) ALT 641 Bili 1.0 important role was also given as combination for treatment of melanoma and both drugs initiated as same time Liver Biopsy (b) (6) "prominent cholestasis eosinophilia" "compatible with DILI"

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2015-115224/ (b) (6) /PLX-108-08/UNITED STATES/Male/74 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	also on famozolamide (b) (6) on drug (b) (6) Rash, jaundice	Cholestatic hepatitis pattern <hr/> ? which drug caused cholestasis

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-117700/ (b)(6)/PLX-108-08/UNITED STATES/Male/53 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed AP abnormal ↑ throughout on (b)(6) hepatocell. mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Chills, rash also on temozol. (b)(6) also on dilantin <hr/> ? role of other drug <hr/> Apparent Stevens-Johnson Syndrome <hr/> Negative dechallenge	one drug (b)(6) Lab tests normal unheld (b)(6) (b)(6) ALT 241 AST 83 <hr/> Also received temozolomide Labs ↑ AP

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b)(4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-123981/ (b)(6)/IIS-UCSF-12751/UNITED STATES/Female/58 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Also on eribulin Liver masses Ductopenia on liver biopsy	On SO (b)(6) (b)(6) started eribulin added drug ALT 352, AST 238 bilirubin 2.5 Total bilirubin 4.2 MRI multiple liver masses (b)(6) ALT 56 AST 51 AP 302 TBS 7.8 Pro time 15.8 ALT 194 AST 160 AP 659 Prol 10.3

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT > 2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos > 2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB > 2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b)(4)

Update
10/11/17

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/11/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-133092(DSU-2015-135086)/(b)(6)/IIS-SPY2-097517/UNITED STATES/Female/60 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <i>No</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 <i>Requires liver transplant</i>	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	(b)(6) <i>Cholestatic (acute) likely influenced results of tests T-103</i> <i>Liver Transplant (b)(6) after prolonged jaundice Pt. w/ 2+ and severe pruritus</i>	<i>Cholestatic with T-103 on (b)(6)</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b)(4)

(b)(6)
 Transplant in (b)(6)
 presumed related to liver disease causal by study drug

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2015-134908/ (b) (6) /IIS-UCSF-12751/UNITED STATES/Female/59 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Also on eribulin along with PLX Reaction possibly related to either drug	Study drug (97 days) (b) (6) AST 208, AP 402 Bilirubin 0.7 ALT 45 AP 364 Bilirubin 0.8 ALT 113 AP 347 Bilirubin 1.2

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-106629/ (b) (6)/PLX-108-07/UNITED STATES/Female/50 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		On study (b) (6) on R. Waroxaban (b) (6) also on paclitaxel du (b) (6) ALT 302, PT 14.7/sec on (b) (6) ALT 577 TBil 5.5 (direct 4.5). AP 435 Study drug interrupted Mixed hepatocellular/ cholestatic

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

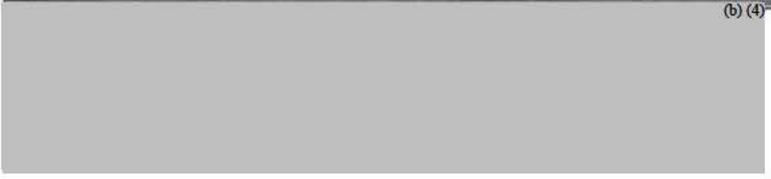
Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-112210/ (b) (6) /PLX-108-01/UNITED STATES/Female/44 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>See note</i>	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) (PBC) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	PBC / (+) AMA	Diagnosis of Primary Biliary Cholangitis. <i>Associated</i> on study drug (b) (6) Liver Biopsy - portal inflammation bridging fibrosis Difficult to determine roles of drug and PBC

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/2017

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-125207/ (b) (6) PLX-108-10 (Blinded)/GERMANY/Female/75 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	No other suspect drug	Ductopenia on Liver Biopsy on drug (b) (6) was jaundiced

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-128875/DSU-2016-131117//PLX-108-14/UNITED STATES/Female/60 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Combination therapy with Pembrolizumab —————→ Either or both drug may contribute	Either drug may be related

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-129240/ (b) (6)/PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Exact dates of treatment uncertain	On treatment (b) (6) (?) Not interpreted on (b) (6) (?) because of bilirubin increase (b) (6) TB 7.40 (direct 5.6) AST 174 ALT 371 9/2/16 AP 229 (prior AP value on (b) (6) 75 CT - no bile duct obstruction

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-130954/ (b) (6)/PLX-108-10 (Blinded)/UNITED STATES/Male/52 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		on study (b) (6) Positive rechallenges on different doses

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age			DSU-2016-133478/ (b) (6)/PLX-108-10 (Blinded)/SPAIN/Female/67 Years		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		On Study drug (b) (6) "Acute cholangitis" (b) (6) AP472, TB 60 umol

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/16

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2016-142567(2016PLX000087) (b)(6)/PLX108-07/UNITED STATES/Female/61 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Episode of acute Kidney injury Portal vein thrombosis (b)(6) ALT 12 AP 81 TB 0.3	Study drug (13 days). Fever (b)(6) Paclitaxel (b)(6) ALT 169, AST 273 Pacl 0.8 mg/dl (b)(6) ALT 169 AP 159 Bili 3.4 mg/dl. Also AKI

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b)(4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/22/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2017-110948/ (b)(6)/PLX108-13/China/Female/61 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Study drug (b)(6) Normal labs at baseline (b)(6) ALT 69. Direct Bilirubin 12.9 umol TB 20.6 umol, AP 311, ALT 569 (b)(6) ALT 424, TB 23.6 umol Later back to normal as regards labs Viral serologies negative

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b)(4)

*Re-evaluation
Update based on
additional information.*

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/4/17

Case Control #/Subject ID/Study#/Country/Gender/Age		DSU-2017-118366/ (b) (6) /PLX108-13/China/Female/66 Years			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 <i>Death</i>	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		<i>Vaginal melanoma Mild elevation ALT before therapy. Apparent positive dechallenge. TB 9.4 and 6 ? cholelithiasis Apparent vanishing bile duct syndrome. subsequently died → no autopsy</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib HEAC (b) (4)
Group 2 Case Review Meeting Minutes
Teleconference
Tuesday, October 17th 2017
1:00-1:35 PM EDT

HEAC Attendees:

(b) (4)
(Chair)

(b) (4) Attendees:

(b) (4)

Summary Notes:

The HEAC met and reviewed each of the 11 Group 2 cases and arrived at HEAC consensus decisions on liver injury pattern, severity score, relationship to study drug, and hepatic adaptation (yes/no) during their discussion. Specific case assessments are described within the case review forms. With respect to the Group 2 cases discussed today, the HEAC would like to note to DSI that the information presented was limited, particularly the lack of patient narratives, as were provided in Group 1 cases. By design, this limited the assessment the HEAC could make. For example, in some cases, additional information provided through narratives or other source materials may reveal confounding factors. Based on evaluation of all the data submitted, the HEAC must assume that changes in lab results are a result of the study drug. As such, the HEAC concludes it would have been in the best interest of DSI to provide patient narratives for these cases. Comments by individual members are included in the individual reviews along with the committee decision. With respect to the pattern of liver injury, the HEAC noted in their assessments that for some cases the elevations of liver tests fall below the criteria for the designated types of liver injury, and in those cases 'N/A' has been indicated in the appropriate location, without a specific choice made from the submitted form.

The attached By Committee case reviews have been adjudicated by the HEAC.

(b) (4)
HEAC Chair

10/26/17
Date

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 29 Sept 2017

Study-Subject ID		PLX108-10- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	none	62 y.o female with giant cell tumor (PVNS) develops marked ALT (891) and AST (307) about 1 mo after start of Tx from normal baseline values ; responds to dose reduction on 2 separate occasions and liver tests normalize 5 mo later.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT > 2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos > 2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB > 2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 9/29/17

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	no cn meds; DILI is possible; limited data	48 y.o male with PVNS has mild baseline elevations ALT with further increase 5-6 wks later on Tx ; there is a decrease back to near baseline with dose reduction within the next 3 wks; DILI is probable although the data are limited

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- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
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<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	none listed	27 y.o. female wit PVNS right knee devlops headache, itching, nausea, abd pain 1 day after randomization and 2 weeks later ALT (306)and AST(169) are elevated with a rise in alk phos. Despite dose reduction the values are increased 1 wk later and still elevated 3 wks after that (but lower). No workup is provided; the narrative mentions early termination one month after the last set of LFTs. I rate the drug as possibly related based on a partial dechallenge response.

Liver Injury pattern:

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 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
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Liver Injury pattern:

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 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
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Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed R=1 (but no LFTs are >2X); should be considered non-applicable	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	NSAIDs	40 y.o female with PVNS right knee with normal baseline AST? ALT and slightly elevated Alk phos has dose decreased per protocol and mild increase in AST>ALT 7-8 months after start of Tx. DILI is considered unlikely due to study med given the long latency; but could be due to con meds, including diclofenac

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

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2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
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<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed R=3	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		47 y.o female with PVNS left ankle and normal baseline LFTs has mild elevation ALT (96) and AST (74) with min rise in alk phos (123) and normal bili. 2 wks after start. These values occur 2 days before a migraine - but it is unclear if she takes and medication for migraine prior. Information is limited but DILI is possible, including possible tolerance

Liver Injury pattern:

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 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

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1. Elevation of AST/ALT usually transient and reversible (by adaptation)
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<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	lactobacillus for diarrhea	50 y.o male with PVNS right hip and normal baseline LFTs has mild rise in ALT (65), AST (67) and alk phos (128) after 6 months - and then normal LFTs for the next 8 months followed by an acute increase (ALT 216), AST (85) after receiving adenometionia (NAC?). DILI is considered unlikely based on the atypical time course

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
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<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly	NSAIDs	61 y.o. male with PVNS of right ankle has normal baseline LFTs and develops mild rise in ALT/AST after 30 days and further elevations peaking with ALT (136), AST (100) at day 165 ; with slow decline after dose reductions back to normal 4 mo later. NSAIDs are alternative causes; therefore DILI from study drug is possible as is possible drug tolerance

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/3/17

Study-Subject ID		PLX108-01 Subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed R=4.8	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		37 y.o female with PVNS develops acute rise in ALT>AST and AP with pruritus at the start of TX with the IP; thereafter the values decline and remain normal for >2.5 years on the IP . Total bili remains normal. There is no CIOMS or narrative.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10-3-17

Study-Subject ID		PLX108-01 Subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed R=0.36	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Augmentin started prior to mild rise in AST in Dec '12-Jan'13 for strep pharyngitis and influenza but ALT and AP were unchanged	32 y.o. male with PVNS has a marked elevation in alk phos at baseline that fluctuate mildly over the course of the IP; similarly the ALT remains WNL throughout. AST has a mild increase to <3X about 6 months after the start of the IP at a time when he is treated for strep pharyngitis and influenza-like symptoms

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<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed R=1.45	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	AST had a mild rise after use of sulindac (a classic cholestatic hepatotoxin) after about 6 mo after start of the IP (but alk phos was unchanged)	63 y.o male with PVNS develops a mild rise in AST>ALT and alk phos after about 1 month on IP with associated nausea, pruritus and rash . Thereafter, there are mild flucuations either just above or within the normal ranges with normal bilirubin consistent with a form of adaptation.

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Date: 10/10/17

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<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly	None	Normal ALT, AST, Pnl at baseline C (b) (6) on 2/1/16 (b) (6) ALT 846 AST 329, Luteinemia normal (b) (6) platelet count 104K ALT 31; AST 15 ALT 370 AST 189 Abnormalities resolved & while drug continued

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Liver Injury pattern:

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
- Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
- Mixed: $R 2-5$

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

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Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT > 2-3X ULN with normal Alk Phos)
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$$R = (ALT/ULN)/(Alk Phos/ULN)$$

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Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/10/17

Study-Subject ID		PLX108 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	<i>None noted</i>	<i>Early modest changes with increases in ALT, AST No change AP or Bilirubin</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/10/17

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		Late (>180 d on therapy) increases in ALT and AST. No elevations in bilirubin or ALP

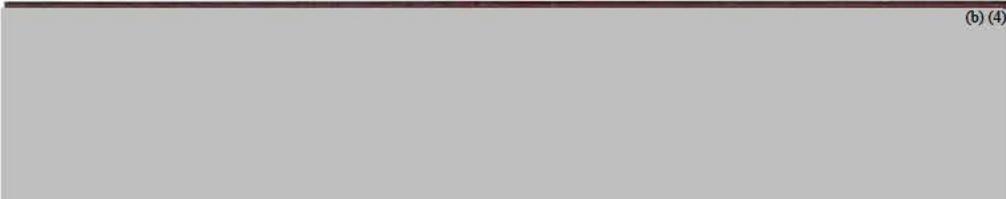
Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/10/17

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		Late appearing 140-160 day increase in ALT, AST with no evident progression. No change bilirubin or AP

Liver Injury pattern:

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
- Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
- Mixed: $R 2-5$

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB $> 2X$ ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/10/17

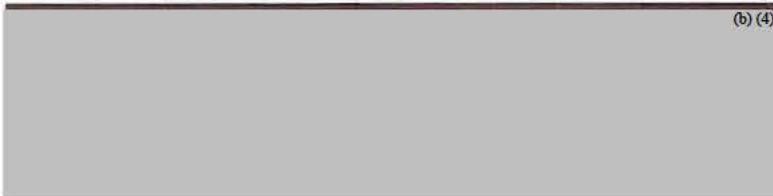
Study-Subject ID		PLX108-01 Subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <i>Really borderline changes</i>	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/10/17

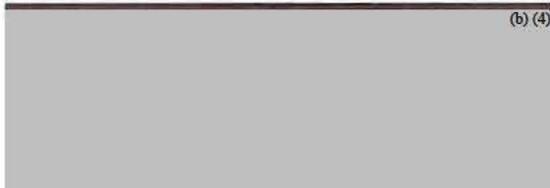
Study-Subject ID		PLX108-01 Subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>Trivial Changes</i>	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		<i>Trivial Lab Changes AST to 2-3x & 17% then fell ALT and AP stable</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/10/17

Study-Subject ID		PLX108-01 Subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		63 y M Only minimal changes in ALT/AST/AP during 360d treatment Designated minimal hepatocellular injury with early treatment normal & AP

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

*This case is trivial
 might be called mixed
 some slight ↑ ALT and AP appearing early*

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
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5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed N/A	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	con meds	N/A = liver pattern insufficient to judge

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		-limited information

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		-3 different stop dates included in source materials listed -about 1/2 year after therapy when event began

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 17Oct2017

Study-Subject ID		PLX108- (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		-multiple drug stop dates noted in provided source materials

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 17Oct2017

Study-Subject ID		PLX108-01 subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 17Oct2017

Study-Subject ID		PLX108-01 subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 17Oct2017

Study-Subject ID		PLX108-01 subject (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed N/A	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108-10- (b) (6) 62 yo female			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		Study drug: start date? (b) (6), modified dose (b) (6), dose modified (b) (6) NI transaminases at baseline, spike on (b) (6) down to nl on (b) (6) then spike (b) (6) down to nl (b) (6) (near) normal alk phos.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2, Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108- (b) (6) 46 yo latino male			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		Study dose (b) (6) elevated liver tests (b) (6) Baseline ALT 49. Elevated ALT373 and alk phos 179 (r-6.5) with nl dbili on (b) (6) sharp drop over 3 weeks. Drug resumed (b) (6) Negative rechallenge with modified dose

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108- (b) (6) 27 yo white female			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Drug started (b) (6) drug held (b) (6) for elevated transaminases, ALT 306, bili 26 $\mu\text{mol/l}$ (dbili 18), alk phos peak 206. 87 on (b) (6) Drug restarted (b) (6) ALT 197 (b) (6) Positive rechallenge.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4) Page 3

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/2017

Study-Subject ID		PLX108- (b) (6) 48 yo Hawaiian/Pacific Islander female			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly	No info provided on possible confounders	Drug start (b) (6) dose reduced (b) (6) last dose (b) (6) Baseline tests nl, ALI starts rising (b) (6) peak 174 on (b) (6) nl (b) (6) ni alk phos and bill.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108- (b) (6) 40 yo white female			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed N/A	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Drug started (b) (6) nl baseline transaminases, alk phos elevated at baseline, nl transaminases, trivial elevations ALT& AST; alk phos stays at baseline elevation. NAFLD (not on diabetes drugs)?

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/2017

Study-Subject ID		PLX108- (b) (6) 47 yo white female			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		Drug started (b) (6) (b) (6) NI baseline. Single spike of ALT and alk phos on (b) (6) then fluctuating trivial elevations of transaminases.R2.4. Likely adaptation plus underlying NAFLD, but could just be NAFLD. Pt is diabetic

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108- (b) (6) 50 yo white male			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Augmentin (b) (6)	Drug (b) (6)?? but at least still on drug (b) (6) elsewhere last dose (b) (6) (also stated as date of AS I elevation, day ~90). Transaminases start rising (b) (6) peak - (b) (6) nl alk phos and bili. Hard to adjudicate with conflicting stop dates of drug.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/2017

Study-Subject ID		PLX108- (b) (6) 61 yo white male			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Possibly		Drug (b) (6)? (should this be (b) (6)? Transaminase nl at baseline, elevated (b) (6) (b) (6) up to ALT136 at peak (3.3xULN), trivial increase dbili to 6 in (b) (6) ULN5μmol/l). unclear stop date drug makes it difficult to adjudicate

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108-01 Subject (b) (6) 37 yo white male			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		Drug (b) (6) drug held and then dose reduced for elevated liver tests; seems pt still on drug (b) (6) Elevated transaminases (b) (6) alk phos (b) (6) ALT 378, alk phos peak 249.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108-01 Subject (b) (6) 32 yo white male			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		Drug (b) (6) Baseline elevation of alk phos, remained elevated in the same range. Single value of elevated bili to 30 (ULN17). AST elevated up to 90 and fluctuating day 154-264 but nl ALT

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 10/13/17

Study-Subject ID		PLX108-01 Subject (b) (6) 63 yo white male			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed N/A	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		Drug (b) (6) (b) (6) Early elevation single value ALT 1.4ULN and AST 1.8ULN. ALT normalizes, AST fluctuates just above ULN, alk phos 3 values above ULN. All tests remain below 2ULN

Liver Injury pattern:

- Hepatoellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Adjudication Committee
Case Review Meeting Minutes
Teleconference
Friday, April 5th 2019

HEAC Attendees:

(b) (4)
[Redacted] (Chair)

Summary Notes:

The HEAC met and reviewed each of the 9 cases and arrived at HEAC consensus decisions on liver injury pattern, severity score, relationship to study drug, and hepatic adaptation (yes/no) during their discussion. Specific case assessments are described within the case review forms.

The attached By Committee case reviews have been adjudicated by the HEAC.

