CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211810Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Drug Application (NDA)/New Molecular Entity (NME)
Application Number(s)	211810
Priority or Standard	Priority
Submit Date(s)	December 01, 2018
Received Date(s)	December 03, 2018
PDUFA Goal Date	August 03, 2019
Division/Office	DOP2/OHOP
Review Completion Date	July 31, 2019
Established Name	Pexidartinib
(Proposed) Trade Name	TURALIO
Pharmacologic Class	Kinase inhibitor
Code name	PLX3397; PLX3397 hydrochloride
Applicant	Daiichi Sankyo Inc.
Formulation(s)	200 mg Capsules
Dosing Regimen	400 mg (2 capsules) orally twice daily on an empty stomach
Applicant Proposed Indication(s)/Population(s)	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
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the 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

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OPQ = Office of Pharmaceutical Quality
OPDP = Office of Prescription Drug Promotion
OSI = Office of Scientific Investigations
OSE = Office of Surveillance and Epidemiology
DEPI = Division of Epidemiology
DMEPA = Division of Medication Error Prevention and Analysis
DRISK = Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BICR	blinded independent central review
BLA	biologics license application
BPI	Brief Pain Inventory
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CR	complete response
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent-to-treat
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat

MMRM	mixed model for repeated measurements
MRI	magnetic resonance imagining
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NRS	numeric rating scale
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMM	pattern-mixture model
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PR	partial response
PREA	Pediatric Research Equity Act
PRO	patient-reported outcome
PROMIS	Patient-Reported Outcomes Measurement Information System
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
ROM	range of motion
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TGCT	tenosynovial giant cell tumor
TVS	tumor volume score

1. Executive Summary

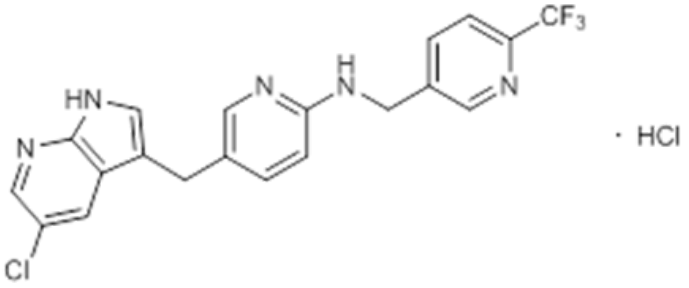
1.1. Product Introduction

On December 3, 2018, Daiichi Sankyo, Inc., (Daiichi Sankyo) submitted NDA 211810 under 21 CFR 314.50 and section 505(b) (1) of the Federal Food, Drug and Cosmetic Act, seeking approval of pexidartinib capsules (200 mg) for the following 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.*

Pexidartinib, a new molecular entity, is a small molecule tyrosine kinase inhibitor of the 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 (FLT3-ITD). The chemical name for pexidartinib hydrochloride is 5-[(5-Chloro-1H-pyrrolo[2,3-b]pyridin-3-yl)methyl]-N-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyridin-2-amine monohydrochloride. The molecular formula for pexidartinib hydrochloride is $C_{20}H_{15}ClF_3N_5$•HCl. The molecular weight is 454.28 for the hydrochloride salt and 417.81 for the free base. The chemical structure is:

Figure 1. Chemical Structure of Pexidartinib Hydrochloride



Pexidartinib capsules (200 mg) are for oral use. Each capsule contains 200 mg pexidartinib which is equivalent to 217.5 mg pexidartinib hydrochloride. The capsule contains the following inactive ingredients: poloxamer 407, mannitol, crospovidone, and magnesium stearate. The hypromellose capsule shell contains hypromellose, titanium dioxide, black iron oxide and yellow iron oxide.

The proposed dosage is 400 mg orally twice daily.

On February 26, 2019 during the review of the New Drug Application (NDA), FDA issued a "Proprietary Name Request - Conditionally Acceptable" letter, stating that the Applicant's proposal for the proprietary name, TURALIO, was found to be conditionally acceptable.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team unanimously agrees that NDA 211810 for pexidartinib capsules meets the statutory standards for regular approval of pexidartinib for the following indication:

> *Pexidartinib for the 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 recommendation for approval is based primarily on the results of the ENLIVEN trial, a randomized (1:1), double-blind, placebo-controlled trial in patients with TGCT not amenable to surgical resection. The NDA also included the results of Study PLX108-01 which provides supportive evidence of efficacy and safety in the indicated population, and pooled data from several studies of patients with and without TGCT which provides additional supportive evidence of safety.