(b) (4)
[Redacted]

HEAC Chair

Date 4/5/19

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Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-10 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <input checked="" type="checkbox"/> none	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-05 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 <i>not relevant</i>	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-05 subject No (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <i>not relevant</i>	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-04 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5 <i>unrelated to drug</i>	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Adjudication Form (by Committee)

Date: 4/5/19

Study-Subject ID		PLX108-10 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input checked="" type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		

Could be repleting HAV. Relationship of drug to second peak unclear

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/28/19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <i>(Note comments)</i> <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Multiple other drug including <u>Levetiracetam</u> <u>Presence of fever</u> Possible gall bladder disease	Difficult to assess Factors: <u>Fever</u> Elevations <u>ALT and AP</u> Very elevated <u>AP</u> Marked elevation bilirubin Note: Study drug was not given for 10 days before jaundice appeared. No obvious alternatives but reports of gall bladder thickening, fever, must be considered. No evidence of cholelithiasis. I conclude a mixed pattern with consider increases in ALT and Alkaline Phosphatase Also must consider a contribution to levetiracetam

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/28/19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed (?) <i>Could be judged to be a mixed pattern</i>	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>None Noted</i>	<i>Very complicated and confusing protocol Does meet brochures criteria for Hy's law Had an acute onset and subsequent return to baseline after study drug discontinued.</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/29/19

Study-Subject ID		PLX108-10 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>Not much evidence of important liver changes</i>	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>Note clearly related to liver</i> <i>issue as to why PT prolonged</i>	<i>Very late onset (2 yrs) of any notable abnormalities</i> <i>Only test of concern is prolonged PT on 9/20/16 - not clear if cause for how long or poss on that date</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Case 4

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/29/19

Study-Subject ID		PLX108-05 subject No. (b) (6)		onset of treatment 12/26/13	
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <i>NR became of treatment events well after</i>	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No (see note) <input type="checkbox"/> Possibly	<i>Multiple</i> →	<i>Acute myeloid leukemia hx of unrelated donor stem cell transplantation. Hx GVHD Hx of vancomycin resistant enterococci Hx chronic Hepatitis B AT screen (b) (6)</i>

Liver Injury pattern: *initiation of treatment with 50*

- Hepatocellular: R > 5 (or AST/ALT > 2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos > 2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

*platelet count 59K
 absolute neutrophil (ANC) 0.22
 K/at
 Episodes documented sept 15
 (b) (6)
 on (b) (6) ALT 1165
 TB 3.5 - drug
 2.2
 Arrerial and drug (b) (6)*

- DILIN method definition of severity score:**
1. Elevation of AST/ALT usually transient and reversible (by adaptation)
 2. Also TB > 2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
 3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
 4. Acute liver failure with secondary brain or kidney failure due to liver injury
 5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Case 5 ↓

Case 5

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/28/19

Study-Subject ID		PLX108-05 subject No (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>abnormalities during terminal liver events sepsis/multiple</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input checked="" type="checkbox"/> <i>Not relevant to liver</i>	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly <i>see note)</i>	<i>Multiple AMU Multiple drops for cancer (AMU) Many infections and confounding hemt and blood tests Sepsis major</i>	<i>No reason to incriminate study drug in this complex setting</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Case 6

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 5/29/19

Study-Subject ID		PLX108-04 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Prolonged PT (was on warfarin)	58 year old female - (glioblastoma) Normal liver tests at baseline (b) (6) GI bleed (b) (6) Prolonged PT developed. (was on 12/27/12 treatment with warfarin) in hospital paxi interrupted (never again subsequently) (b) (6) Markedly increased (b) (6) AST on (b) (6) ACT 336, AST 612 TB 2.8 ALT 312 mg/dl Evidence of disease progression.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT > 2-3X ULN with normal Alk Phos)
 - Cholestatic: R < 2. Benign: Alk Phos > 2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB > 2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/29/19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <i>Cholestatic component apparently more prominent</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input checked="" type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>One gallstone Exclusion metastases</i>	<i>Exclusion metastases to liver. Cholestatic features prominent. Onset of cholestatic injury apparent soon after initiation of drug Clearly progression of function in liver</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
- 3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/30/19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <i>or Cholestatic</i> <i>R ~ 2</i>	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>Widespread metastases</i> <i>Role of additional agent pembrolizumab</i>	<i>TSF (fallopian - ovarian ca)</i> <i>On pexi + pembro (onset (b) (6))</i> <i>Normal baseline liver labs</i> <i>at 28 days on treatment ALT 135</i> <i>and nl bilirubin AST 89</i> <i>Liver Biopsy (b) (6) portal inflammation</i> <i>with ascospheps</i> <i>Subsequent con continuing</i> <i>additional elevations</i> <i>Peak (b) (6) ALT 246, ALP 294</i> <i>Bilirubin never increased</i> <i>Treatment interrupted (b) (6)</i> <i>Abnormalities gradually resolved</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/31/19

Study-Subject ID		PLX108-10 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <i>All could be from acute Hepatitis B and Hepatitis E</i>	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <i>Note comment</i>	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly <div style="border: 1px solid black; padding: 2px; display: inline-block;">Really NA</div>	Hepatitis B Hepatitis E	<i>Complicated made because of evidence supporting diagnosis of Hepatitis A and Hepatitis E</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/29/15

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Sepsis	Pex started Pt adm. then fever, chill, jaundice elevation ALP, AST, bili Lost lab, 29' ago r pt then to hospice

- Pt r glioblastoma.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/29/19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	None	43yo F, Taiwan, T6CT, Pex started 17 Aug 18. ALT/AST peak 4 Sep. but 11 Sep ALT + ALP 5xULN Last ALP 23 Oct still 2.5x uLN

Liver Injury pattern:

- Hepatocellular: $R > 5$ (or $AST/ALT > 2-3X$ ULN with normal Alk Phos)
- Cholestatic: $R < 2$. Benign: Alk Phos $> 2-3X$ ULN.
- Mixed: R 2-5

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB $> 2X$ ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/25/19

Study-Subject ID		PLX108-10 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>Abd pain</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly		Pex (b) (6) Almost 2 years into the drug, pt developed ldy of abd. pain. CT only showed hemangioma.

7/25/19, TGCS

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

4

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 4/3/19

Study-Subject ID		PLX108-05 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	Sepsis, starting, (b) (6), coded + direct (b) (6)	61y Asian F, U.S., F AMK On 11 th day of neutropenia Sepsis, AST 4270, ALT 1165, t bil: 3.5, d bil: 23, no ALP

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

5

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 4/3/19

Study-Subject ID		PLX108-05 subject No (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	CHF, hypotension	44yo AA ♀, c-AML, U/A. Pex started (b) (6) then (b) (6) (b) (6) bili grade 3 → resolved (b) (6) cardiac/respir failure on pressors, (b) (6) AST 39x ULN ALT 6x ULN, minimal change bili + ALk P

likely ischemic hepatitis

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 4/3/19

Study-Subject ID			PLX108-04 subject No. (b) (6)		
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <input checked="" type="checkbox"/>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		SB, ♀, glioblastoma, (b) (6) Pex 1000mg/d started (b) (6) AST 6xULN, ALT nb: nl ALP 1.2xULN on d, 17. Pex held (b) (6) D, 21, ALT 6xULN, AST (b) (6) 18xULN, ALP 2xULN, nb: (d, 17) ALT nb, d, 45, ALP nb, d, 45

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3/29/19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	Baseline ALP elevation. Extensive liver metastases	Pex started (b) (6) ALP gradually increases from 3x to 5x over 1 month ALT gradually increases to 3x. Pex + pembrolizumab stopped (b) (6) CT + labs including liver 54yo ♀ breast ca. baseline ALP ~ 3x ULN

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$$R = (ALT/ULN)/(Alk Phos/ULN)$$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 4/3/2019

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>R = 1.84</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>Pembrolizumab</i>	<i>75% P, fallopian tube oma. (b) (6) started Pembrolizumab + Pex 600mg. (b) (6) (d2) ALT AST ALP start increasing peak (b) (6) NL (b) (6) (b) (6)</i>

*peak ALT 246 (ULN 54) ~~11.4~~ 4.6 x ULN
 ALP 314 (ULN 126) 2.5 x ULN*

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 4/3/19

Study-Subject ID		PLX108-10 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed <i>R = 3.2</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input checked="" type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Possibly	<i>acute hepatitis A and E</i>	<i>54yo AA ♀ TGCT PEX 1000mg/d (b) (6) 800mg (b) (6) drug held (b) (6) (b) (6) Pex restarted 400mg/d (week 25). Second episode of mixed/cholestatic between week 26-29. ALP still elevated week 49</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

1

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-27-19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>R = 1</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input checked="" type="checkbox"/> Insufficient data <i>plh</i>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>con meds (Keppra) gallbladder disease (but ducts not dilated and no liver mets noted)</i>	<i>study drug was held 10 days prior to the event of jaundice and not restarted. No baseline values are provided and no outcome given (pt in hospice). but DILI seems unlikely</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-28-19

Study-Subject ID		PL3397-A-U126 (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed (R < 2)	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	none identified	Acute symptomatic cholestatic injury after about 3 wks on pexi with no sign of extrahepatic biliary obstruction. Complete resolution after 1 month off pexi (+ dechallenge).

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure



(b) (4)

Pexidartinib Hepatic Event Individual Case Adjudication Form

③

Date: 3-21-19

Study-Subject ID		PLX108-10 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed not elevated	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		baseline INR 1.45 that normalized and low platelets that normalized are unrelated abd pain, hepatomegaly, hepatic hemangioma, day 700 unrelated edema unlikely ↑ CPK day 700 unlikely

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

$R = (ALT/ULN)/(Alk\ Phos/ULN)$

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



4

Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-29-19

Study-Subject ID		PLX108-05 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>despite no Alk Phos with AST > 4000</i>	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>sepsis hypotension septic shock</i>	<i>Glyco. female with AMN s/p stem cell develops febrile neutropenia leading to septic shock with marked AST >> ALT consistent with hepatic hepatitis associated with hypotension.</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-29-19

Study-Subject ID		PLX108-05 subject No (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	septic shock with cardio-vascular collapse, AFib from effusion + pneumonia	44 y.o. female with AML develops pneumonia + respiratory failure leading to hypotension requiring vasopressors with AST >> ALT consistent with hypoxic hepatitis with relatively rapid recovery.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-29-19

Study-Subject ID		PLX108-04 subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input checked="" type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	likely had hypotension and kept having. ↑ INR on coumadin with GI bleeding.	58 y.o. female with glioblastoma develops hypoprothrombemiemia on coumadin and marked elevation in AST >> ALT which worsens after pexi is held and is most consistent with ischemic injury (hypoxic hepatitis) as it resolves quickly but due to disease progression she is discontinued from the study.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
- Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-28-19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed R < 2	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input checked="" type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input checked="" type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly		progressive increase from: ALP, AST > ALT and Silybinin that continued after 1 wk of pexi and pembro in the setting of progressive metastatic breast Ca (liver mets, possible carcinomatosis) with death 1 month after drugs were stopped Random liver biopsy findings did not suggest immune-mediated hepatitis from pembro (PD-1) and were nonspecific. Given the baseline abnormalities with progressive worsening of her underlying disease and negative dechallenge I consider pexi as unlikely to be related.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT > 2-3X ULN with normal Alk Phos)
- Cholestatic: R < 2. Benign: Alk Phos > 2-3X ULN.
- Mixed: R 2-5

R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB > 2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



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Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 3-29-19

Study-Subject ID		PLX108-14 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input type="checkbox"/> Hepatocellular <input checked="" type="checkbox"/> Cholestatic <input type="checkbox"/> Mixed <i>R = 1.95</i>	<input type="checkbox"/> 1 <input checked="" type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input checked="" type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	<i>pembrolizumab Liver mets (biopsy proven)</i>	<i>75 y.o. female with Papanian/ovarian carcinoma develops cholestatic injury with bile duct inflamm. on the combo of pexi + pembro after 6 weeks. There is a full dechallenge response after both agents are discontinued. Liver biopsy is not inconsistent with DILI (not autoimmune injury). seen with other cases of pexi.</i>

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R < 2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)



Pexidartinib Hepatic Event Individual Case Adjudication Form

Date: 4/11/19

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Study-Subject ID		PLX108-10 Subject No. (b) (6)			
Liver Injury Pattern	Severity Score	Relationship to Study Drug	Hepatic Adaptation	Confounding Factors	Comments by Individual Reviewer
<input checked="" type="checkbox"/> Hepatocellular <input type="checkbox"/> Cholestatic <input checked="" type="checkbox"/> Mixed	<input checked="" type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5	<input type="checkbox"/> Probable (>50% likelihood) <input type="checkbox"/> Possible (24-49% likelihood) <input type="checkbox"/> Unlikely (<24% likelihood) <input checked="" type="checkbox"/> Unrelated (excluded by another obvious cause) <input type="checkbox"/> Insufficient data	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Possibly	Acute hepatitis A = E	54 y.o female develops acute rise in ALT, AST, ALP on day 44 for which serology is positive for Hep A IgM and Hep E IgM with a gradual recovery back to normal over 4 months. She may have had the relapsing form of cholestatic Hep A.

Liver Injury pattern:

- Hepatocellular: R > 5 (or AST/ALT >2-3X ULN with normal Alk Phos)
 - Cholestatic: R <2. Benign: Alk Phos >2-3X ULN.
 - Mixed: R 2-5
- R = (ALT/ULN)/(Alk Phos/ULN)

DILIN method definition of severity score:

1. Elevation of AST/ALT usually transient and reversible (by adaptation)
2. Also TB >2X ULN after or concurrent (in the absence of cholestasis), indicating early functional loss (Hy's Law case)
3. Serious, meaning disabling, requiring or prolonging hospitalization because of liver dysfunction
4. Acute liver failure with secondary brain or kidney failure due to liver injury
5. Fatal or requiring liver transplant due to liver failure

(b) (4)

Appendix

Assessment of potential drug-induced liver injury of the present cases uses the grading system for likelihood of attribution and liver disease severity developed by the National Institutes of Health's Drug-Induced Liver Injury Network (DILIN) Study Group.*

Likelihood of Causality			
Score	Causality	Likelihood (%)	Textual Definition
1	Definite	≥ 95	Causality is "beyond a reasonable doubt"
2	Highly Likely	75-94	Causality supported by "clear and convincing evidence"
3	Probable	50-74	Causality supported by the "preponderance of the evidence"
4	Possible	25-49	Less than the preponderance of evidence but still possible
5	Unlikely	< 25	Causality unlikely or excluded

Disease Severity Scale		
Score	Grade	Definitions
1	Mild	Elevated ALT and/or Alk P but serum bilirubin < 2.5 mg/dL and INR < 1.5
2	Moderate	Elevated ALT and/or Alk P and serum bilirubin ≥ 2.5 mg/dl or INR ≥ 1.5
3	Moderate-Severe	Elevated ALT and/or Alk P and bilirubin or INR and new or prolonged hospitalization due to dili
4	Severe	Elevated ALT and/or Alk P and serum bilirubin ≥ 2.5 mg/dl and there is one of the following: -Hepatic failure (INR ≥ 1.5 , ascites or encephalopathy) -Other organ failure (renal/pulmonary) d/t dili
5	Fatal	Death or liver transplant from dili

*Fontana RJ, Seeff LB, Andrade RJ, Bjornson E, DayCP, Serrano J, Hoofnagle HJ. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology 2010;52:73-742

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BINDI M NIKHAR
06/23/2019 09:25:11 AM

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

PATIENT LABELING REVIEW

Date: June 18, 2019

To: Patricia Keegan, MD
Director
Division of Oncology Products 2 (DOP2)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)
Emily Dvorsky, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): TURALIO (pexidartinib)

Dosage Form and Route: capsules, for oral use

Application Type/Number: NDA 211810

Applicant: Daiichi Sankyo, Inc.

1 INTRODUCTION

On December 3, 2018, Daiichi Sankyo, Inc., submitted for the Agency's review an original New Drug Application (NDA) 211810 for TURALIO (pexidartinib) capsules. The proposed indication is for the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on December 18, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for TURALIO (pexidartinib) capsules.

2 MATERIAL REVIEWED

- Draft TURALIO (pexidartinib) capsules MG received on March 8, 2019, and revised on May 16, 2019, and received by DMPP and OPDP on June 7, 2019.
- Draft TURALIO (pexidartinib) capsules Prescribing Information (PI) received on December 3, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 7, 2019.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG, free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20

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

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
06/18/2019 02:17:15 PM

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

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

Memorandum

Date: June 17, 2019

To: Christy Osgood, M.D.
Division of Oncology Products 2 (DOP 2)

Nataliya Fesenko, PharmD, Regulatory Project Manager, (DOP 2)

Stacy Shord, PharmD, Associate Director for Labeling, (DOP 2)

From: Emily Dvorsky, PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Susannah O'Donnell, MPH, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for TURALIO™ (pexidartinib) capsules, for oral use

NDA: 211810

In response to DOP 2's consult request dated December 18, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for TURALIO™ (pexidartinib) capsules, for oral use.

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DOP 2 (Missiratch Biable for Nataliya Fesenko) on June 7, 2019, and are provided below.

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

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor on April 12, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Emily Dvorsky at (240)402-4256 or emily.dvorsky@fda.hhs.gov.

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EMILY M DVORSKY
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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2018372
IND/NDA/BLA Number/ Referenced IND for NDA/BLA:	NDA 211810/IND 117332
Sponsor/Applicant:	Daiichi Sankyo
Established Name/Trade Name:	Pexidartinib
Indication:	Treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT)
Meeting Type/Deliverable:	NDA Review
Review Division:	Division of Oncology Products 2
Clinical Reviewer	Christy Osgood
Clinical Team Leader (TL)	Lola Fashoyin-Aje
Review Division Project Manager:	Nataliya Fesenko
COA Reviewer:	Julia Ju, PharmD., PhD
COA TL:	Selena Daniels, PharmD., MS
COA Associate Director:	Elektra Papadopoulos, MD., MPH
Date Consult Request Received:	12/18/2018
Date COA Review Completed:	5/2/2019

Please check all that apply:

- Rare Disease/Orphan Designation
 Pediatric

A. EXECUTIVE SUMMARY

This Clinical Outcome Assessment (COA) consult review is related to NDA 211810 for pexidartinib currently under review. The proposed indication is treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

The Applicant used the following COAs in their randomized, double-blind, two-part, multi-center, placebo-controlled phase 3 trial (ENLIVEN):

Table 1. COAs Included in ENLIVEN Study

COA Name (COA Type)	Concept(s)	Endpoint Position ¹	Copy of COA
Range of motion (ROM) assessment (ClinRO)	Range of motion	Secondary	Appendix A
Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function (PRO)	Physical function	Secondary	Section 15.7 of Protocol PLX108-10 version 9.0
Worst stiffness (PRO)	Stiffness	Secondary	Section 15.6 of Protocol PLX108-10 version 9.0

¹ Please see Section C 1.3 of this COA review for the complete endpoint hierarchy.

ClinRO= Clinician-reported outcome; **PRO**= Patient-reported outcome

This submission included PRO evidence dossiers for the respective PRO instrument, as well as other study documents (e.g., clinical study protocol, clinical study report). However, the PRO data were not interpretable due to the high extent of missing data for the PRO instruments.

At the request of the Division, this review is restricted to the adequacy of the ROM assessment, including what constitutes a within-patient meaningful change in the assessment.