ENLIVEN demonstrated a statistically significant improvement in overall response rate (ORR) in patients randomized to the pexidartinib arm compared to patients randomized to placebo: ORR 38% (95% CI: 26, 50) compared to 0% (95% CI: 0, 6); p-value<0.0001. Responses appeared durable; among responders, duration of response (DoR) ranged from 6.9+ to 24.9+ months. A total of 22 of 23 responders who had been followed for a minimum of 6 months post the initial response maintained their response for 6 or more months and a total of 13 of 13 responders who had been followed for a minimum of 12 months post the initial response maintained their response for 12 or more months. With longer follow-up, increased tumor response rates were observed in patients enrolled in ENLIVEN, including in patients who crossed-over from placebo to pexidartinib. Among patients who were randomized to pexidartinib in Part 1 and in patients who crossed over to receive pexidartinib in Part 2, the ORR was 52% (95% CI: 40, 64; n=61) and 53% (95% CI: 36, 70; n=30), respectively, with additional follow-up. A similar effect was observed in the PLX108-01 study.

Patients also demonstrated statistically significant improvements in the secondary endpoints of mean change in range of motion (ROM), ORR per tumor volume score (TVS), mean change in physical function per the Patient-Reported Outcomes Measurement Information System (PROMIS), and mean change in worst stiffness for patients randomized to the pexidartinib arm compared to patients randomized to the placebo arm; however, the clinical significance of these results was limited by the high proportion of missing data at Week 25 for ROM, physical function, and worst stiffness [27%, 43%, and 43%, respectively], and by uncertainty regarding the threshold for what constitutes a clinically meaningful within-patient change in ROM.

1.3. Benefit-Risk Assessment

Tenosynovial giant cell tumor or TGCT, is a rare, proliferative, and rarely malignant disease which may manifest as one or more tumors that grow in extra-articular synovial tissues, such as the tendon sheaths, or can be an intra-articular process involving the synovium and bursae. The tumor mass typically expands in a slowly progressive or indolent manner. Patients often experience symptoms such as pain, stiffness, swelling, and reduced range of motion (ROM), the severity of which depends on the size, and the location of the tumor or tumors. TGCT can cause significant impairment and adversely affect how patients feel and function.

The spectrum of the therapeutic approaches to managing this disease ranges from observation and use of supportive measures to treat symptoms, to surgical interventions aimed to excise the tumor mass. In patients for whom surgical excision of the tumor is feasible, this approach is usually taken. However, approximately one third of patients experience tumor recurrence, requiring additional surgical procedures including in some cases, joint replacement or amputation. There are no systemic therapies approved for the treatment of this disease, representing an unmet medical need for patients with TGCT who are not candidates for surgery or for whom surgical resection would be associated with excess morbidity.

The assessment of efficacy and safety in this NDA is based primarily on the results of the ENLIVEN trial (NCT02371369), a randomized (1:1), double-blind, placebo-controlled trial in patients with symptomatic TGCT [also referred to as giant cell tumor of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS)], for whom surgical removal of the tumor would be associated with worsening functional limitation or severe morbidity. The primary efficacy outcome measure in ENLIVEN was overall response rate (ORR) at Week 25 as assessed by blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Secondary efficacy outcome measures were also evaluated at Week 25 and included: tumor volume score, range of motion (ROM), Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function items, Worst Stiffness numeric rating scale (NRS) item, and Brief Pain Inventory (BPI)-Worst Pain NRS item.