The review concludes the following:

- The ROM assessment appears fit-for-purpose² to measure range of motion in the context of use of this drug development program based on face validity and historical use of this type of assessment in clinical practice.
- The ROM assessment in the ENLIVEN Study appears to have been administered in a standardized manner, in principle. Raters appeared to be trained consistently upon review of the training materials.
- While there was concern regarding the use of different assessors within patients for baseline and follow-up visits, patients in both arms had a similar pattern and number of different assessors which mitigated concern of bias.
- There is insufficient evidence to support the reliability of the ROM assessment. Reliability was unable to be evaluated using the existing data because raters differed across and within-patients.
- There is insufficient evidence to support that a positive 6.7% threshold (i.e., 10-degree improvement) constitutes a clinically meaningful within-patient change for ROM at the knee. The Applicant's justification for this threshold at the knee was based on input from a single expert and review of literature, which is also very limited. No other thresholds were proposed for the other joints.
- Although the ENLIVEN study included patient global anchor scales, due to the substantial amount of missing data in these scales and all the other PRO instruments, an anchor-based approach was not feasible to derive a threshold or range of threshold(s) for meaningful within-patient change in the ROM assessment. While, Biostatistics generated waterfall plots that demonstrated that the range of within-patient change for all joints was between 7% and 19%, the threshold for meaningful within-patient change is unknown. Without knowledge of this threshold, it is difficult to link the ROM assessment to a clinical benefit attributable to the treatment.
- While there are limitations to data interpretation of ROM due to missing data (27%), based on discussions with Clinical and Biostatistics, the level of missing data is not as great of a concern as the PRO data.

²Fit-for-purpose: A conclusion that the level of validation associated with a tool is sufficient to support its context of use. (Source: BEST (Biomarkers, Endpoints and Other Tools) Resource; <https://www.ncbi.nlm.nih.gov/books/NBK338448/>)

For future medical product development, we recommend sponsors prospectively put in place procedures for minimizing missing data, including obtaining COA data from patients at time of early withdrawal, and include these procedures in the protocol. Reasons for missing COA data at the overall score- and item-level should be documented and included in the analysis dataset. Further, the threshold for meaningful within-patient change (improvement or deterioration) should be derived from anchor-based methods supplemented with empirical cumulative distribution function and probability density function curves. We recommend sponsors to engage FDA early (e.g., Pre-IND) and throughout drug development to discuss the COA endpoint strategy to ensure the selected instruments are fit-for-purpose and are well-defined and reliable for the context of use prior to initiation of pivotal studies.

B. CLINICAL OUTCOME ASSESSMENT REVIEW

1 BACKGROUND AND MATERIALS REVIEWED

Previous COA Reviews: None.

Disease Background: Tenosynovial Giant Cell Tumor (TGCT) is a rare, usually monoarticular, nonmalignant neoplasm involving the synovium and tendon sheaths that presents in young and middle-aged adults of both genders. Patients are usually diagnosed between the ages of 20 and 60 years and most often present with pain and swelling at the affected joint. Symptoms generally are minimal initially due to the slowly progressive nature of the disease; however, as the tumors expand within the intra-articular space and surrounding tissue tumors present with pain, stiffness, swelling, and reduced range of motion. TGCT is diagnosed from pathological evaluation; however, features highly suggestive of the disease may be found on radiologic imaging, particularly on magnetic resonance imaging (MRI).

Giant cell tumor of the tendon sheath (GCT-TS) is the localized type of TGCT most commonly occurring the wrist and finger joints. Pigmented villonodular synovitis (PVNS) is the diffuse type of TGCT most frequently involving the knee, but also may involve the ankle and hip. GCT-TS and PVNS have an estimated annual incidence of 1.8 cases per million and 9.2 cases per million, respectively, in the United States.

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.

Investigational Product: Pexidartinib is a first-in-class, oral small molecule inhibitor of molecule tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication (ITD) mutation. In preclinical studies pexidartinib inhibited the proliferation of cell lines that depend on CSF1R at concentrations below 1 $\mu\text{mol/L}$. Ligand-induced autophosphorylation of CSF1R is also inhibited by pexidartinib.

Other materials reviewed:

- Clinical Study Protocol PLX108-10 version 9.0
- Clinical Study Report PLX108-10
- Patient-reported Outcome (PRO) Evidence Dossiers
- Sponsor’s information request (IR) responses dated March 18, 25, 27 and April 2, 2019

2 FIT-FOR-PURPOSE SUMMARY

Table 2 summarizes the fit-for-purpose assessment.

Table 2. Fit-for-purpose assessment of ROM (based on available evidence)

COA Name(s)	Attribute sufficiently established ³	Supported by:	Location of Supporting Materials
ROM Assessment	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Potentially - insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> Fit for regulatory purposes (i.e., COA can be linked to a clinical benefit attributable to the treatment) <input type="checkbox"/> Evidence of content validity <input checked="" type="checkbox"/> Face validity (concepts/items appear relevant, e.g., based on discussion with clinical reviewer, clinician input, etc.) <input type="checkbox"/> COA well-defined and concept is able to be accurately communicated <input type="checkbox"/> COA is sensitive to detect change <input type="checkbox"/> COA is culturally adapted and adequately translated, if appropriate	ROM user manual

3 CONTEXT OF USE

3.1 Clinical Trial Population

The target population for the ENLIVEN Study are adult patients with diagnosis of PVNS or GCT-TS (i) that has been histologically confirmed either by a pathologist at the treating institution or a central pathologist, and (ii) where surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease), with morbidity determined consensually by qualified personnel (e.g., two surgeons or a multidisciplinary tumor board).

A complete list of the inclusion and exclusion criteria is summarized in the Clinical review.

Reviewer’s comment(s): *Most patients participated in the phase 3 trials had tumors in the knee (56% in the Study arm and 66% in the placebo arm). Many patients had tumors in the ankle (23% and 12% in the Study arm and the placebo arm, respectively). Some patients had tumors in*

³ See Sections 5 and 6 of this COA review for more detailed information.

the hip (10% and 12% in the Study arm and the placebo arm, respectively). About 10% patients had tumors in other joints.

3.2 Clinical Trial Design

Table 3 describes the clinical trial design of Study ENLIVEN.

Table 3. Clinical Trial Design for Study ENLIVEN

Trial Phase	Trial Design	Trial Duration	Registration Intent
Phase 3	<input type="checkbox"/> Single arm <input type="checkbox"/> Open label <input checked="" type="checkbox"/> Double-blind <input checked="" type="checkbox"/> Randomized <input checked="" type="checkbox"/> Placebo-/Vehicle-controlled <input type="checkbox"/> Active comparator-controlled <input type="checkbox"/> Cross-over <input checked="" type="checkbox"/> Multinational <input type="checkbox"/> Non-inferiority	24 weeks	Yes

Reviewer’s comment(s):

The ENLIVEN Study was a randomized, double-blind, two-part, multi-center, placebo-controlled trial designed to evaluate the efficacy and safety of pexidartinib compared with placebo for the treatment of patients with PVNS or GCT-TS. In Part 1, patients were stratified by region (U.S. vs. non-U.S. sites) and extremity involvement (upper extremity vs. lower extremity involvement). Eligible patients were randomly assigned in a 1:1 ratio to the study arm and the placebo arm.

3.3 Endpoint Position, Definition, and Assessment Schedule

Table 4 describes the intended placement of the COA in the endpoint hierarchy, including the endpoint definition and assessment schedule for Study ENLIVEN.

Table 4. Endpoint Position, Definition, and Assessment Schedule for Study ENLIVEN

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Primary	Magnetic resonance imaging (MRI)	Tumor shrinkage	Proportion of patients who achieve a complete response (CR) or partial response (PR) at Week 25.	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> Other: at Screening, Week 13 (Cycle 4, Day 1) and Week 25 <input type="checkbox"/> Assessment at cross-over or early discontinuation

Endpoint Position	Assessment (If COA, specify Name and Type)	Concept	Endpoint Definition	Assessment Frequency
Secondary	Range of motion (ROM; ClinRO)	ROM	Mean change from baseline in range of motion (ROM) of the affected joint, relative to a reference standard for the same joint at Week 25	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> Other: at Screening, at Weeks 13 and 25 <input type="checkbox"/> Assessment at cross-over or early discontinuation
Secondary	PROMIS [®] Physical Function (PRO)	Physical function	Mean change from baseline score in the PROMIS [®] Physical Function Scale	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> Other: at Screening, at Weeks 1, 9, 17 and 25 <input type="checkbox"/> Assessment at cross-over or early discontinuation
Secondary	Worst stiffness (PRO)	Stiffness	Mean change from baseline score in the Worst Stiffness NRS item	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> Other: at Screening, at Weeks 1, 9, 17 and 25 <input type="checkbox"/> Assessment at cross-over or early discontinuation
Secondary	BPI worst pain (PRO)	Pain	Proportion of responders based on BPI Worst Pain NRS item and narcotic analgesic use (BPI-30)	<input type="checkbox"/> Daily <input type="checkbox"/> Weekly <input type="checkbox"/> Monthly <input checked="" type="checkbox"/> Other: at Screening, at Weeks 1, 9, 17 and 25 <input type="checkbox"/> Assessment at cross-over or early discontinuation

ClinRO= Clinician-reported outcome **PRO**= Patient-reported outcome

Reviewer's comment(s): Based on blinded assessments of the database prior to the lock and unblinding of the data, the Applicant found a substantial amount of missing Week 25 PRO assessments, specifically for BPI Worst Pain NRS, PROMIS, and Worst Stiffness NRS. Because

of the high extent of missing data for the PRO instruments, per discussion with the Clinical and Biostatistics, the PRO assessment results are not interpretable. As such, this COA review is restricted to the ROM assessment the adequacy of the ROM assessment, including what constitutes a within-patient meaningful change in the assessment.

Table 5 shows the proportion of patients in the ITT population with missing COA data by treatment arm and visit.

Table 5: Proportion of Patients with Missing Data for COA Secondary Endpoints

	Pexidartinib (N = 61)			Placebo (N = 59)				
ROM								
<i>Visit</i>	<i>Baseline</i>	<i>Week 13</i>	<i>Week 25</i>	<i>Baseline</i>	<i>Week 13</i>	<i>Week 25</i>		
<i>% missing</i>	0	15%	26%	2%	10%	27%		
Physical Function								
<i>Visit</i>	<i>Baseline</i>	<i>Week 9</i>	<i>Week 17</i>	<i>Week 25</i>	<i>Baseline</i>	<i>Week 9</i>	<i>Week 17</i>	<i>Week 25</i>
<i>% missing</i>	2%	38%	36%	38%	3%	31%	32%	47%
Worst Stiffness								
<i>Visit</i>	<i>Baseline</i>	<i>Week 9</i>	<i>Week 17</i>	<i>Week 25</i>	<i>Baseline</i>	<i>Week 9</i>	<i>Week 17</i>	<i>Week 25</i>
<i>% missing</i>	3%	51%	39%	46%	2%	36%	49%	41%
BPI Worst Pain¹								
<i>Visit</i>	<i>Baseline</i>	<i>Week 9</i>	<i>Week 17</i>	<i>Week 25</i>	<i>Baseline</i>	<i>Week 9</i>	<i>Week 17</i>	<i>Week 25</i>
<i>% missing</i>	3%	51%	39%	46%	2%	36%	49%	41%

Source: Reviewer generated table – summarizing range of motion and questionnaire datasets (ADFA and ADQS, March 27, 2017 data cutoff date, submitted by Applicant)

¹Missing data characterized for BPI Worst Pain Questionnaire only. BPI-30 endpoint is defined to include narcotic analgesic use, which is also subject to missingness, increasing Week 25 missing data proportions to 46% and 41% for pexidartinib and placebo arms, respectively.

The reasons for missing ROM assessments at Week 25 are shown in Table 6

Table 6: Reasons for ROM Missing Data at Week 25 in the ITT Population

	Pexidartinib (N = 61)	Placebo (N = 59)
Completed	45 (74%)	43 (73%)
Missing	16 (27%)	16 (26%)
Discontinued Treatment		
Adverse event	8 (13%)	
Disease progression		1 (2%)
Investigator decision		3 (5%)
Subject non-compliance		1 (2%)
Withdrawal by subject	1 (2%)	5 (8%)
Other		
Missing baseline		1 (2%)
Out of window	2 (3%)	2 (3%)
Patient non-compliance		1 (2%)
Unknown	5 (8%)	2 (3%)

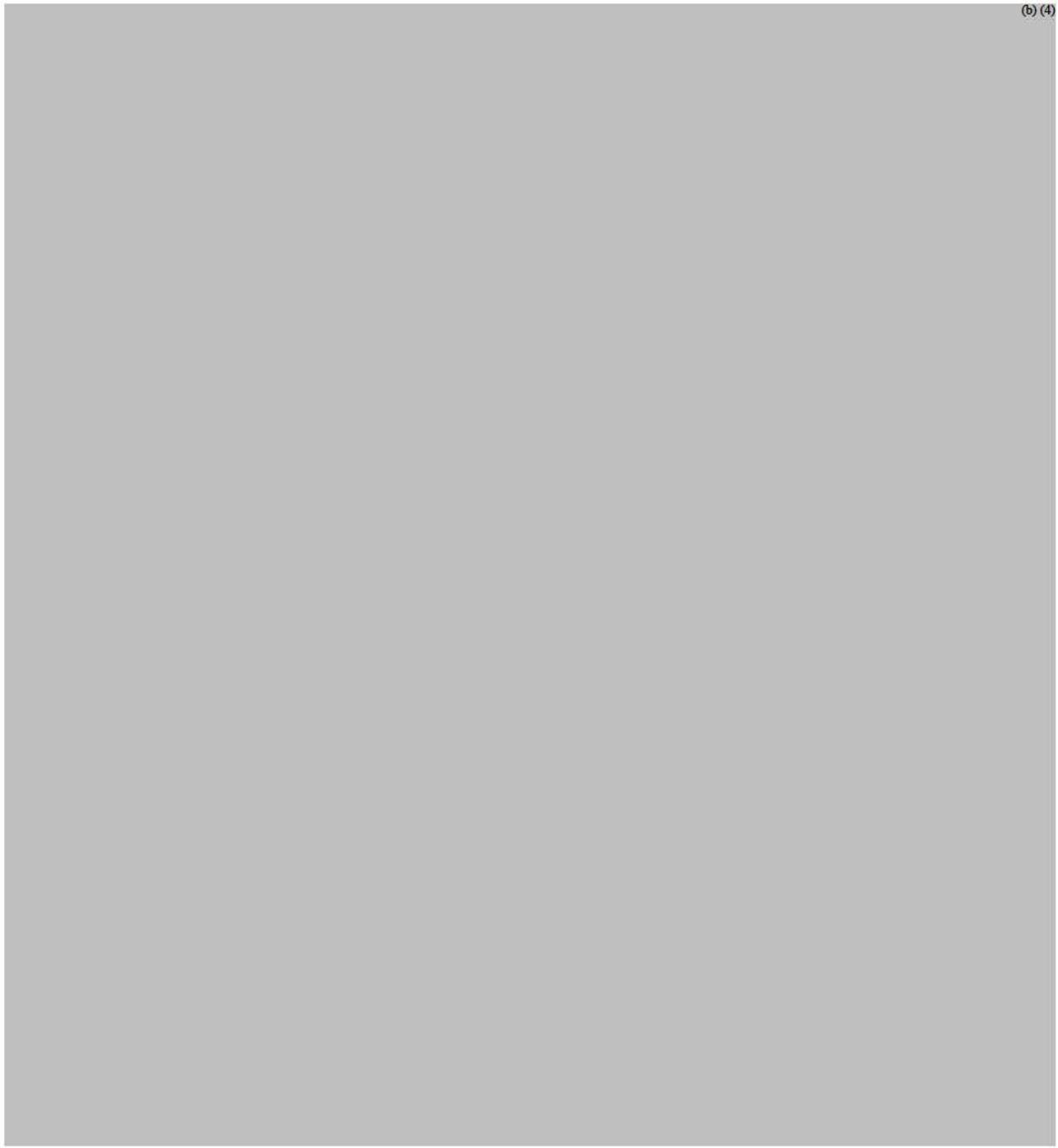
Source: Reviewer generated table – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

The most common reasons for missing data for physical function, worst stiffness, and BPI worst pain scores at Week 25 were site scheduling out of visit, patient non-compliance, discontinuation due to adverse event, and withdrawal by patient. It is unknown whether the missing data in the study arm and placebo arm are at random and impact of informative missing data if there is any.

3.4 Labeling or promotional claim(s) based on the COA

The sponsor has proposed specific targeted COA-related labeling claims

(b) (4)



Reviewer's comment(s): Based on discussion with Clinical and Biostatistics, (b) (4)
[REDACTED] the ROM
data may be presented in a graphical presentation.

4 CONCEPT(S) OF INTEREST AND CONCEPTUAL FRAMEWORK

The concepts of interest for the ROM are summarized in Table 7.

Table 7. Concepts of Interest for ROM Included in Study ENLIVEN

COA name	Concept(s)
ROM	Range of motion

Reviewer’s comment(s): ROM appears to be a clinically relevant concept for this target population based on discussion with Clinical. However, it is unclear how ROM (i.e., degrees of ROM) translates into clinical benefit (i.e., how patients function in their daily lives).

5 CLINICAL OUTCOME ASSESSMENTS

Range of Motion (ROM) Assessment

Range of motion assessment is designed to measure movement of joints in unit of degrees via a goniometer. Per the clinical study protocol, the same assessor evaluated the same patients over time, whenever the institution’s procedures and practical considerations allowed.

Reviewer’s comment(s):

For the ENLIVEN study, ROM was assessed by a qualified, independent, and blinded third-party assessors at the investigational sites, such as an orthopedic surgeon or a physical therapist, using goniometers according to a standardized method based on American Medical Association disability criteria. The assessor was not involved in other aspects of the study and was specially trained on ROM assessment procedures for this study by (b) (4)

At Baseline, the plane of movement with the smallest relative value (worst) was identified, and this plane was used for evaluating the relative change of motion subsequently; ie, only the plane with the most impaired ROM at Baseline was selected for subsequent analyses. In the event of ties, the multiple planes with the same relative value at Baseline were identified, and the average of relative values for each post-Baseline evaluation was calculated for the single ROM value. Details of the measurement procedure for each joint are presented in the Study Reference Manual (Clinical Study Report PLX108-10). Although the Applicant noted that the same assessor would evaluate the same patients over time to the extent possible, this was rarely the case. See Reviewer’s Comments in Section B.8.

In addition to ROM, the ENLIVEN study also included patient-reported outcome (PRO) instruments, which are described below.

Patient-Reported Outcomes Measurement Information System (PROMIS®) Physical Function

PROMIS® Physical Function is a patient reported outcome (PRO) instrument used to assess patients’ perspectives on their physical functioning, including functioning based on use of one’s upper extremities (dexterity), lower extremities (walking or mobility), and central regions (neck, back), as well as instrumental activities of daily living (IADLs).

Table 8 shows the subset of 15 items from the PROMIS® Physical Function item bank that were selected for inclusion in the assessment of functioning of upper extremities and lower extremities as it related to tumor location.

Table 8: PROMIS[®] Physical Function Item Bank Related to Tumor Location

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

The PROMIS[®] Physical Function items were completed via an electronic handheld device (LogPad) at Screening; Weeks 1, 9, 17 and 25; and post-treatment visit for Part 1.

Each item uses a 5-point verbal rating scale (1=“unable to do,” 2=“with much difficulty,” 3=“with some difficulty,” 4=“with a little difficulty,” and 5=“without any difficulty”). There is no specified recall period for the items.

The score for the PROMIS[®] Physical Function items is represented by a T-score (a standardized score with a mean of 50 and a standard deviation of 10) that ranges from 0 to 100, with a higher score indicating better physical function status.