This trial was designed to enroll a total of 126 patients to provide 90% power to detect a difference in ORR at a two-sided alpha level of 0.05, assuming an ORR of 10% in the placebo arm and an ORR of 35% in the pexidartinib arm. A hierarchical procedure was specified in the analysis plan to adjust for multiplicity in testing the secondary efficacy outcomes in the following (descending order): 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; Proportion of responders based on a 50% reduction in tumor volume score (TVS) at Week 25 as measured in centrally evaluated MRI scans; Mean change from baseline score in the Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function Scale at Week 25; Mean change from baseline score in the Worst Stiffness numeric rating scale (NRS)

item at Week 25; and, Proportion of responders based on patients who experienced a decrease of at least 30% in the mean Brief Pain Inventory (BPI) Worst Pain NRS item and did not experience a ≥30% increase in narcotic analgesic use (BPI-30) at Week 25.

ENLIVEN enrolled a total of 120 patients (pexidartinib arm n=61; placebo arm n=59). The study population was 59% female, and 88% White. The median age was 44 years (range: 18-79) and 63% of patients were enrolled ex-US. Fifty-three percent had prior surgery, 88% were diagnosed with diffuse TGCT, and 9% had previously been treated with systemic therapy. Tumor distribution was as follows: knee (61%), ankle (18%), hip (11%), wrist (3%), foot (3%) and other (5%); 8% of patients had upper extremity involvement. ENLIVEN demonstrated a statistically significant improvement in ORR in patients randomized to the pexidartinib arm compared to patients randomized to placebo: ORR 38% (95% CI: 26, 50) compared to 0% (95% CI: 0, 6); p-value<0.0001. Among responders, duration of response (DoR) ranged from 6.9+ to 24.9+ months. A total of 22 of 23 responders who had been followed for a minimum of 6 months post the initial response maintained their response for 6 or more months and a total of 13 of 13 responders who had been followed for a minimum of 12 months post the initial response maintained their response for 12 or more months. With longer follow-up, increased tumor response rates were seen in all cohorts, including patients who crossed-over from placebo to pexidartinib in ENLIVEN. Among patients who were randomized to pexidartinib in Part 1 and in patients who crossed over to receive pexidartinib in Part 2, the ORR was 52% (95% CI: 40, 64; n=61) and 53% (95% CI: 36, 70; n=30), respectively with additional follow-up. A similar effect was observed in the PLX108-01 study.

While there were statistically significant improvements in the secondary endpoints of mean change in ROM, ORR per TVS, mean change in physical function per PROMIS, and mean change in worst stiffness for patients randomized to the pexidartinib arm compared to patients randomized to the placebo arm, the interpretation of clinical significance of these results was limited by the high proportion of missing data at Week 25 for ROM, physical function, and worst stiffness [27%, 43%, and 43%, respectively], and by uncertainty regarding the threshold for what constitutes a clinically meaningful within-patient change in ROM. There was no statistically significant difference between treatment arms for worst pain.

The results of the ENLIVEN trial were the primary basis for FDA's assessment of the risk of pexidartinib; Study PLX108-01 provided additional data to support the assessment of safety in patients with TGCT. Overall, a total of 768 patients constituted the pexidartinib safety database included in the NDA submission; the safety database included studies of pexidartinib monotherapy and in combination with other agents, in patients with TGCT (n=130) and solid tumor and hematologic malignancies, in commercially-sponsored and investigator-initiated trials.

In ENLIVEN, patients received pexidartinib 400 mg orally in the morning and 600 mg orally in the evening each day for 2 weeks

followed by 400 mg orally twice daily until disease progression or unacceptable toxicity. Seventy-nine percent of patients received pexidartinib for 6 months or longer and 66% for greater than one year. The most common (>20%) adverse reactions, including laboratory abnormalities, in patients who received pexidartinib were: increased lactate dehydrogenase (LDH), increased AST, hair color changes, fatigue, increased ALT, decreased neutrophils, increased cholesterol, increased ALP, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia and decreased phosphate.

Serious adverse reactions were reported in 13% of patients; the most frequent (occurring in more than 1 patient) included abnormal liver tests (3.3%) and hepatotoxicity (3.3%). Permanent discontinuation of pexidartinib due to an adverse reaction occurred in 13% of patients; the most frequent adverse reactions (occurring in more than 1 patient) requiring permanent discontinuation included increased ALT (4.9%), increased AST (4.9%) and hepatotoxicity (3.3%). Dose reductions or interruptions occurred in 38% of patients; the most frequent adverse reactions (occurring in more than 1 patient) requiring a dosage reduction or interruption were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

One patient experienced a Grade 5 event (cardiac arrest); this patient was initially randomized to receive placebo in Part 1 of ENLIVEN and received pexidartinib in Part 2; the death was deemed unrelated to the study drug.