Worst Stiffness NRS

This is a single item PRO instrument designed to assess “worst” stiffness at the site of the tumor. This instrument uses an 11-point NRS, ranging from 0 (“no stiffness”) to 10 (“stiffness as bad as you can imagine”). Patients in ENLIVEN were asked to recall their “worst” stiffness at the site of their tumor in the past 24 hours.

Patients used the LogPad to complete the Worst Stiffness NRS instrument at home during the seven consecutive days prior to Screening, Weeks 1, 9, 17 and 25; and post-treatment visit for Part 1. A minimum of four out of the seven days was required to compute the mean; otherwise it was set to missing. At baseline, patients completed the instrument during the two-week period prior to Cycle 1 to be consistent with the protocol schedule of study procedures. If there were multiple 7-day intervals, the most recent Worst Stiffness NRS score was used as the baseline value.

The score for the Worst Stiffness NRS item ranges from 0 to 10, with higher scores indicating greater severity of worst stiffness.

Brief Pain Inventory (BPI) Worst Pain NRS item

This is a single item PRO instrument designed to assess “worst” pain. This instrument uses an 11-point NRS, ranging from 0 (“no pain”) to 10 (“pain as bad as you can imagine”). Patients in ENLIVEN were asked to recall their “worst pain” in the past 24 hours.

Patients used the LogPad to complete the BPI Worst Pain NRS instrument at home during the seven consecutive days prior to Screening, Weeks 1, 9, 17 and 25; and post-treatment visit for Part 1. A minimum of four out of the seven days was required to compute the mean; otherwise it was set to missing. At baseline, patients completed the instrument during the two-week period prior to Cycle 1 to be consistent with the protocol schedule of study procedures. If there were multiple 7-day intervals, the most recent BPI Worst Pain NRS score was used as the baseline value.

The score for the BPI Worst Pain NRS item ranges from 0 to 10, with higher scores indicating greater severity of pain.

6 SCORING ALGORITHM

ROM Assessment

The value for a given joint was normalized to a reference standard, ie, full ROM for the same joint, to provide a relative value (Table 9). The reference standard was derived from American Medical Association disability criteria and was included in the SAP version 2.0.

Table 9: Reference standard for ROM

Joint	Movement	Expected Start Range (SR)	Expected End Range (ER)
Shoulder	1. Flexion	0°	180°
	2. Extension	0°	50°
	3. Abduction	0°	160°
	4. Adduction	0°	30°
	5. Internal Rot	0°	90°
	6. External Rot	0°	90°
Elbow	7. Flexion	0°-10°	150°
Wrist	8. Flexion	0°	80°
	9. Extension	0°	70°
Hip	10. Flexion	0°-10°	120°
	11. Extension	0°	30°
	12. Internal Rot	0°	40°
	13. External Rot	0°	50°
	14. Abduction	0°	45°
	15. Adduction	0°	30°
Knee	16. Flexion	0°-10°	150°
Ankle	17. Dorsiflexion	90°	70°
	18. Plantarflexion	90°	130°

ROM was calculated as follows (expressed in percent):

$$\text{Relative ROM} = 100 \times (\text{absolute ROM measured}) / (\text{reference ROM standard})$$

The value for a given joint was normalized to a reference standard (i.e., the full ROM for the same joint), to provide a relative value. In ENLIVEN, the reference standard was derived from American Medical Association disability criteria (Gerhardt JJ, 2002).

Reviewer's comment(s): The scoring algorithm is appropriate.

7 CONTENT VALIDITY

To date, the following information has been submitted (check all that apply):

- Copy of instrument
- Literature review and/or publications
- Documentation of expert input
- Qualitative study protocols and interview guides for focus group or patient interviews
- Chronology of events for item generation, modification, and finalization (item tracking matrix)
- Synopsis of qualitative findings
- Qualitative summary report with evidence to support item relevance, item stems and response options, and recall period
- Quantitative summary report with evidence to support item retention and scoring
- Transcripts (if available)

Table 10 documents the adequacy of the content validity of the ROM assessment.

Table 10. Review of Content Validity for the ROM assessment

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Face validity	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No	<input checked="" type="checkbox"/> Literature <input checked="" type="checkbox"/> Clinical input e.g. discussion with clinical reviewer	Not applicable
Content validity	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> The item concepts are relevant/important to target patient population and appropriate to the study design and objectives <input type="checkbox"/> The instrument is comprehensive with respect to the concept (i.e., does not omit important content) <input type="checkbox"/> Target sample for qualitative research is appropriate. <input type="checkbox"/> Studied sample for qualitative research adequately represents the	Not submitted

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
		target patient population <input type="checkbox"/> Instructions, item stems, recall period (if applicable), and response options well understood and appropriate for the study design and objectives <input type="checkbox"/> Response options appropriate for the item stems (measure the same dimensions, such as frequency or intensity) <input type="checkbox"/> COA is culturally adapted and adequately translated <input type="checkbox"/> Descriptive statistics (if available) support content relevance <input type="checkbox"/> Other (see Reviewer's comments)	

Testing other measurement properties (reliability, construct validity, and ability to detect change), while important, will not replace or rectify problems with content validity.

Reviewer's comment(s): ROM is considered to have face validity and content validity for this study population per discussion with the Clinical.

8 OTHER MEASUREMENT PROPERTIES

The Applicant did not submit any documentation to support the other measurement properties (reliability, construct validity and ability to detect change).

Table 11 documents the adequacy of the other measurement properties of the ROM assessment.

Table 11. Review of Other Measurement Properties for the ROM assessment

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
Reliability	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> Internal consistency reliability estimates in acceptable range (e.g., Cronbach's $\alpha > 0.70$) <input type="checkbox"/> Test-retest reliability (or intra-rater reliability) estimates in acceptable range (e.g., ICC ≥ 0.70) <input type="checkbox"/> Inter-rater reliability estimates in acceptable range <input checked="" type="checkbox"/> Other (see Reviewer's comments)	Not submitted
Construct validity	<input type="checkbox"/> Yes	<input type="checkbox"/> Relationship to other assessments with similar concepts is as expected	Not submitted

COA Attribute	Attribute sufficiently established	Supported by:	Location (i.e. page number) of Supporting Materials
	<input checked="" type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> Relationship to other assessments with dissimilar concepts is as expected <input type="checkbox"/> COA differentiates between clinically distinct groups (i.e., known groups validity) <input type="checkbox"/> COA scores are related to a known gold standard assessment of the same concept <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	
Ability to detect change	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> COA can identify differences in scores over time in individuals or groups who have changed with respect to the concept <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	Not submitted

Reviewer’s comment(s): *This reviewer sought to assess the reliability of the ROM assessment as the Applicant noted that the same assessor would evaluate the same patients over time to the extent possible. However, patients rarely had the same assessor across and within patients throughout the study as evidenced by the Applicant’s response to an information request.*

This reviewer requested the Applicant to specify the number of patients (including patient ID) and time points in which the same assessor was not used in the same patient for ROM assessment throughout the study period, if any, including the number of different assessors for each patient. The Applicant responded on March 25, 2019 that a total of 69 patients did not have the same assessor for all ROM assessments up to the data cutoff of 31 January 2018. Of these, 21 and 22 patients did not have the same assessor for all of assessments of Part 1, the placebo-controlled portion of the study, in the study arm and the placebo arm, respectively.

While there was concern that there were different assessors within patients for baseline and follow-up visits, the pattern and number of different assessors are similar in these two arms, which may cancel out the concern of potential bias introduced by using different assessors for the ROM measurement.

The existing data does not allow assessment of intra-rater and inter-rater reliability of ROM. In addition, because of the missing PRO data, the assessment of construct validity was not feasible.

9 INTERPRETATION OF SCORES

The Applicant did not submit any documentation to support the score interpretation of the ROM assessment.

Table 12 documents the adequacy of the score interpretability of the COAs.

Table 12. Review of Score Interpretability for ROM

COA Attribute	Attribute sufficiently established	Supported by:	Location of Supporting Materials
Score Interpretability	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> Potentially – insufficient evidence available; additional information is needed <input type="checkbox"/> No	<input type="checkbox"/> Appropriate global anchor scales were included for anchor-based analyses <input type="checkbox"/> Threshold(s) for within-patient meaningful change identified (anchor-based methods) <input type="checkbox"/> Threshold(s) for within-patient meaningful change identified (eCDF/PDF curves) <input type="checkbox"/> Qualitative data supports meaningful change threshold(s) (e.g., cognitive interviews, exit surveys/interviews) <input checked="" type="checkbox"/> Other (see Reviewer’s comments)	<i>No supportive evidence submitted except for the literature review¹⁻⁴</i>

Reviewer’s comment(s): *The clinically meaningful within-patient improvement in a joint’s range of motion (ROM) depends upon the specific joint involved and the degree of impairment at baseline, and consequently, there is not a widely used standard. The clinical meaning of ROM is most well established for the knee, which was the tumor location for 60.8% of patients in the Phase 3 Study PLX108-10, but even in this joint, a clinically meaningful improvement depends on the baseline ROM. A value of +6.7% (as % of reference range of motion) as the minimum clinically meaningful improvement difference (MCID) is suggested, based upon conversation with an expert orthopedic surgeon experienced with tenosynovial giant cell tumor* ^{(b) (4)}

experienced with tenosynovial giant cell tumor (TGCT) and a review of the literature.

The normal ROM for the knee is 150 degrees (Study PLX108-10 Clinical Study Report Appendix 16.1.10 Training Manual for Joint Range of Motion Assessment), and an improvement of 6.7% corresponds to a 10-degree improvement. The AMA Guide to Evaluation of Permanent Impairment Sixth Edition defines knee motion impairment by amount of knee flexion with mild impairment as 80-109 degrees, moderate impairment as 60-79 degrees, and severe impairment as <60 degrees. Based on the AMA classification, it is unclear whether a 10-degree improvement represents clinical benefit to patients with moderate or severe knee joint impairment. In conclusion, there is insufficient evidence to support that a positive 6.7% threshold (i.e., 10-degree improvement) constitutes a clinically meaningful within-patient change for ROM at the knee. The Applicant’s justification for this threshold at the knee was based on

input from a single expert and review of literature, which is also very limited. No other thresholds were proposed for the other joints.

Study PLX108-10 assessed ROM in parallel with Worst Stiffness Numerical Rating Scale (NRS) and Patient-Reported Outcomes Measurement Information System -Physical Function (PROMIS-PF), which are directly related to ROM; clinically meaningful improvement in range of motion should be also reflected by these other secondary endpoints. Although the ENLIVEN study included patient global anchor scales, due to the substantial amount of missing data in these scales and all the other PRO instruments, an anchor-based approach was not feasible to derive a threshold or range of threshold(s) for meaningful within-patient change in the ROM assessment. While Biostatistics generated waterfall plots that demonstrated that the range of within-patient change for all joints was between 7% and 19%, the threshold for meaningful within-patient change is unknown. Without knowledge of this threshold, it is difficult to link the ROM assessment to a clinical benefit attributable to the treatment.

While there are limitations to data interpretation of ROM due to missing data (27%), based on discussions with Clinical and Biostatistics, the level of missing data is not as great of a concern as the PRO data.

C. KEY REFERENCES

1. Beaupre LA, Davies DM, Jones CA, Cinats JG. Exercise combined with continuous passive motion or slider board therapy compared with exercise only: A randomized controlled trial of patients following total knee arthroplasty. *Physical Therapy*. 2001; 81(4):1029-37.
2. Bruun-Olsen V, Heiberg KE, Mengshoel AM. Continuous passive motion as an adjunct to active exercises in early rehabilitation following total knee arthroplasty – a randomized controlled trial. *Disability and Rehabilitation*. 2009;31(4):277-83.
3. Denis M, Moffet H, Caron F, Ouellet D, Paquet Ju, et al. Effectiveness of continuous passive motion and conventional physical therapy after total knee arthroplasty: A randomized clinical trial. *Physical Therapy*. 2006;86(2):174-85.
4. Rondinelli RD. *Guides to the Evaluation of permanent impairment* 6th ed. American Medical Association; 2007:543-550.

D. APPENDICES

Appendix A: Range of motion (ROM) assessment

Appendix A. ROM Assessment

Range of Motion Assessment:

Refer to manual for each joint regarding start range and end range points and recording instructions.

Subject Name: _____ Subject #: _____ Date: _____
(print name) (4 digit site # - 4 digit subject #) (DD MMM YYYY)

Assessor: _____ Assessor: _____
(print name) (signature)

Joint to be assessed will be identified by research coordinator and Assessor will confirm the affected joint with the subject before initiating assessment.

Affected Joint: _____ Right N/A
 Left

Joint	Movement	Start Range	End Range
Shoulder	Flexion		
	Extension		
	Abduction		
	Adduction		
	Internal Rotation		
	External Rotation		
Elbow	Flexion		
Wrist	Flexion		
	Extension		
Hip	Flexion		
	Extension		
	Abduction		
	Adduction		
	Internal Rotation		
	External Rotation		
Knee	Flexion		
Ankle	Dorsiflexion		
	Plantarflexion		
If OTHER Joint, please specify Joint and applicable Plane(s) of Movement below:			
Joint	Planes of Movement	Start Range	End Range

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/s/

JING JU
06/07/2019 09:47:24 AM

SELENA R DANIELS
06/07/2019 09:57:05 AM
Signing on behalf of Elektra Papadopoulos and Sarrit Kovacs (covering for Elektra) as they are on leave. Elektra reviewed and commented on COA review prior to her leave.

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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

Date of This Memorandum: April 18, 2019
Requesting Office or Division: Division of Oncology Products 2 (DOP2)
Application Type and Number: NDA 211810
Product Name and Strength: Turalio (pexidartinib) Capsules, 200 mg
Applicant/Sponsor Name: Daiichi Sankyo, Inc.
FDA Received Date: April 12, 2019
OSE RCM #: 2018-2054-1
DMEPA Safety Evaluator: Colleen Little, PharmD
DMEPA Team Leader: Chi-Ming (Alice) Tu, PharmD

1 PURPOSE OF MEMORANDUM

Division of Oncology Products 2 (DOP2) requested that we review the revised container labels and carton labeling for Turalio (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised container labels and carton labeling for Turalio are acceptable from a medication error perspective. We have no further recommendations at this time.

^a Little, C. Label and Labeling Review for Turalio (NDA 211810). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 APR 03. RCM No.: 2018-254.

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

/s/

COLLEEN L LITTLE
04/18/2019 11:24:10 AM

CHI-MING TU
04/18/2019 12:17:24 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
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Division of Pediatric and Maternal Health Memorandum

Date: April 15, 2019 **Date Consulted:** January 7, 2019

From: Jane Liedtka M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Nataliya Fesenko, Pharm.D, R.Ph, Regulatory Project Manager (RPM)
Office of Hematology and Oncology Products (OHOP)
Division of Oncology Products 2 (DOP2)

Drug: Tulario (pexidartinib)

NDA: NDA 211810

Proposed Indication:

Treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.

Applicant: Daiichi Sankyo, Inc.

Subject: Pregnancy and Lactation labeling [New Drug Application (NDA) for an NME (new molecular entity), Pregnancy and Lactation Labeling Rule (PLLR) content and format]

Materials Review

- Applicant's submitted background package for NDA 211810, 12/3/18.

Consult Question: Please review the clinical data for pregnant women (see excerpted text from labeling subsection 8.1 that refers to this data). The summary of clinical safety identified 2 “pregnant” patients – 1 with elective termination and 1 with spontaneous abortion... Please provide your comments regarding clinical data in pregnant women.

INTRODUCTION AND BACKGROUND

On January 7, 2019, DOP2 consulted DPMH to provide input for appropriate format and content of the pregnancy and lactation sections of Tulario (pexidartinib) labeling to be in compliance with the Pregnancy and Lactation Labeling (PLLR) format.

- On December 3, 2018, the Agency received an NDA, 211810 for Tulario (pexidartinib) for adult patients with TGCT.

REVIEW

TGCT

TGCT is a rare non-malignant neoplasm involving the synovium and tendon sheaths that typically presents in young and middle-aged adults of both sexes. TGCT is usually a mono-articular disease that involves the bone, soft tissue, synovium, or tendon sheath of small or large joints.¹ Symptoms initially may be minimal due to the slowly progressive nature of the disease, but as the tumor mass grows and gradually expands within the intra-articular space and surrounding tissue; symptoms such as pain, stiffness, swelling, and reduced range of motion (ROM) of the affected joint can become severe and result in marked functional limitation.

The localized type of TGCT, also known as GCT-TS, is usually a benign neoplasm, most commonly occurring in the digits. The diffuse type of TGCT (also referred to as PVNS), is a locally aggressive, non-malignant neoplasm which may be intra-articular or extra-articular. Diffuse TGCT most commonly occurs in large joints, particularly the knee as well as the ankle and hip. Diffuse TGCT and localized TGCT have an estimated annual incidence of 1.8 cases per million and 9.2 cases per million, respectively, in the US based on a study from 1980.² A more recent study in Denmark reported an estimated incidence in digits, localized-extremity, and diffuse-type TGCT of 34, 11 and 5 per million person-years, respectively. All 3 groups showed a female predilection and highest number of new cases was in the age category of 40 to 59 years³.

The current standard of care for TGCT is surgical resection of the tumor as completely as possible to: (1) reduce pain, stiffness, and joint destruction caused by the disease process; (2) improve function; and (3) minimize the risk of recurrence, but diffuse disease can be challenging to manage surgically. The overall recurrence rate for patients with focal disease

¹ Monaghan H et al. Giant cell tumour of tendon sheath (localized nodular tenosynovitis): clinicopathological features of 71 cases. *J Clin Pathol.* 2001; 54:404-7.

² Myers BW, and Masi AT. Pigmented villonodular synovitis and tenosynovitis: a clinical epidemiologic study of 166 cases and literature review. *Medicine.* 1980; 59(3):223-38.

³ Mastboom MJL et al. Higher incidence rates than previously known in tenosynovial giant cell tumors. *Acta Orthop.* 2017 Dec; 88(6):688-694.

is low, ranging from 0% to 6%; however, in patients with diffuse forms of the disease, recurrence is considerably more common, and is estimated to be in the range of 15% to 40%.⁴ Diffuse disease carries a risk of multiple recurrences, and affected patients often have more extensive involvement and a poorer likelihood of success with surgery. Surgical resection may involve removal of major tendons or neurovascular structures, leading to significant post-surgical morbidity. Limb amputation may be required in severe, recurrent cases.⁵

TGCTs predominantly consist of mononuclear and multinucleated giant cells. Expansion of the tumor mass appears to be driven by the presence of abundant colony stimulating factor-1 (CSF-1) expressing cells, a subset of neoplastic cells within the tumor.⁶

No systemic antitumor agents are approved for this indication. Pexidartinib demonstrated strong tumor response in TGCT in Phase 1 clinical studies.⁷ Pexidartinib is a novel, orally active, small molecule receptor tyrosine kinase inhibitor that selectively targets CSF-1R and the kinase receptors KIT and FLT3-ITD. As a selective inhibitor of CSF-1R, pexidartinib was developed as a possible new therapeutic option for patients with TGCT.

Pregnancy

Nonclinical Experience

In animal reproduction studies, administration of pexidartinib during organogenesis resulted in embryo-fetal toxicities in rats and rabbits (approximately 0.9 times and 0.8 times the exposure (AUC) at the recommended human dose of 800 mg/day, respectively). These included adverse effects on embryo-fetal survival and fetal malformations including urogenital and skeletal anomalies.