Overall, the risk of liver injury in patients who are exposed to pexidartinib was a major review issue. In the ENLIVEN trial, serum transaminase elevations occurred in a majority of patients; elevations in alanine transaminase (ALT) and aspartate transaminase (AST) occurred in 67% and 90% of patients, respectively; bilirubin increases occurred less frequently in 12% of patients. Approximately 5% of patients in the ENLIVEN trial experienced a pattern of serum transaminase and bilirubin elevation that is indicative of severe liver injury, characterized by AST or ALT greater than 3 times the upper limit of normal (ULN) with concurrent bilirubin increases greater than 2 times the ULN. Across the overall development program in patients with and without TGCT, a similar frequency and severity in serum transaminase and bilirubin abnormalities was observed.

There were 2 cases of irreversible liver injury among the 768 patients in the overall development program of pexidartinib; one patient subsequently underwent liver transplantation and another died due to several factors including liver failure. In the few patients with evidence of liver severe injury whose workup included biopsies, including the 2 patients with irreversible liver injury, there was evidence of bile duct injury or ductopenia.

There remain uncertainties about the long-term effects of treatment with pexidartinib. Although the majority of patients who

experienced serum transaminase and bilirubin elevations while receiving pexidartinib had improvement to baseline levels with dose reductions, dose interruption, and/or discontinuation of pexidartinib, some patients had a prolonged time to recovery despite the implementation of these measures. Because serial biopsies were not performed in most patients with evidence of liver injury, the scope of the liver injury that may occur in the setting of clinically 'normal' or 'improved' serum transaminase and bilirubin levels is unknown. Furthermore, it is unclear whether exposure to pexidartinib causes subacute and/or chronic/indolent injury which is not initially detectable with laboratory monitoring, but which may eventually result in adverse clinical outcomes.

For the majority of patients in ENLIVEN who experienced transaminase elevations with or without concomitant elevations in serum bilirubin, the risk of hepatotoxicity was manageable through dose modifications and/or withdrawal of pexidartinib, including in those who patients who experienced serious events with long recovery periods. In the post-approval setting, the risk of hepatotoxicity can be mitigated with careful selection of patients so that they reflect the indicated population, laboratory and clinical monitoring, dosage modifications, and drug withdrawal as outlined in the prescribing information, and with implementation of a restricted distribution program.

The review team recommends a boxed warning for hepatotoxicity and distribution through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program, which will include a patient registry to provide additional information to further characterize the risk of hepatotoxicity in the indicated population outside of the clinical trial setting and to elucidate the potential long-term risk of liver injury associated with pexidartinib treatment. The review team also recommends that the applicant conduct a study to evaluate the long-term risk of pexidartinib in patients who experience severe liver injury, as a postmarketing requirement.

In summary, patients with TGCT may experience significant physical impairment, particularly when the disease is not amenable to surgical resection; there are no available systemic therapies for the treatment of these patients. FDA acknowledges that TGCT is not a fatal disease and thus, the balance of benefit and risk must be weighed differently than would typically be done for therapies indicated for the palliative treatment of life-threatening or fatal conditions.

- FDA considers robust anti-tumor effects supported by equally robust effects in the clinical outcome assessment endpoints that are clinically relevant to patients with TGCT, as important criteria to demonstrate clinical benefit in this disease; the results of the ENLIVEN trial demonstrated a statistically significant and clinically meaningful improvement in ORR, and thus satisfied the first criterion. Whether the results of ENLIVEN demonstrated robust effects on the clinical outcome assessment endpoints is less clear, given the limitations in the estimation of effects on these endpoints, and in the interpretation of the COA results.

- While the vast majority of patients who were randomized to the pexidartinib arm who experienced serum transaminase and bilirubin elevations had improvement to baseline values with adequate monitoring of the relevant laboratory parameters and the implementation of dose modifications, or withdrawal of the drug, some patients experienced severe liver injury despite these measures. In the overall safety database which included patients without TGCT, this finding was observed, including 2 patients with irreversible liver injury, and biopsies in a few patients indicating ductopenia. Additionally, there remain uncertainties regarding long-term effects of this drug for both injury that is identifiable with laboratory monitoring and injury that may be subclinical, progressive and that may result in adverse outcomes.