For further details, the reader is directed to the Nonclinical Review by Jeanne Fourie Zirkelbach, Ph.D.

Applicant's Review of Literature

The Applicant did not perform a review of the literature.

DPMH's Review of Literature

DPMH conducted a search of published literature in PubMed and Embase using the search terms “pexidartinib and pregnancy”, “pexidartinib and pregnancy outcomes”, “pexidartinib and pregnant women,” “pexidartinib and pregnancy and birth defects,” “pexidartinib and pregnancy and congenital malformations,” “pexidartinib and pregnancy and stillbirth,” “pexidartinib and spontaneous abortion” and “pexidartinib and pregnancy and miscarriage.”

⁴ Ushijima M et al. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. *Cancer*. 1986; 57(4):875-84.

⁵ Mastboom MJL et al. Limb amputation after multiple treatments of tenosynovial giant cell tumour: series of 4 Dutch cases. *Case Reports in Orthopedics*. 2017; 1-6.

⁶ Molena B et al. Synovial colony stimulating factor-1 mRNA expression in diffuse pigmented villonodular synovitis. *Clin Exp Rheumatol*. 2011; 29:547-50.

⁷ Tap WD et al. Structure-guided blockade of CSF1R kinase in tenosynovial giant-cell tumor. *N Engl J Med*. 2015; 373:428-37.

No reports of adequate and well-controlled studies of use in pregnant women were identified. No case reports were identified.

Pexidartinib is not referenced in *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*⁸ or in Micromedex⁹.

Pharmacovigilance Database (PVDB) Summary

According to the Applicant, two subjects became pregnant during pexidartinib clinical trials while on treatment; both were TGCT subjects in the PLX108-10 study.

- PLX108-10 Subject No. (b) (6): a 36-year-old female with localized pigmented villonodular synovitis of the elbow received pexidartinib 1000mg on day 1 for the study; the dose of pexidartinib was reduced to 800mg/day starting on day 15 of the study. The patient had no relevant medical history but was taking ethinyl estradiol/norgestimate, ibuprofen gel, zolpidem, oxycodone/paracetamol, oxycodone and tramadol. The subject had a positive B-human chorionic gonadotropin (B-HCG) on day 225 of the study, and a transvaginal ultrasound revealed an intrauterine pregnancy. Treatment with study drug was interrupted after the positive pregnancy test and resumed after elective termination of the pregnancy on day 232 of the study. There is no further information provided on the pregnancy.
- PLX108-10 Subject No. (b) (6): a 42-year-old female with localized pigmented villonodular synovitis of the ankle became pregnant while on pexidartinib. The patient had no other medical history and had two normal prior pregnancies. The patient was also taking celecoxib. On (b) (6) (Day 776), the subject had a urinary pregnancy test positive for B-HCG. On the same day, the subject underwent an ultrasound, which confirmed pregnancy. At the time when pregnancy was diagnosed, the subject's estimated gestational age was reported as 4 weeks. Pexidartinib was interrupted due to pregnancy, with the last dose taken on (b) (6) the subject experienced genital bleeding, associated with pelvic pain and the subject was admitted to the emergency room. Ultrasounds revealed an empty gestational chamber. The subject was reported with miscarriage (b) (6). The treatment with pexidartinib was resumed (b) (6) at a dose of 800 mg once daily.

Lactation

Nonclinical Experience

There is no information from animal studies regarding pexidartinib and lactation.

Applicant's Review of Literature

The Applicant did not perform a review of the literature.

DPMH Review of Literature

DPMH conducted a search of *Medications and Mother's Milk*¹⁰, the Drugs and Lactation Database (LactMed),¹¹ Micromedex⁸, and of published literature in PubMed and Embase

⁸ Briggs, GG, Freeman, RK, & Yaffe, SJ. (2015). *Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk*. Philadelphia, Pa, Lippincott Williams & Wilkins.

⁹ Truven Health Analytics information, <http://www.micromedexsolutions.com/>. Accessed 10/18/18.

using the search terms “pexidartinib and lactation”, “pexidartinib and breastfeeding”. No reports of adequate and well-controlled studies of pexidartinib use in lactating women were found. No case reports were found.

According to proposed labeling, the molecular weight of pexidartinib is ≈ 454 for the hydrochloride salt and ≈ 418 for the free base. Pexidartinib is $> 99\%$ protein bound. The mean elimination half-life is ≈ 27 hours. The most common adverse reactions (incidence $> 20\%$) are hair color changes, increase in serum transaminases (AST, ALT, ALP), fatigue, nausea, eye edema, rash, and dysgeusia.

Pexidartinib is not referenced in LactMed¹⁰, in Hale’s *Medications and Mother’s Milk⁹ or in Drugs in pregnancy and lactation: a reference guide to fetal and neonatal risk.*⁷

Use in Females and Males of Reproductive Potential

Nonclinical Experience

Carcinogenicity study was conducted in rats and mice, both studies were negative. Pexidartinib was not genotoxic in in vitro or in vivo assays.

In a fertility and early embryonic development study, at the highest dose in male rats, approximately 0.9 times the exposure (AUC) at the recommended human dose of 800 mg/day, lower testicular and epididymal weights and adverse effects on sperm concentration, production, motility, and morphology were associated with lower mean fertility and copulation/conception indices indicating an effect on male reproductive performance...

In a 26-week repeat dose rat study, germ cell depletion of the testes and hypospermia and cellular debris in the epididymis were noted in male reproductive tissues at doses of 20 and 60 mg/kg/day (approximately 0.6 times and 1.5 times the exposure (AUC) at the recommended human dose of 800 mg/day). In females, necrosis of corpora lutea in ovaries was noted at approximately 0.01 times the exposure (AUC) at the recommended human dose of 800 mg/day and pigment deposition within the interstitium of the ovaries, an increased incidence of luteal cysts and incidence/severity of hemorrhage of corpora lutea, and a decreased incidence of retained antral follicles and decreased corpora lutea of the ovaries was noted at 60 mg/kg/day. Following a 16-week recovery period, persistent changes in animals given 60 mg/kg/day included germ cell depletion of testes and hypospermia.

For further details, the reader is directed to the Nonclinical Review by Jeanne Fourie Zirkelbach, Ph.D.

¹⁰ Hale, Thomas (2012) Medications and Mothers’ Milk. Amarillo, Texas Hale Publishing, pg. 422-423.

¹¹ <http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?LACT>. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

Applicant's Review of Literature

The Applicant did not conduct a review of the literature regarding pexidartinib and its effects on fertility.

DPMH's Review of Literature

DPMH conducted a search of the published literature in PubMed and EMBASE using the terms "pexidartinib and fertility", "pexidartinib and infertility", and "pexidartinib and reproduction" and found no relevant human literature.

DISCUSSION AND CONCLUSIONS

Pregnancy

There are no human pregnancy outcome data for pexidartinib in the published literature and just two cases of pregnancy in the applicant's PVDB. The findings in animal studies were suggestive of risk to the fetus. The Applicant recommended a (b) (4) "Warning and Precaution" (W&P) regarding the use of pexidartinib in pregnancy based on the animal studies. However, DPMH does not agree with the Applicant and recommends a W&P alone, (b) (4) This would be consistent with other kinase inhibitors with similar findings in animal studies that have (b) (4) been labeled with a W&P. DPMH discussed the findings in the animal studies with the pharmacology toxicology (PT) team and the clinical team from DOP2 via email, and the division agreed with our proposal. See DPMH proposed labeling below for further details.

Lactation

There are no data on the presence of pexidartinib in animal or human milk. Although pexidartinib has a molecular weight that is less than 800 Daltons (≈ 454 Daltons), the drug's high protein binding would limit the amount of the drug getting into breastmilk. However, because of the potential for serious adverse reactions in the breastfed infant (or child), including hepatotoxicity, advise patients that breastfeeding is not recommended during treatment with pexidartinib. See DPMH proposed labeling below for further details.

Females and Males of Reproductive Potential

Due to evidence of embryofetotoxicity seen in animals, pregnancy testing is recommended for females and reproductive potential, and effective contraception is recommended for both males and females of reproductive potential during treatment with pexidartinib based on the updated *Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations: Guidance for Industry* from September 2017. According to the guidance, the following are recommendations for nongenotoxic drugs that have the potential to cause teratogenicity:

- Male patients with female partners should use effective contraception for one month after the last dose of pexidartinib (5 x half-life (27 hours) +3 weeks)
- female patients taking pexidartinib should use effective contraception for 1 month after the last dose of the drug (5 x half-life or one menstrual cycle (30 days, whichever is longer).

Animal reproductive studies of administration of pexidartinib did show adverse effects on fertility in male and female rats. There are no human data available on the effect of

pexidartinib on fertility. Therefore, labeling will include information about fertility in subsection 8.3.

See DPMH proposed labeling below for further details.

LABELING RECOMMENDATIONS

DPMH revised the HPI, sections 4, 5.3, 8.1, 8.2, 8.3 and 17 of pexidartinib labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Tulario (pexidartinib) Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

-----WARNINGS AND PRECAUTIONS-----

Embryo-Fetal Toxicity: May cause fetal harm. Advise (b) (4) of reproductive potential of the potential risk to a fetus and to use an effective method of contraception (5.3, 8.1, 8.3)

-----USE IN SPECIFIC POPULATIONS-----

- Lactation: Advise not to breastfeed. (8.2)

FULL PRESCRIBING INFORMATION

5.3 Embryo-fetal Toxicity

(b) (4)

Advise pregnant women of the potential risk to the fetus.

Advise females of reproductive potential to use effective contraception during treatment with TURALIO and for 1 month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with TURALIO and for (b) (4) after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

8 Use in Specific Populations

8.1 Pregnancy

Risk Summary

(b) (4)

Oral administration of pexidartinib to pregnant animals during the period of organogenesis resulted in malformations, post-implantation loss, and abortion at maternal exposures that were approximately (b) (4) (see *Data*).

Advise pregnant women of the potential risk to the fetus.

(b) (4)

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

Embryo-fetal development studies investigating the administration of pexidartinib during the period of organogenesis were conducted in rats and rabbits. In rats, pexidartinib resulted in increased post-implantation loss and fetal malformations including localized fetal edema, absence of kidney and ureter, abnormalities of the reproductive tract, and (b) (4) (approximately (b) (4) the human exposure at the recommended dose of 800 mg). In rabbits, administration of pexidartinib resulted in increased post-implantation loss, abortion, and fetal malformations including absence of kidney or ureter, misshapen or mal-positioned kidney, rib abnormalities, and accessory skull bones at doses of 60 mg/kg (approximately (b) (4) the human exposure at the dose of 800 mg).

8.2 Lactation

Risk Summary

There are no data on the presence of pexidartinib in human milk, the effects on the breastfed infant, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed infant, including hepatotoxicity, advise patients that breastfeeding is not recommended during treatment with TULARIO and for one week after the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

(b) (4)

Contraception

(b) (4)

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TULARIO and for 1 week after the last dose. [see *Nonclinical Toxicology (13.1)*].

Infertility

Based on findings in animals, TULARIO may impair male and female fertility [see *Nonclinical Toxicology (13.1)*].

17 PATIENT COUNSELING INFORMATION

Embryofetal Toxicity

- Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions (5.X)* and *Use in Specific Populations (8.X)*].
- Advise females of reproductive potential to use effective contraception during treatment with TULARIO and for one month after the last dose [see *Use in Specific Populations (8.3)*]
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for one week after the last dose

Lactation

- Advise females not to breastfeed during treatment with TULARIO and for one week after the final dose [see *Use in Specific Populations (8.2)*].

Infertility

- Advise females and males of reproductive potential that TULARIO may impair fertility [see *Use in Specific Populations (8.3)* and *Nonclinical Toxicology (13.1)*].

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/s/

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Clinical Inspection Summary

Date	April 11, 2019
From	Navid Homayouni, M.D., Medical Officer Susan Thompson, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Nataliya Fesenko, Pharm.D., Regulatory Project Manager Christy Osgood, M.D., Clinical Reviewer Lola Fashoyin-Aje, M.D., Cross Discipline Team Leader Division of Oncology Products 2
NDA #	211810
Applicant	Daiichi-Sankyo, Inc.
Drug	Pexidartinib
NME	Yes
Therapeutic Classification	Standard
Proposed Indication	Treatment of tenosynovial giant cell tumor, also known as giant cell tumor of the tendon sheath and previously referred to as pigmented villonodular synovitis.
Consultation Request Date	December 27, 2018
Summary Goal Date	April 15, 2019
Action Goal Date	August 2, 2019
PDUFA Date	August 3, 2019

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data from Clinical Study, Protocol PLX108-10 was submitted to the FDA in support of a proposed indication for NDA 211810. This was “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.” The data for Study Protocol PLX108-10 submitted by the sponsor to the Agency in support of NDA 211810 appear reliable based on available information from the inspections of one domestic and two foreign clinical sites.

Three clinical sites, Marilena Cesari, M.D. (Site 1432), Hans Gelderblom, M.D. (Site 1476), and William Tap, M.D. (Site 1425) were selected for audit.

There were no significant inspectional observations for the Clinical Investigators, Marilena Cesari, M.D. and William Tap, M.D. The final compliance classification for the inspection of Dr. Tap and the preliminary compliance classification for the inspection of Dr. Cesari is No Action Indicated (NAI).

Although GCP violations were observed during the inspection of the Clinical Investigator, Dr. Hans Gelderblom, M.D., they were unlikely to substantially impact the determination of efficacy and safety of the clinical trial, and the preliminary compliance classification for the inspection is Voluntary Action Indicated (VAI).

A Clinical Inspections Summary Addendum will be provided if the final compliance classification of the inspection of the Clinical Investigators, Drs. Cesari and Gelderblom, is significantly different following receipt and review of the Establishment Inspection Report.

II. BACKGROUND

Daiichi Sankyo, Inc., as the sponsor of NDA 211810, seeks accelerated approval for the use of pexidartinib for the treatment of tenosynovial giant cell tumor (TGCT), also known as giant cell tumor of the tendon sheath (GCT-TS). Pexidartinib is an orally active small-molecule selective tyrosine kinase inhibitor that targets colony-stimulating factor-1 receptor (CSF-1). GCT-TS tumors cause pathogenesis by secreting elevated levels of CSF-1. Inhibition of this pathogenetic pathway would induce tumor regression and control further tumor regrowth by directly targeting the CSF-1 receptor that drives the recruitment of cells.

The key clinical study supporting this application is Study Protocol PLX108-10. This was a 2-part, multi-center, double-blind, randomized, placebo-controlled Phase 3 study designed to compare the response rate of pexidartinib with that of placebo per RECIST 1.1 at Week 25 in subjects with symptomatic TGCT for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease).

The trial initiation date was May 11, 2005 (first subject enrolled). The date that the last subject completed Part 1 was March 27, 2017. Study Protocol PLX108-10 was conducted at 36 study sites with most enrolled subjects from 4 countries as follows: 45 subjects from the U.S., 17 subjects from Italy, 12 subjects from Australia, and 11 from the Netherlands.

Overall, 126 subjects were screened, and 121 subjects enrolled and randomized to treatment arms. One Hundred twenty (120) subjects with TGCT in Part 1 randomly assigned to 2 treatment groups were treated, 61 subjects assigned to pexidartinib and 59 subjects to the placebo control. A total of 100 subjects completed Part 1 of the study with similar rates for completion and early discontinuation between the 2 treatment groups.

A total of 78 subjects received at least 1 dose of open-label pexidartinib in Part 2: Thirty (30) subjects who crossed over to pexidartinib from the placebo group of Part 1 and 48 subjects from the pexidartinib arm of Part 1. Similar rates of discontinuation were observed between subjects continuing treatment with pexidartinib from Part 1 and for those who crossed over to pexidartinib in Part 2.

In Part 1, the double-blind phase, eligible candidates were centrally 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. study sites and by upper extremity versus lower extremity involvement.

Study treatment was administered twice a day, every day. For the first 2 weeks in Part 1,

subjects took 2 capsules in the morning and 3 capsules in the evening, 1000 mg/d pexidartinib or matching placebo. Thereafter, dosing was reduced to 2 capsules in the morning and 2 capsules in the evening, 800 mg/d pexidartinib or matching placebo. Subjects who had a dose reduction during the first 2 weeks continued treatment at their reduced dose. Each treatment cycle was 28 days in duration and subjects were treated for up to 6 cycles.

Subjects who were in the pexidartinib treatment group and completed Part 1 were eligible to advance to Part 2, a long-term treatment phase where all subjects took open-label pexidartinib twice a day, every day (800 mg/day). Subjects who were in the placebo treatment group who completed Part 1 were initially eligible to advance to Part 2. After the Data Monitoring Committee (DMC) recommendation on 29 Sep 2016 (see DMC Recommendation Section below), subjects who were receiving placebo in Part 1 and had already initiated treatment with pexidartinib in Part 2 continued in the study, but all subjects in the placebo treatment group who reached the end of Part 1 after September 29, 2016 were discontinued.

MRI was performed at Baseline, Week 13, and Week 25. If disease progression was indicated clinically or by local radiologic assessment according to RECIST 1.1, the disease progression was verified by a central MRI reading. Part 2 continued until all subjects had either reached at least the Week 49 Visit or withdrew from the study.

Part 1 was 24 weeks in duration for all but those who qualified for early entry into Part 2 because of disease progression. The duration of Part 2 varied among subjects, as it continued until all subjects either completed 24 weeks of open-label treatment or withdrew from the study. Thereafter, subjects could continue pexidartinib treatment for longer efficacy and safety follow-up.

The primary efficacy endpoint was proportion of subjects who achieved a complete response (CR) or partial response (PR) at the Week 25 Visit based on RECIST 1.1.

Data Monitoring Committee (DMC) Recommendations: In September 2016, updated safety information became available including 2 SAEs in the study consistent with cholestatic liver dysfunction. There were an estimated 90 subjects who had been exposed to pexidartinib in the study at the time of this finding. Additionally, prolonged hyperbilirubinemia (ongoing >8 months at the time of the DMC meeting) occurred in 1 case and 2 other cases took 2 months to 3 months to resolve. All cases occurred between 14 days and 57 days of the start of pexidartinib treatment, suggesting a higher risk within the first 8 weeks of treatment.

In response to the emerging program-wide safety profile regarding cholestatic liver injury as a recognized risk, the study DMC was requested to review the unblinded safety data related to these cases, and safety data for similar cases in other studies. The DMC recommended safety measures that were implemented effective September 30, 2016:

1. Enrollment was stopped and subjects in screening and randomized subjects who had not started treatment were discontinued.
2. Subjects on placebo in Part 1 were no longer allowed to enter Part 2 to receive open-label pexidartinib. After completion of the end of Part 1 assessments, subjects who

wished to continue onto the open-label part of this study (Part 2) were unblinded and those on placebo were discontinued; subjects on pexidartinib in Part 1 were allowed into Part 2 and continued to receive pexidartinib.

3. Investigators and subjects were informed of the new safety information, and they decided whether to continue in the study. If, after consultation with the subject, it was deemed to be in their best interest to continue treatment, the subject had to re-sign informed consent.
4. The frequency of liver function testing was increased, and gamma-glutamyl transpeptidase (GGT) was added to the laboratory panel.

GCP inspection was conducted at two foreign and one domestic Clinical Investigator sites. Although 9 U.S. centers were opened for enrollment, only 11 patients enrolled across these centers. The sites selected for inspection are among the highest enrolling sites with high weighted efficacy in favor of study drug.

III. RESULTS (by site):

Name of CI, Site #, Address	Protocol # # of Subjects	Inspection Dates	Classification
Marilena Cesari, M.D. Site #:1432 SSD Chemioterapia dei Tumori dell'Apparato Locomotore Istituto Ortopedico Rizzoli Via Pupilli, 1, Via G. Venezian, 1, Bologna 40136, Italy	Study: PLX108-10 Enrolled: 9	March 11-15, 2019	NAI*
Hans Gelderblom, M.D. Site #: 1476 Leiden University Medical Center, Department of Clinical Oncology, Albinusdreef 2, Leiden, South Holland 2333 ZA Netherlands	Study: PLX108-10 Enrolled: 11	March 4-8, 2019	VAI*
William Tap, M.D. Site #: 1425 Memorial Sloan Kettering Cancer Center 300 E. 66th Street New York, NY 10065	Study: PLX108-10 Enrolled: 4	January 29-30, 2019	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data may be unreliable.

*Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Marilena Cesari, M.D. (Site 1432)

The site screened 15 subjects and 9 were enrolled and randomized. Six (6) subjects completed the trial and 3 remain on open-label treatment. An audit of all enrolled subject's records was conducted.

The inspection evaluated all subject's informed consent forms. The inspection reviewed Ethics Committee approvals, regulatory authority approvals, monitoring visit reports, training documentations, delegation of authority logs, and subject enrollment logs. Additionally, the inspection reviewed source documentations including MRI summaries, worksheets for ECG, medication dosing and laboratory draw times, range of motion assessments, local and central laboratory reports, worksheets for physical examinations, concomitant meds, adverse events, pre-randomization review forms, surgical assessment questionnaires, unblinding forms for Week 25 evaluation, pharmacy accountability logs, and Interactive Voice Response System (IVRS) documentation for drug dispensing as well as a brief review of the Electronic Data Capture (EDC) system in place. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1432 appear reliable based on available information.

2. Hans Gelderblom, M.D. (Site 1476)

The site screened 11 subjects, and all were enrolled and randomized. All Subjects completed the trial. An audit of all enrolled subject's records was conducted.

The inspection evaluated all Subject's informed consent forms. The inspection reviewed FDA Form 1572s, Ethics Committee approvals, regulatory authority approvals, monitoring visit reports, training documentations, delegation of authority logs, and subject enrollment logs. Additionally, the inspection reviewed source documentations including lab requisition forms, local and central laboratory forms, tumor sample requisition forms, pre-randomization review forms, surgical assessment questionnaires, concomitant meds, AE reporting, MRI transmittal forms, local MRI assessments, pharmacy accountability logs and IVRS documentation for drug dispensing as well as a brief review of the EDC system in place. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

An inspectional observation was noted, and at the conclusion of the inspection, a one-item Form FDA 483 was issued to the Clinical Investigator for failure to maintain adequate case histories with respect to observations and data pertinent to the investigation. Specifically, a review of source data for all 11 subjects revealed multiple deficiencies as follows:

- a) Times reported for study medication dosing, laboratory sample collections, and electrocardiograms initially documented a deviation from the investigational plan; these

were later changed without justification to reflect times in compliance with the protocol. For example, for Subject (b) (6) during Study Visit P1C1D1 (b) (6), source documentation states the subject received medication at 1050. The original pre-dose ECG time was 1101, and it was changed to 1045, bringing it into compliance with the protocol. For Subject (b) (6) during Study Visit P2C1D1 on (b) (6) laboratory requisition forms for this visit indicate the pre-dose pharmacokinetic samples were drawn at 1000. The subject source document for this visit originally indicated that the subject took the study medication at 1000, but this was later changed to 1001, bringing it into compliance with the protocol.

- b) Laboratory safety and pharmacokinetic samples were routinely reported as collected at the nearest 5-minute interval, rather than the actual time. Some examples include:

<u>Subject No.</u>	<u>Study Visit</u>	<u>Date</u>	<u>Laboratory Sample Time</u>
(b) (6)	P1C1D1	(b) (6)	1015
	P1C2D1		1010
	P1C3D1		1020
	P1C1D15		0905
	P1C1D15		1135
	P1C2D1		1330
	P1C3D1		1115
	P1C1D1		1325
	P1C3D1		1030
	P1C1D1		0950
	P1C1D1		0935

- c) Source documents for all subjects indicate that all study medication dosing timepoints occur on minutes that are a multiple of 5. Some examples include:

<u>Subject No.</u>	<u>Study Visit</u>	<u>Date</u>	<u>Laboratory Sample Time</u>
(b) (6)	P2C1D1	(b) (6)	1040
	P1C1D15		1340
	P1C1D15		1040
	P1C1D15		0930
	P1C1D15		1140
	P1C1D1		1100
	P1C1D15		1030
	P1C1D1		1120
	P1C1D15		1020
	P1C1D1		1005
	P1C1D1		1515

In his response to the Form FDA 483, Dr. Gelderblom's written response dated March 28, 2019 acknowledged the inspectional observation and outlined the Corrective and Preventative Actions (CAPAs). With respect to Item a discussed above, the preventative actions include retraining the research staff to improve source documentation including proper documentation of time and date, and in the event that changes are made to the source documentation, the research team will add an explanation as to why it was done and document the date/time along with the initials of the person making the change. As for studies that require the use of ECG machine, the research team will use a single ECG machine and a synchronization of exact time and date will be performed. According to Dr. Gelderblom, different ECG machines were used during the study, but the time on each ECG machine was not always in line with the actual time that the ECG reading was taken for subjects which prompted the changes made to the source documents.

In regard to Items b and c, Dr. Gelderblom acknowledges the errors and commits to GCP compliance through retraining the staff on proper source documentation including the exact timing of medication administration or blood draws. This will be part of Standard Operating Procedure (SOP) which will be updated to include instructions and training provided by the Primary Investigator to the research staff during weekly research meetings.

Although GCP deficiencies were noted at the clinical site, they do not appear to significantly impact study outcomes. The investigator determined primary efficacy endpoint data were verifiable. Furthermore, the described deficiencies are unlikely to placed subjects at undue risk. There was no evidence of under reporting of AEs. The data from Site 1476 appear reliable based on available information.

3. William Tap, M.D. (Site 1425)

The site screened 9 subjects and 4 were enrolled. Two (2) subjects completed the trial and 2 remain on open-label treatment. An audit of all enrolled subject's records was conducted.

All subject's informed consent forms were reviewed. Additionally, the inspection included a review of FDA Form 1572s, Institutional Review Board (IRB) approvals, financial disclosures, monitoring visit reports, training logs, delegation of authority logs, subject enrollment logs, inclusion/exclusion criteria, test article accountability, MRI summaries, tumor (RECIST) assessment forms, and AE reporting to determine overall protocol compliance. Study source documents and records of the audited subjects were compared to the data listings and found to be the same.

There were no objectionable conditions noted and no Form FDA-483, Inspectional Observations, was issued. The investigator determined primary efficacy endpoint data were verifiable. There was no evidence of under reporting of AEs. Study conduct at the site appeared to be in compliance with good clinical practice. The data from Site 1425 appear reliable based on available information.

{See appended electronic signature page}

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OSI/Database PM/Dana Walters

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KASSA AYALEW
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LABEL AND LABELING REVIEW

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

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

Date of This Review:	April 3, 2019
Requesting Office or Division:	Division of Oncology Products 2 (DOP2)
Application Type and Number:	NDA 211810
Product Name and Strength:	Turalio (pexidartinib) Capsules, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Daiichi Sankyo, Inc.
FDA Received Date:	March 8, 2019 and April 2, 2019
OSE RCM #:	2018-2054
DMEPA Safety Evaluator:	Colleen Little, PharmD
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD

1 REASON FOR REVIEW

As part of this NDA, this review evaluates the proposed Turalio prescribing information (PI), container labels, and carton labeling to identify areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E-N/A
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the materials submitted found the proposed Turalio PI, container labels, and carton labeling may be improved to promote safe use of this product.

We note the proposed Turalio PI provides a dose reduction schedule to manage adverse reactions (see Appendix A). We also note that although the PI provides dosage modifications, it does not clearly state the lowest recommended dose. Therefore, we are concerned that prescribers may further reduce the dose beyond the second dose reduction (b) (4) resulting in confusion and underdose errors. Thus, we defer to the Review Team to determine if the Turalio PI should state the lowest recommended daily dose.

Additionally, the statement (b) (4) has been removed from Section 2 in the full PI response to a previous recommendation from the Review Team; however, the statement is still present in the Highlights, Dosage and Administration section in the PI. Therefore, we recommend removal of the aforementioned statement to ensure the information presented in the Highlights, Dosage

and Administration section is consistent with the information presented in the Dosage and Administration section in the full PI.

4 CONCLUSION & RECOMMENDATIONS

The proposed Turalio PI, container labels, and carton labeling can be revised to promote the safe use of this product as described in Section 4.1 and Section 4.2 below.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Highlights, Dosage and Administration Section

- a. Revise "... (b) (4) ..." to "... (b) (4) ..." for clarity and consistency with the Dosage and Administration Section in the full PI.
- b. Remove the statement (b) (4) (b) (4) for consistency since it does not appear in the Dosage and Administration Section in the full PI.

2. Full PI, Dosage and Administration Section

- a. In Section 2.1, consider relocating the duration of therapy statement, "(b) (4) until disease progression..." to appear at the end of the recommended dosage statement for clarity. For example, "The recommended dose of... (b) (4) until disease progression or unacceptable toxicity."
- b. Section 2.2 does not clearly state the lowest recommended daily dose. (b) (4) we are concerned that prescribers may further reduce the dose beyond the second dose reduction (b) (4) resulting in confusion and underdose errors. We recommend clearly stating the lowest recommended daily dose. We defer to the Review Team to determine the appropriate lowest recommended daily dose.
- c. In Table 1, ensure each dose and the number of capsules required to achieve each dose are presented in a consistent format. We recommend the following format: (b) (4)

3. Medication Guide

- a. In the "How should I take Turalio" section, in addition to the missed dose instruction, consider including instructions to address vomiting to minimize the risk of overdose medication errors and for consistency with the PI.

4.2 RECOMMENDATIONS FOR DAIICHI SANKYO, INC.

We recommend the following be implemented prior to approval of this NDA:

A. General Comments (Container labels & Carton Labeling)

1. As presented, the lowercase letter “t” in the proprietary name, Turalio, appears similar to the letter “J” in your selected font style. We recommend that you consider capitalizing the first letter of the proprietary name or modifying the font style to improve readability and minimize misinterpretation.
2. Identify the location and header for the lot number. Ensure that there are no other numbers located in close proximity to the lot number where it can be mistaken as the lot number^a and the lot number is clearly differentiated from the expiration date.^b
3. As currently presented, the header and format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

^a Institute for Safe Medication Practices. Safety briefs: The lot number is where? ISMP Med Saf Alert Acute Care. 2009;14(15):1-3.

^b Institute for Safe Medication Practices. Safety briefs: Lot number, not expiration date. ISMP Med Saf Alert Acute Care. 2014;19(23):1-4.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Turalio received on March 9, 2019 from Daiichi Sankyo, Inc.

Table 2. Relevant Product Information for Turalio							
Initial Approval Date	N/A						
Active Ingredient	pexidartinib						
Indication	For the treatment of adult patients with symptomatic tenosynovial giant cell tumor (TGCT) also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery.						
Route of Administration	Oral						
Dosage Form	Capsules						
Strength	200 mg						
Dose and Frequency	<div style="background-color: #cccccc; height: 20px; width: 100%;"></div> <div style="text-align: right;">(b) (4)</div> <p>Dose Reductions</p> <table border="1" style="width: 100%;"> <thead> <tr> <th style="width: 30%;">Dose level</th> <th>Dose</th> </tr> </thead> <tbody> <tr> <td>First dose reduction</td> <td>200 mg capsule <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4) in the morning and 400 mg <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4) in the evening</td> </tr> <tr> <td>Second dose reduction</td> <td>200 mg twice daily <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4)</td> </tr> </tbody> </table>	Dose level	Dose	First dose reduction	200 mg capsule <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4) in the morning and 400 mg <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4) in the evening	Second dose reduction	200 mg twice daily <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4)
Dose level	Dose						
First dose reduction	200 mg capsule <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4) in the morning and 400 mg <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4) in the evening						
Second dose reduction	200 mg twice daily <div style="background-color: #cccccc; width: 100px; height: 1em; display: inline-block;"></div> (b) (4)						
How Supplied	28 count bottles 120 count bottles						
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F ° to 86°F) [see USP Controlled Room Temperature].						
Container Closure	High density polyethylene (HDPE) with a <div style="background-color: #cccccc; width: 150px; height: 1em; display: inline-block;"></div> (b) (4) <div style="background-color: #cccccc; width: 50px; height: 1em; display: inline-block;"></div> (b) (4) cap.						

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^c along with postmarket medication error data, we reviewed the following Turalio labels and labeling submitted by Daiichi Sankyo, Inc.

- Container label received on April 2, 2018
- Carton labeling received on April 2, 2018
- Medication Guide (Image not shown) received on March 8, 2019
- Prescribing Information (Image not shown) received on March 8, 2019

G.2 Label and Labeling Images

Container Labels



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

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

/s/

COLLEEN L LITTLE
04/03/2019 01:56:22 PM

CHI-MING TU
04/03/2019 10:17:55 PM

Interdisciplinary Review Team for QT Studies Consultation Review

Submission	NDA 211810
Submission Number	004
Submission Date	12/3/2018
Date Consult Received	12/11/2018
Clinical Division	DOP2

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

This review responds to your consult regarding the sponsor's QT evaluation. The QT-IRT reviewed the following materials:

- Previous QT-IRT reviews under IND (b)(4) dated 04/18/2017 and 06/16/2017 in DARRTS;
- Proposed [label](#) (Submission 0004);
- [Summary of clinical pharmacology](#) (Submission 0004); and
- pl3397-a-u125 [clinical trial report](#) and [cardiac safety report](#) (Submission 0004).

1 SUMMARY

No significant QTc prolongation effect of pexidartinib was detected in this QT assessment.

The effect of pexidartinib (PLX3397) was evaluated in a double-blind, placebo- and active-controlled, 3-treatment, single-dose, crossover study in 36 healthy subjects (Study PL3397-A-U125). The highest dose that was evaluated was 1800 mg, which provides approximately 2 times the mean maximum exposure of the 400 mg twice daily (BID) dose and covers the worst case exposure scenario (CYP3A inhibition, section 3.1). The data was analyzed using exposure-response analysis as the primary analysis, which suggests that pexidartinib is associated with QTc shortening effect (refer to section 4.5) – see Table 1 for overall results. The findings of this analysis are further supported by the available nonclinical data (section 3.1), central tendency analysis (section 4.3) and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs by Exposure-Response analysis (FDA Analysis)

ECG parameter	Treatment	Concentration	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
QTc	Pexidartinib	1.9 ug/mL	-5.1	(-7.0, -3.3)
QTc	Moxifloxacin	1.8 ug/mL	15.9	(13.5, 18.3)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

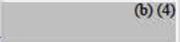
The nonclinical data for pexidartinib suggests that pexidartinib has the potential to cause clinical QTc prolongation as evidenced by a low hERG potassium channel safety margin (Appendix 5). However, concentration-dependent shortening of the QTcF interval was

observed for pexidartinib in this thorough QT study (Figure 8). The observed QTcF shortening is not expected to be clinically significant.

The nonclinical results suggest the presence of L-type calcium channel block, which offsets the effects of the hERG potassium channel inhibition (Appendix 5). These results are consistent with a concentration-response analysis for exploratory ECG biomarkers ($J-T_{peakc}$ and $T_{peak}-T_{end}$), which shows the QTcF shortening is due to inward current block (Figure 9). Interestingly, despite blocking the L-type calcium channel no prolongation of the PR interval was observed in this study (Figure 3). The lack of PR prolongation could indicate that the inhibition of the L-type calcium channel by pexidartinib takes time to develop.

2 PROPOSED LABEL

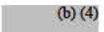
The following is the sponsor's proposed QT-related labeling language for section 12.2. Our changes are highlighted (addition, ~~deletion~~). We defer the final labeling decisions to the Division.

12.2 Pharmacodynamics
<u>Cardiac Electrophysiology</u>
 (b) (4)
<u>At 2 times the mean maximum exposure of the 400 mg twice daily dose,</u>  (b) (4)

<i>We propose to use labeling language for this product consistent with the "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" guidance.</i>

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

The QT-IRT reviewed the QT assessment proposal previously under IND  (b) (4) (04/18/2017 and 06/16/2017 in DARRTS). The study protocol and QT assessment were found acceptable. There have been no major changes to study design, PK/ECG sampling schedule, or study endpoint.

Reviewer's comment: *According to the summary of clinical pharmacology, the steady state C_{max} of pexidartinib at the proposed 400 mg BID dose is 8625 ng/mL and the maximum effect on C_{max} by intrinsic/extrinsic factors is less than 2-fold. The mean C_{max} pexidartinib in the current study is 19098 ng/mL. Therefore, this study provides approximately 2-fold coverage of the maximum therapeutic exposure as well as exposure at the worst-case scenario for pexidartinib.*

The major metabolite, ZAAD-1006a, is an N-glucuronide of pexidartinib. The predicted steady state C_{max} of the major metabolite, ZAAD-1006a, is 13564 ng/mL at 400 mg BID dose. Severe renal impairment doubles the maximum exposure to ZAAD-1006s. The mean

C_{max} in this study is 17900 ng/mL. Therefore, this study does not provide coverage of the worst-case scenario exposure for ZAAD-1006s. That being said, exploratory exposure-response analysis does not suggest larger QT prolonging effect at higher ZAAD-1006a exposure (4.5).

3.2 SPONSOR'S RESULTS

3.2.1 Central tendency analysis

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

Both FDA's analysis and sponsor's analysis confirm that the assay sensitivity was established. FDA analysis is presented in section 5.2.

3.2.1.1.1 QT bias assessment

No QT bias assessment was conducted by the sponsor.

3.2.2 Categorical Analysis

The results of the reviewer's analysis are similar to the sponsor's results. Please see section 4.4 for additional details.

3.2.3 Safety Analysis

No subject experienced an AE leading to death, other SAE, or discontinuation. The most frequently reported TEAEs were pruritus (33%) and neutropenia (11%).

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

3.2.4 Exposure-Response Analysis

The sponsor evaluated the relationship between $\Delta\Delta QTcF$ and plasma concentrations of both analytes (pexidartinib and its major metabolite, ZAAD-1006a) using a linear mixed-effects modeling approach. The full model included separate slope parameters for pexidartinib, ZAAD-1006a and their interaction as the fixed effects. Model comparison of the full model and a reduced model with a single exposure metric was conducted using AIC and t-value for the intercept estimator. The model with two exposure terms without interaction was selected as the final model. The estimated $\Delta\Delta QTcF$ at PLX3397 geometric mean C_{max} and geometric mean concentrations of ZAAD-1006a observed at T_{max} of PLX3397 was -5.89 ms (90% CI: -7.76, -4.02). The estimated $\Delta\Delta QTcF$ at ZAAD-1006a geometric mean C_{max} and geometric mean concentrations of PLX3397 observed at T_{max} of ZAAD-1006a was -2.18 ms (90% CI: -3.86, -0.49).