Overall, the review team determined that despite the limitations in interpreting the clinical significance of the COA results, and the unknown risk of long-term exposure to pexidartinib, the benefit-risk assessment was favorable for a patient population with no treatments (i.e., surgical interventions) available or for whom treatment with surgery would not be possible due to predicted morbidity. The risks of pexidartinib can be managed with withdrawal of the drug or dose modification. The REMS will ensure that prescribers are informed of the serious risks associated with pexidartinib, and of the recommended monitoring to mitigate this risk. A patient registry will enable an assessment of this risk outside of the clinical trial setting and, along with a post-marketing safety study, will provide information about outcomes in patients with long-term exposure to pexidartinib.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	TGCT is a rare, proliferative, but rarely malignant disease which may manifest as one or more tumors that grow in extra-articular synovial tissues, such as the tendon sheaths, or can be an intra-articular process involving the synovium and bursae. Tumor mass typically expands in a slowly progressive or indolent manner. Patients experience pain, stiffness, swelling, and reduced range of motion (ROM)	TGCT is a rare, infrequently malignant disease; patients typically experience symptoms that may cause significant impairment and adversely affect how patients feel and function.
Current Treatment Options	Excision of tumor is mainstay of treatment; up to 40% of patients may require repeated surgical procedures to treat recurrences, sometimes leading to joint replacement or amputation. There are no approved systemic therapies for patients who are not candidates for surgery.	Patients with TGCT whose disease is not amenable to surgical management or for whom surgery would cause significant morbidity have an unmet medical need for effective systemic therapies.
Benefit	ENLIVEN demonstrated a statistically significant improvement in ORR in patients randomized to the pexidartinib arm compared to patients	ENLIVEN demonstrated a clinically significant improvement in ORR in patients who received

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	randomized to placebo: ORR 38% (95% CI: 26, 50) compared to 0% (95% CI: 0, 6); p-value <0.0001. Among responders, duration of response (DoR) ranged from 6.9+ to 24.9+ months. A total of 22 of 23 responders who had been followed for a minimum of 6 months post the initial response maintained their response for 6 or more months and a total of 13 of 13 responders who had been followed for a minimum of 12 months post the initial response maintained their response for 12 or more months. Among patients who were randomized to pexidartinib in Part 1 and who crossed over to receive pexidartinib in Part 2, with additional follow-up, the ORR was 52% (95% CI: 40, 64) and 53% (95% CI: 36, 70), respectively.	pexidartinib compared to no responses in the placebo arm. ORR was large in magnitude , durable, and clinically meaningful. Additionally, over time, more patients achieved responses. The evidence in the NDA submission meets the evidentiary standard for regular approval.
Risk and Risk Management	A total of 768 patients constituted the pexidartinib safety database, including patients enrolled on studies of pexidartinib monotherapy and in combination with other agents, of whom 130 were patients with TGCT. Seventy-nine percent of patients in ENLIVEN received pexidartinib for 6 months or longer and 66% for greater than one year. The most common (>20%) adverse reactions, including laboratory abnormalities, in patients who received pexidartinib were: increased lactate dehydrogenase (LDH), increased AST, hair color changes, fatigue, increased ALT, decreased neutrophils, increased cholesterol, increased ALP, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia and decreased phosphate. Serious adverse reactions occurred in 13% of patients who received pexidartinib including abnormal liver tests (3.3%) and hepatotoxicity (3.3%). Permanent discontinuation of pexidartinib due to an adverse reaction occurred in 13% of patients including increased ALT (4.9%), increased AST (4.9%) and hepatotoxicity (3.3%). Dose reductions or interruptions occurred in 38% of patients, including increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%). One patient experienced a Grade 5 event (cardiac arrest); this patient was initially randomized to receive placebo in Part 1 or ENLIVEN and received pexidartinib in Part 2; the death was considered unrelated to the study drug. The risk of liver injury in patients who are exposed to pexidartinib was a	Hepatotoxicity occurs frequently in patients who are exposed to pexidartinib; hepatocellular injury is the most common mechanism of injury although in a subset of patients, a mixed pattern of injury is observed. There have been cases of irreversible liver injury. There remain uncertainties about the long-term effects of treatment with pexidartinib. Although the majority of patients who experienced serum transaminase and bilirubin elevations while receiving pexidartinib had improvement to baseline levels with dose reductions, dose interruption, and/or discontinuation of pexidartinib, some patients had a prolonged time to recovery despite the implementation of these measures. Because serial biopsies were not performed in most patients with evidence of liver injury, the scope of the liver injury that may occur in the setting of clinically 'normal' or 'improved'