The reviewer evaluated the relationship between $\Delta QTcF$ and pexidartinib concentrations. The conclusions from reviewer's analysis are similar to the sponsor's conclusions. Please see section 4.5 for additional details.

4 REVIEWER'S ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no significant increases in heart rate (i.e. mean < 10 bpm) were observed (see Sections 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Overall ECG acquisition and interpretation in this study appears acceptable.

4.2.2 QT bias assessment

Not conducted.

4.3 CENTRAL TENDENCY ANALYSIS

4.3.1 QTc

The statistical reviewer used a mixed model to analyze the Δ QTcF effect. The model included treatment, time, sequence, period, time by treatment interaction as fixed effects. Subjects (sequence) were included in the model as a random effect. Baseline values were also included in the model as a covariate. The results are presented in Table 2. The largest upper bound of the 90% confidence interval is 4.8 ms.

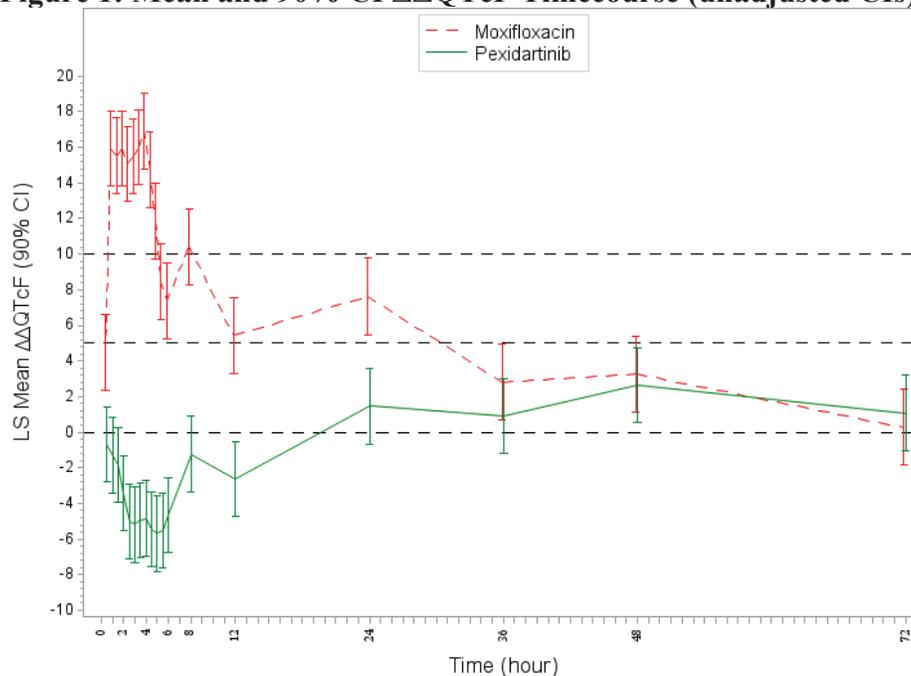
Table 2: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for pexidartinib

	Treatment Group			
	Pexidartinib			
	Δ QTcF	Placebo	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-3.7	-3.0	-0.7	(-2.8, 1.4)
1	-6.2	-4.9	-1.3	(-3.4, 0.8)
1.5	-7.0	-5.1	-1.8	(-3.9, 0.3)
2	-7.3	-3.9	-3.4	(-5.5, -1.3)
2.5	-8.2	-3.2	-5.0	(-7.1, -2.9)
3	-8.1	-2.9	-5.2	(-7.3, -3.1)
3.5	-7.7	-2.7	-4.9	(-7.1, -2.8)
4	-7.8	-3.0	-4.9	(-7.0, -2.7)
4.5	-6.0	-0.6	-5.4	(-7.6, -3.3)
5	-6.6	-0.9	-5.7	(-7.8, -3.6)
5.5	-6.8	-1.2	-5.5	(-7.6, -3.4)
6	-6.3	-1.7	-4.7	(-6.8, -2.5)
8	-5.8	-4.5	-1.2	(-3.3, 0.9)

	Treatment Group			
	Pexidartinib			
	Δ QTcF	Placebo	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
12	-3.7	-1.0	-2.6	(-4.8, -0.5)
24	-2.2	-3.7	1.5	(-0.7, 3.6)
36	-1.8	-2.8	0.9	(-1.2, 3.0)
48	1.1	-1.5	2.6	(0.5, 4.8)
72	0.4	-0.7	1.1	(-1.1, 3.2)

The Figure 1 displays the time profile of $\Delta\Delta$ QTcF for different treatment groups.

Figure 1: Mean and 90% CI $\Delta\Delta$ QTcF Timecourse (unadjusted CIs).



4.3.1.1 Assay sensitivity

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in Table 3. In QTcF correction method, the largest lower bound of the unadjusted 90% confidence interval is 14.8 ms. By considering Bonferroni multiple endpoint adjustment, the largest lower bound is 14.0 ms, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study. The time profile of moxifloxacin is consistent with ascending, peak, and descending phase of historical moxifloxacin profile. Overall, assay sensitivity was demonstrated in this study.

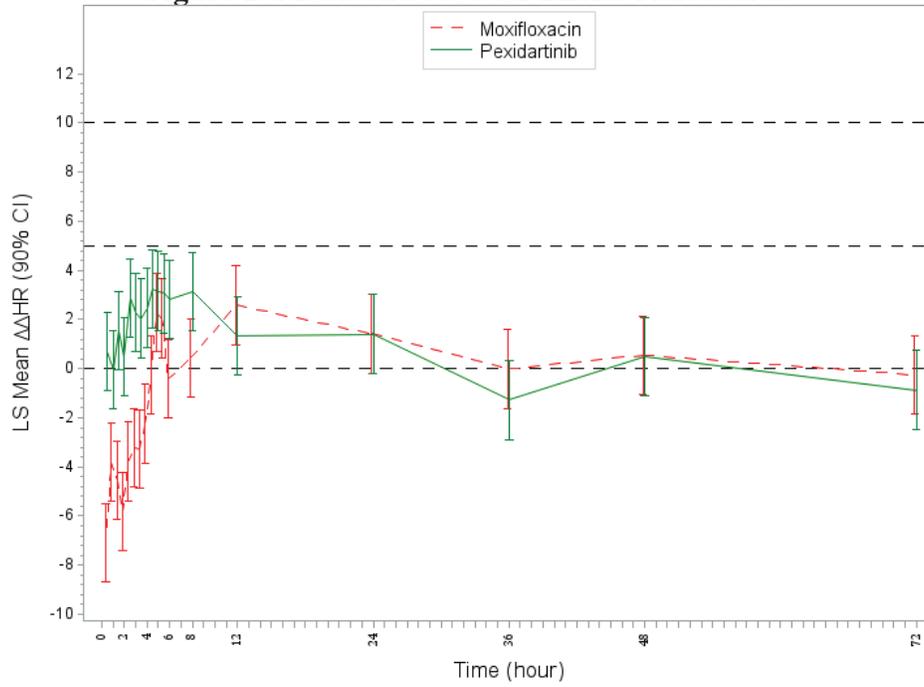
Table 3: Analysis Results of Δ QTcF and $\Delta\Delta$ QTcF for moxifloxacin

	Treatment Group				
	Moxifloxacin				
	Δ QTcF	Placebo	$\Delta\Delta$ QTcF		
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
0.5	1.4	-3.0	4.5	(2.4, 6.6)	(1.6, 7.4)
1	11.1	-4.9	15.9	(13.8, 18.0)	(13.0, 18.8)
1.5	10.4	-5.1	15.5	(13.4, 17.6)	(12.6, 18.4)
2	12.1	-3.9	15.9	(13.8, 18.0)	(13.0, 18.8)
2.5	11.9	-3.2	15.1	(13.0, 17.2)	(12.2, 18.0)
3	12.6	-2.9	15.5	(13.4, 17.6)	(12.6, 18.4)
3.5	13.3	-2.7	16.0	(13.9, 18.1)	(13.1, 18.9)
4	14.0	-3.0	16.9	(14.8, 19.1)	(14.0, 19.8)
4.5	14.1	-0.6	14.7	(12.6, 16.8)	(11.8, 17.6)
5	10.9	-0.9	11.8	(9.7, 14.0)	(9.0, 14.7)
5.5	7.2	-1.2	8.4	(6.3, 10.6)	(5.6, 11.3)
6	5.7	-1.7	7.4	(5.3, 9.5)	(4.5, 10.3)
8	5.9	-4.5	10.4	(8.3, 12.5)	(7.5, 13.3)
12	4.4	-1.0	5.4	(3.3, 7.5)	(2.5, 8.3)
24	4.0	-3.7	7.6	(5.5, 9.8)	(4.7, 10.6)
36	0.1	-2.8	2.8	(0.7, 4.9)	(-0.1, 5.7)
48	1.7	-1.5	3.3	(1.2, 5.4)	(0.4, 6.2)
72	-0.4	-0.7	0.3	(-1.9, 2.4)	(-2.6, 3.2)

4.3.2 HR

The same statistical analysis was performed based on HR (Figure 2). The largest upper limits of 90% CI for the HR mean differences between pexidartinib and placebo was 4.8 bpm.

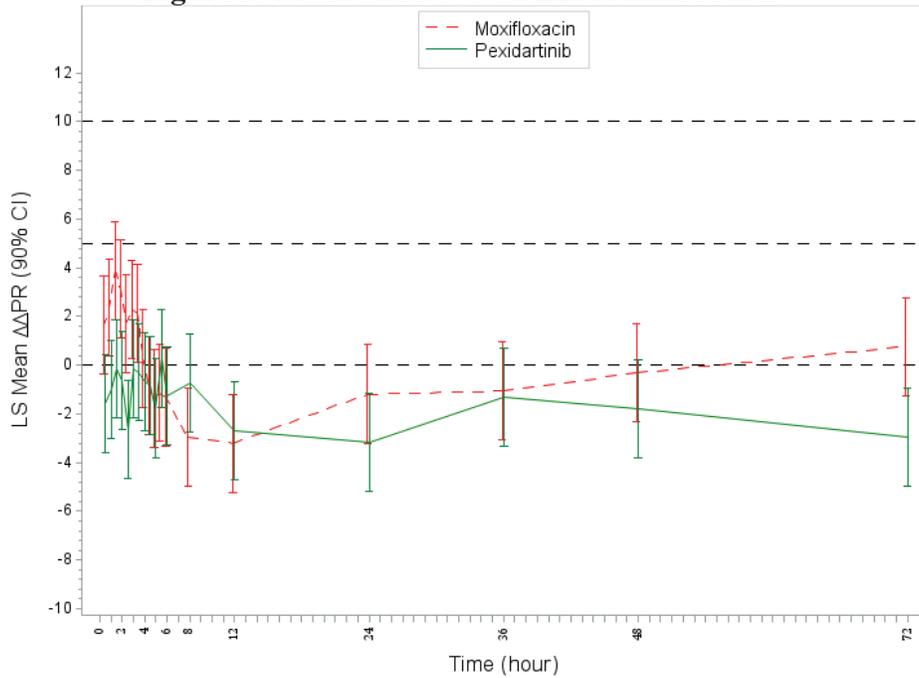
Figure 2: Mean and 90% CI $\Delta\Delta$ HR Timecourse



4.3.3 PR

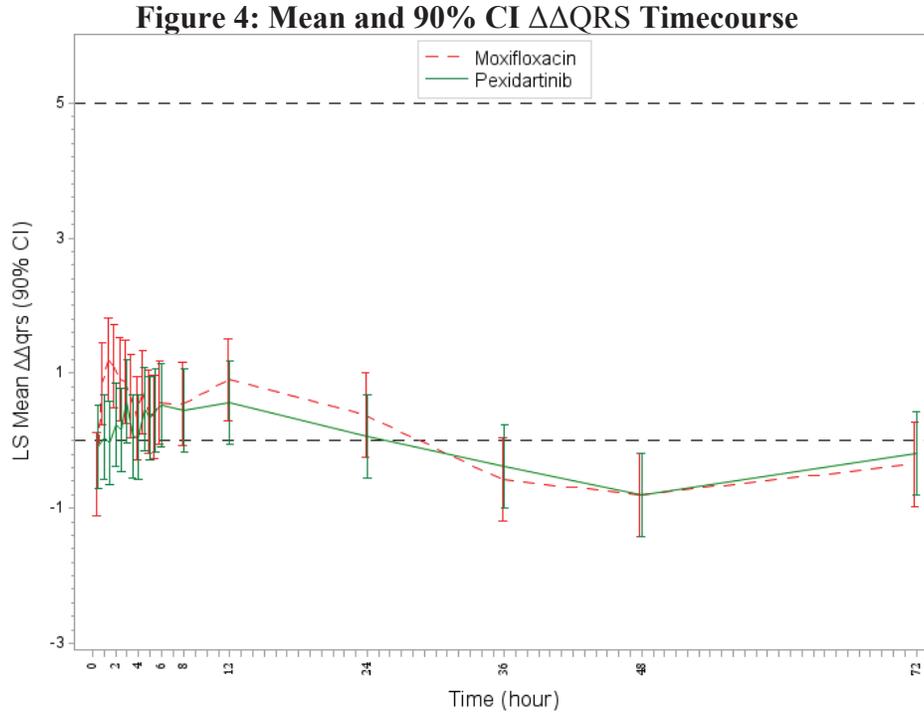
The same statistical analysis was performed based on PR interval (Figure 3). The largest upper limits of 90% CI for the PR mean differences between pexidartinib and placebo was 2.3 ms.

Figure 3: Mean and 90% CI $\Delta\Delta$ PR Timecourse



4.3.4 QRS

The same statistical analysis was performed based on QRS interval (Figure 4). The largest upper limits of 90% CI for the QRS mean differences between pexidartinib and placebo was 1.2 ms.



4.4 CATEGORICAL ANALYSIS

4.4.1 QTc

Table 4 lists the number of subjects as well as the number of observations whose QTcF values are ≤ 450 ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

Table 4: Categorical Analysis for QTcF

Treatment Group	Total (N)		Value \leq 450 ms		450 ms<Value \leq 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	36	647	35 (97.2%)	644 (99.5%)	1 (2.8%)	3 (0.5%)
Pexidartinib	36	646	36 (100%)	646 (100%)	0 (0.0%)	0 (0.0%)
Placebo	36	645	36 (100%)	645 (100%)	0 (0.0%)	0 (0.0%)

Table 5 lists the categorical analysis results for Δ QTcF. No subject's change from baseline was above 60 ms.

Table 5: Categorical Analysis of Δ QTcF

Treatment Group	Total (N)		Value \leq 30 ms		30 ms<Value \leq 60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	36	647	35 (97.2%)	646 (99.8%)	1 (2.8%)	1 (0.2%)
Pexidartinib	36	646	36 (100%)	646 (100%)	0 (0.0%)	0 (0.0%)
Placebo	36	645	36 (100%)	645 (100%)	0 (0.0%)	0 (0.0%)

4.4.2 PR

There were no subjects who experienced PR interval greater than 200 ms in pexidartinib group.

4.4.3 QRS

The outlier analysis results for QRS are presented in Table 6. There were 16 subjects who experienced QRS interval greater than 110 ms in Pexidartinib group, no QRS changes > 25% over baseline.

Table 6: Categorical Analysis for QRS

Treatment Group	Total (N)		Value \leq 100 ms		100 ms<Value \leq 110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin	36	647	3 (8.3%)	119 (18.4%)	19 (52.8%)	357 (55.2%)	14 (38.9%)	171 (26.4%)
Pexidartinib	36	646	4 (11.1%)	103 (15.9%)	16 (44.4%)	363 (56.2%)	16 (44.4%)	180 (27.9%)
Placebo	36	645	3 (8.3%)	138 (21.4%)	19 (52.8%)	343 (53.2%)	14 (38.9%)	164 (25.4%)

4.4.4 HR

There were no subjects who experienced HR greater than 100 bpm in pexidartinib group.

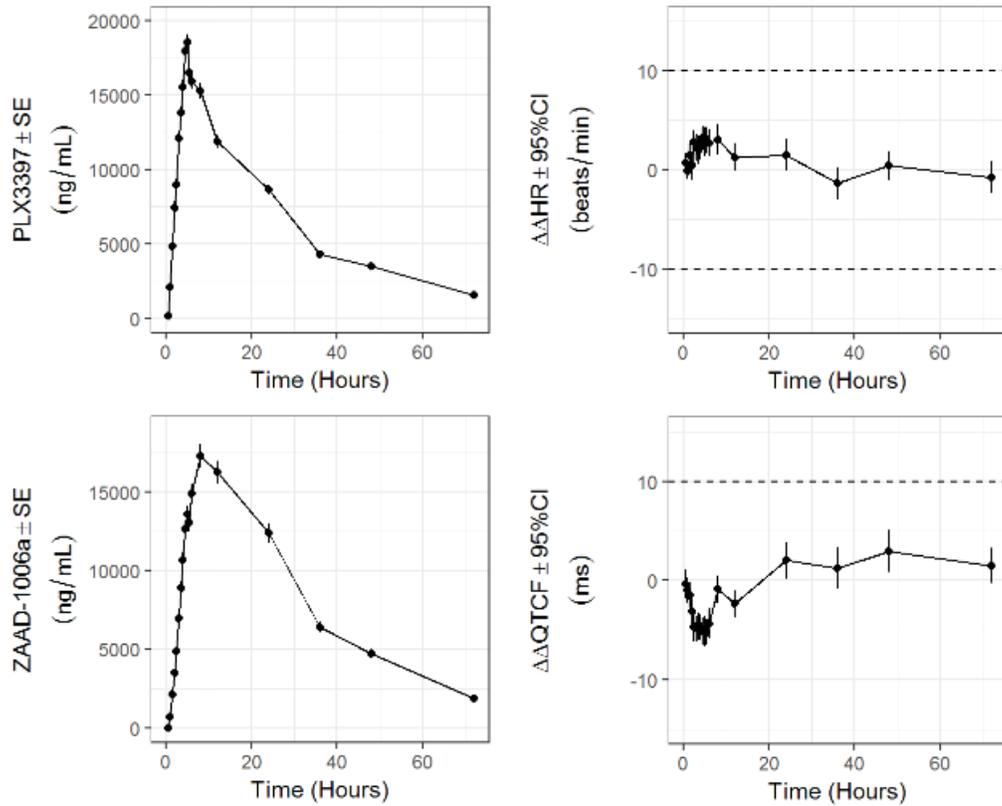
4.5 EXPOSURE-RESPONSE ANALYSIS

4.5.1 QTc

The objective of the clinical pharmacology analysis is to assess the relationship between PLX3397 concentration and Δ QTcF.

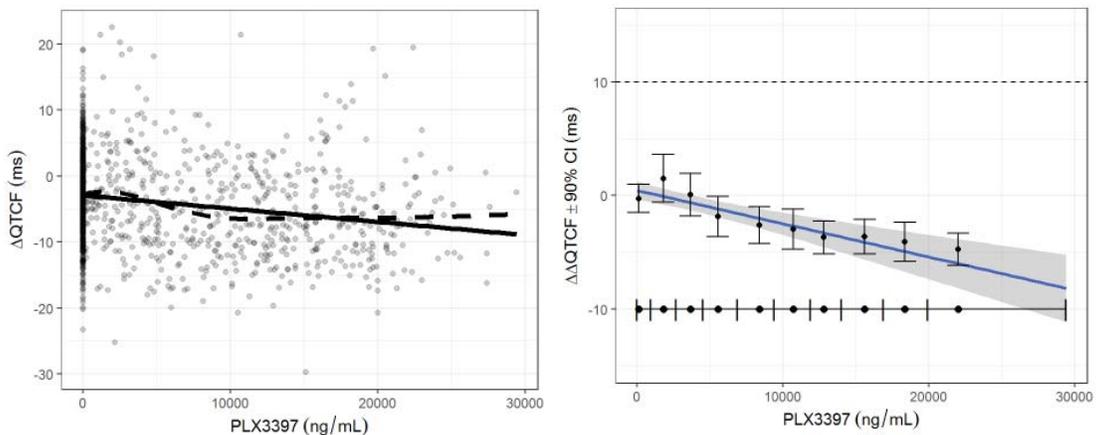
Prior to evaluating the relationship using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 bpm increase or decrease in mean HR); 2) delay between plasma concentration and Δ QTcF and 3) presence of non-linear relationship. An evaluation of the time-course of drug concentration and changes in Δ HR and Δ QTcF is shown in Figure 5, which shows an absence of significant changes in HR and do not appear to show significant hysteresis for either PLX3397 or ZAAD-1006a. The time-course of PLX3397 and ZAAD-1006a follows similar trend; it's unlike to differentiate the potential contribution from two moieties. Therefore, the exposure-response analysis was conducted using parent drug concentrations as the exposure metrics

Figure 5: Time course of PLX3397 concentration, ZAAD-1006a concentration, heart rate and QTcF



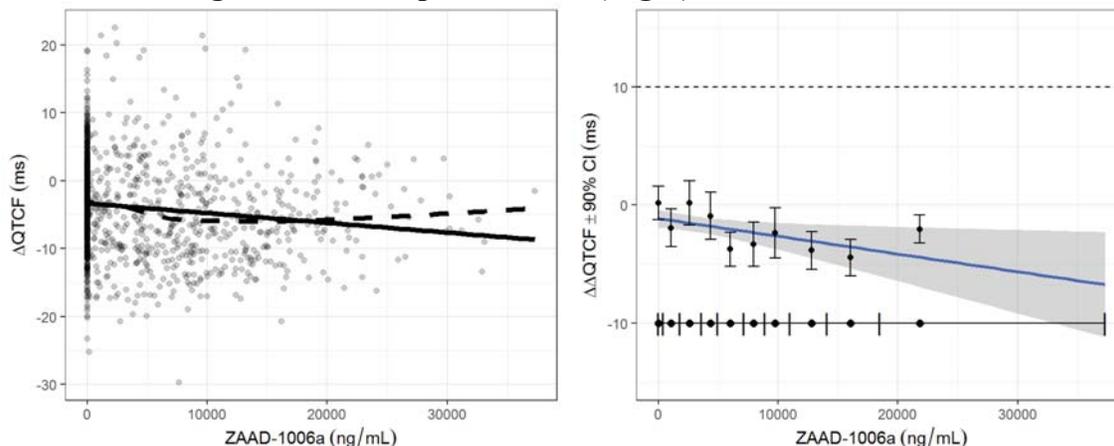
After confirming the absence of significant heart rate changes or delayed QTc changes, the relationship between drug concentration and Δ QTcF was evaluated to determine if a linear model would be appropriate. Figure 6 (Left) shows the relationship between drug concentration and Δ QTcF and supports the use of a linear model. Finally, the linear model (Δ QTcF \sim 1 + TRT + $\text{CONC}_{\text{PLX3397}}$ + TIME + baseline adjustment) was applied to the data and the goodness-of-fit plot is shown in Figure 6 (Right).

Figure 6: Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right) for PLX3397.



Exploratory analysis using the same linear mixed effect model suggests a lack of QT prolonging effect with ZAAD-1006a exposure.

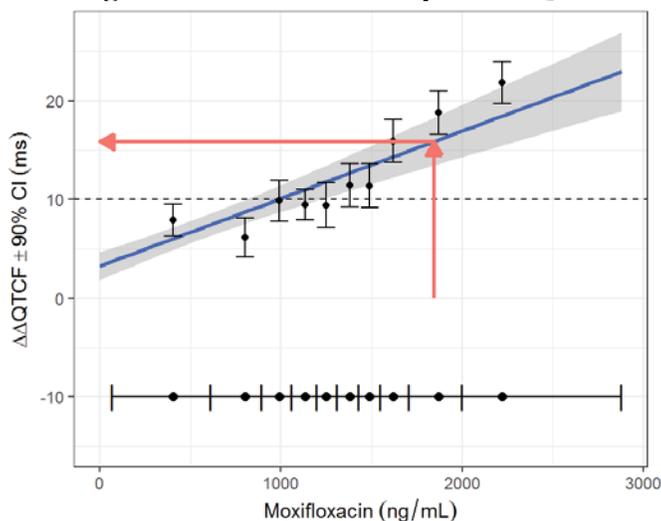
Figure 7. Assessment of linearity of concentration-QTc relationship (Left) and goodness-of-fit plot for QTc (Right) for ZAAD-2006a.



4.5.1.1 Assay sensitivity

Assay sensitivity was established as the lower bound of the 2-sided 90% CI of the estimated $\Delta\Delta\text{QTcF}$ is above 5 ms at the observed geometrical mean C_{max} .

Figure 8. Goodness-of-fit plot for QTc

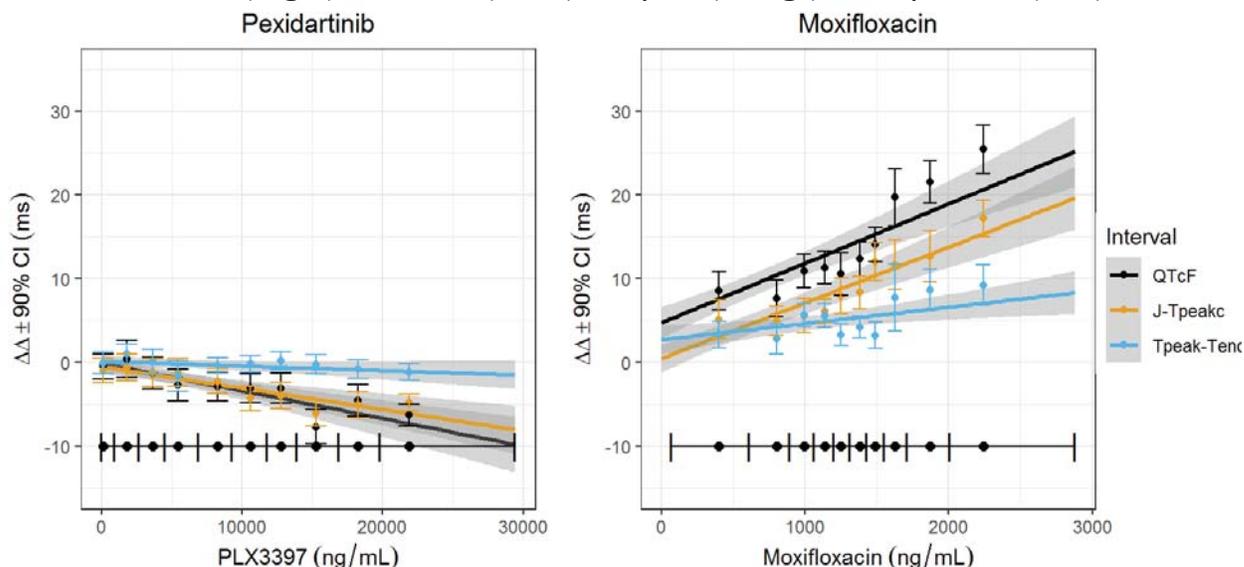


4.5.2 Other ECG intervals

The nonclinical data for pexidartinib suggests inhibition of the hERG potassium channel as well as the L-type calcium channel (Appendix 5) and the concentration-response relationship was therefore explored for $J\text{-}T_{\text{peak}c}$ and $T_{\text{peak}}\text{-}T_{\text{end}}$ (Figure 9). This analysis shows that observed QTcF shortening is due to shortening of the $J\text{-}T_{\text{peak}c}$ interval. Shortening of the $J\text{-}T_{\text{peak}c}$ has been associated with the presence of inward current block (e.g., L-type calcium or late sodium current). A similar analysis was carried out for moxifloxacin, which revealed an ECG signature consistent with selective hERG

potassium channel block. Of note, in both analyses data from one subject was excluded due to notched T-waves observed in the placebo arm.

Figure 9. Comparison of concentration-response relationship for pexidartinib (Left) and moxifloxacin (Right) for QTcF (black), J-T_{peakc} (orange) and T_{peak}-T_{end} (blue).



4.6 SAFETY ASSESSMENTS

See section 3.2.3. No additional safety analysis was conducted.

4.7 OTHER ECG INTERVALS

No clinically significant changes in PR or QRS were observed.

5 APPENDIX: IN VITRO ASSAY REVIEW BY THE DIVISION OF APPLIED REGULATORY SCIENCE

5.1 EXECUTIVE SUMMARY

Pexidartinib (PLX3396) is associated with a small decrease in $\Delta\Delta$ QTcF, which appears to track with the parent compound, and no change in HR, PR, or QRS. One mechanism for QTcF decrease is inward current block. Thus, three non-clinical study reports associated with this submission were reviewed in detail to understand the drug effect on cardiac ion channels and action potentials.

Whole cell patch clamp studies performed on human hERG and Ca_v1.2 channels expressed in recombinant cells showed that PLX3397 blocks these channels within the therapeutic exposure level. The estimated free C_{max} is 0.23 μM, and the estimated IC₅₀s for hERG and Ca_v1.2 channels are 0.7 and 0.2 μM, respectively. The reviewer suspects that drug potency for Ca_v1.2 channels provided in the study report is underestimated due to reasons provided below. Concomitant block of inward current along with hERG channel block explains why QTcF was not prolonged. The slight decrease in QTcF may reflect greater potency of the drug for Ca_v1.2 than hERG channels. The lack of PR prolongation also suggests that drug block of Ca_v1.2 channels is slow and takes time to develop, thereby sparing the fast Ca²⁺

transient driving Ca^{2+} AP. AP recordings from rabbit purkinje fiber suggest no effect any AP parameter, including APD_{60} and APD_{90} . While this may reflect balanced multi-ion channel block, the possibility that PLX3397 is specific to human cardiac ion channels cannot be ruled out.

5.2 HERG CHANNELS.

Non-clinical study report DRN-108-036 ([link](#)) describes the potential effects of PLX3397 on hERG current, a surrogate for I_{Kr} that mediate membrane potential repolarization in cardiac myocytes. The studies were conducted in accordance with GLP (b) (4) in Jan. 2009.

Methods. Manual whole cell patch clamp experiments were performed at near physiological temperature (33-35°C, temperature measured with a thermistor probe in the recording chamber) on HEK293 cells that stably express cloned hERG channels (presumably hERG1a subunit only). From a holding potential of -80 mV, cells were depolarized to +20 mV for 1 s, then ramped down to -80 mV in 0.2 s (-0.5 V/s). The voltage protocol was repeated at 5 s intervals, and the peak current was measured during ramp down voltage step. Each recording ended with a supra-saturating concentration of E-4031 to eliminate hERG current completely, and the residual current was subtracted offline from the recorded current to isolate the hERG component for drug potency assessment. For pharmacology experiments, a steady state was maintained for at least 20 s (4 current traces) before applying test article. In the presence of test or positive control article, peak current was monitored until a new steady state emerged. One or more test article concentrations were applied sequentially in ascending concentration to each cell. Solution samples were collected from the outflow of the perfusion apparatus for concentration analysis. Of the 4 tested concentrations, 0.1, 0.3, and 1 μM were below the limit of detection (1.08 μM) by the analytical method. However, the sponsor felt that 1 μM was close enough to the limit of detection. For concentration-inhibition analysis used to determine drug potency, the actual measured values for 1 and 3 μM drug solutions were used; 0.1 and 0.3 μM were used as is.

FDA reviewer's comments and study results. Sponsor's voltage protocol is quite similar to the recommended hERG current protocol by the FDA (<http://cipaproject.org/wp-content/uploads/sites/24/2018/06/CiPA-protocol-100918.pdf>). The reviewer did not expect protocol difference to impact hERG current pharmacology. Representative hERG current traces shown in figure 1 and time course plot shown in figure 2 seem of reasonable quality. Data analysis methods are sound. Positive control terfenadine gave the expected percentage of hERG current suppression. The FDA reviewer thus accepted data as presented: hERG IC_{50} of 0.7 μM with the Hill coefficient of 1.3.

From the submitted TQT study, C_{max} is 9548.8 ng/mL (or 22.85 μM ; MW = 417.82 g/mol). Assuming 99% protein-binding, free C_{max} is 0.23 μM . Safety margin ($\text{IC}_{50}/\text{free } C_{\text{max}}$) is estimated to be 3.0 for PLX3396. Acute block of hERG channels by PLX3396 within the therapeutic exposure level is thus expected. Since QT_C prolongation was not observed, drug effect on inward $\text{Ca}_\text{v}1.2$ current was evaluated next to determine whether this mechanism was involved to offset hERG channel block.

5.3 CAV1.2 CHANNELS.

Non-clinical study report 130725.QMF ([link](#)) describes the potential effects of PLX3397 on L-type Ca^{2+} current in CHO cells stably expressing the human $\text{Ca}_V1.2\text{-}\beta 2\text{-}\alpha 2\delta$ Proteins. The studies were conducted [REDACTED] ^{(b) (4)} between Aug. and Sept. 2013.

Methods. Manual whole cell patch clamp experiments were performed at near physiological temperature (33-35°C, temperature measured with a thermistor probe in the recording chamber). Four concentrations of PLX3397 were tested: 0.03, 0.3, 1, and 3 μM . From a holding potential of -80 mV, cells were depolarized to +10 mV for unknown duration. The voltage protocol was repeated at 5 s intervals. For pharmacology experiments, a steady state was maintained for at least 20 s (4 current traces) before applying test article. Drug solutions were not analyzed to verify applied concentrations.

FDA reviewer's comments and study results. Explanation of experimental procedure for this study report was inadequate compared to that for hERG channels. More details regarding the voltage protocol used, method to assess current rundown, isolation of $\text{Ca}_V1.2$ -mediated current in this cell line should have been provided. Sponsor's voltage protocol was pulsing at the same frequency as the FDA recommended protocol (<http://cipaproject.org/wp-content/uploads/sites/24/2018/06/CiPA-protocol-100918.pdf>). The reviewer thus did not expect protocol difference to impact $\text{Ca}_V1.2$ current pharmacology using current measured at the beginning of the voltage step.

$\text{Ca}_V1.2$ current is known for run-down in whole cell configuration, and current run-down was not reported. While positive control nifedipine produced the expected percentage of $\text{Ca}_V1.2$ current suppression, the reviewer was concerned about data quality hence accuracy of drug potency estimation since no current traces or time course plot were shown in this report.

The sponsor reported that PLX3397 inhibits Ca^{2+} current with an IC_{50} of 0.2 μM and a Hill coefficient of 1.1. This is equivalent to the calculated free C_{max} for 0.23 μM and would lead one to expect PR prolongation and pronounced QT_C shortening. Neither was observed. The reviewer suspected that $\text{Ca}_V1.2$ IC_{50} was underestimated for two reasons: 1) time-dependent current rundown added onto drug effect, yielding larger degree of inhibition at each tested concentration; and 2) cells were likely exposed to drug concentrations lower than intended. Regarding the second point, both hERG study report DRN-108-036 and rabbit purkinje fiber study report DRN-108-089 conducted by the same CRO showed that drug concentration could deviate by more than 30% the intended concentrations. In all, PLX3397 blocks $\text{Ca}_V1.2$ channels, but drug potency estimation is likely unreliable.

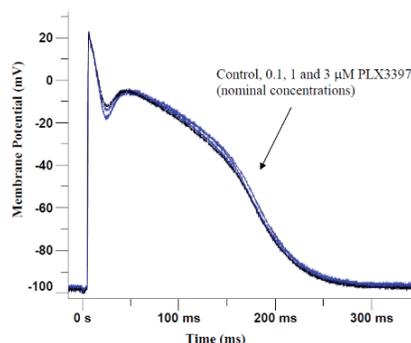
5.4 RABBIT PURKINJE FIBER STUDY.

Non-clinical study report DRN-108-089 ([link](#)) describes the effects of PLX3397 on action potentials (APs) recorded from isolated rabbit purkinje fibers. The studies were conducted in accordance with GLP [REDACTED] ^{(b) (4)} in Jan - March. 2009.

Methods. Sharp electrode recordings were used to measure APs stimulated at basic cycle length of 1 (60 bpm) and 0.5 s (120 bpm) from freshly isolated purkinje fibers from young adult female rabbits at 37°C. Three drug concentrations were tested: 0.1, 1, and 3 μM . Drug concentrations were applied sequentially in ascending order to each fiber. Vehicle was applied to 6 fibers with exposure times that approximated those of the test group. At the

end of vehicle exposure period positive control dl-sotalol was applied. Dose formulation analysis was performed on samples taken from the outflow of the perfusion apparatus to verify test concentrations.

FDA reviewer's comments and study results. The study design and results are sound. AP parameters measured include AP duration at 60% repolarization (APD_{60}), APD_{90} , resting membrane potential (RMP), AP amplitude, and maximum upstroke velocity (dV/dt_{max}). Drug effects on these parameters are informative of drug action on the repolarizing hERG current, inward currents that contribute to the AP plateau including $Ca_v1.2$ current, and peak Na^+ current. There was no now time-dependent change in these AP parameters in vehicle solution, whereas dl-sotalol application significantly increased APD_{60} and APD_{90} , indicating that recorded parameters from this tissue preparation was stable and sensitive to detect hERG channel block. No concentration-dependent effect of PLX3397 on any AP parameter was detected at either basic cycle length. According to figure 2 of the study report (see right), morphology of APs from a representative fiber was unaffected by bath application of 3 concentrations of PLX3397. This was unexpected to the reviewer. Considering the distinct time course and voltage dependence of inward and outward currents that mediate ventricular AP, the reviewer still expected changes in AP morphology based on drug effects on hERG and $Ca_v1.2$ channels obtained in recombinant cell lines even if APD were to remain unchanged. These results raise a question: whether PLX3397 blocks rabbit cardiac ion channels or not, or whether recombinant cell data were an artifact.



5.5 SUMMARY.

Whole cell patch clamp studies performed on human hERG and $Ca_v1.2$ channels expressed in recombinant cells showed that PLX3397 blocks these channels within the therapeutic exposure level. Concomitant block of inward current along with hERG channel block explains why QTcF was not prolonged. The slight decrease in QTcF may reflect greater potency of the drug for $Ca_v1.2$ than hERG channels. However, drug potency for $Ca_v1.2$ channels provided in the study report is likely underestimated due to reasons provided. The lack of PR prolongation also suggests that drug block of $Ca_v1.2$ channels takes time to develop, thereby sparing the peak Ca_{2+} transient driving Ca^{2+} AP. AP recordings from rabbit purkinje fiber suggest no effect any AP parameter, including APD_{60} and APD_{90} . While this may reflect balanced multi-ion channel block, the possibility that PLX3397 is specific to human cardiac ion channels cannot be ruled out.

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/s/

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