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	major review issue. In the ENLIVEN trial, elevations in ALT and AST occurred in 67% and 90% of patients, respectively; bilirubin increases occurred in 12% of patients. In ENLIVEN, 4.9% of patients experienced a pattern of serum transaminase and bilirubin elevation that is indicative of severe liver injury, characterized by AST or ALT >3 times the upper limit of normal (ULN) with concurrent bilirubin increases >2 times the ULN. Across the overall development program in patients with and without TGCT, a similar frequency and severity in serum transaminase and bilirubin abnormalities was observed. There were 2 cases of irreversible liver injury among 768 patients (0.3%) - one patient subsequently underwent liver transplant and another died due to several factors including liver failure. In the 8 patients with evidence of liver severe injury whose workup included biopsies, including the 2 patients with irreversible liver injury, there was evidence of bile duct injury or ductopenia.	serum transaminase and bilirubin levels is unknown. Furthermore, it is unclear whether exposure to pexidartinib causes subacute and/or chronic/indolent injury which is not detectable at first with laboratory monitoring, but which may eventually result in adverse clinical outcomes. The review team recommends a boxed warning for hepatotoxicity and distribution through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program, which will include a patient registry to provide additional information to further characterize the risk of hepatotoxicity in the indicated population outside the clinical trial setting. The review team also recommends that the applicant conduct a study to evaluate the long-term risk of pexidartinib in patients who experience severe liver injury, as a postmarketing requirement. These measures in addition to adequate labeling, will mitigate the risk of hepatotoxicity and will help to further address the uncertainties regarding the risk.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as			
			X	Patient reported outcome (PRO)	Section 8.1
			□	Observer reported outcome (ObsRO)	
			X	Clinician reported outcome (ClinRO)	Section 8.1
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

Lola Fashoyin-Aje, MD, MPH
Cross-Disciplinary Team Leader

2. Therapeutic Context

2.1. Analysis of Condition

TGCT is a rare, usually monoarticular, nonmalignant neoplasm involving the synovium and tendon sheaths that presents in young and middle-aged adults (Kramer DE, 2009). There are two subtypes of TGCT, namely, giant cell tumor of the tendon sheath (GCT-TS) and pigmented villonodular synovitis (PVNS). GCT-TS is more likely to be localized and to occur in the digits. GCT-TS is estimated to occur at an incidence of 1.8 cases per million in the United States. PVNS is more likely to be diffuse and to occur in large joints, particularly the knee, ankle and hip. PVNS is estimated to occur at an incidence of 9.2 cases per million in the United States (Myers, 1980). Patients are usually diagnosed between the ages of 20 and 60 years and most often present with pain and swelling at the affected joint (Fletcher CDM, 2013). Symptoms are generally minimal at first due to the slowly progressive nature of the disease; however, as the tumors expand within the intra-articular space and surrounding tissue, patients develop pain, stiffness, swelling and reduced range of motion. TGCT is diagnosed based on pathological evaluation; however, features highly suggestive of the disease may be found on radiologic imaging, particularly on magnetic resonance imaging (MRI) (Mendenhall WM, 2006).

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 (Dal Cin P, 1994; West RB, 2006).

2.2. Analysis of Current Treatment Options

The current standard of care is surgical resection using arthroscopic synovectomy or open resection. The goals of surgical resection of the tumor is to remove the tumor mass as much as possible, so as to reduce pain, stiffness and joint destruction, improve function, and minimize risk of recurrence. Patient outcome following surgery depends on the location and extent of the disease. The recurrence rate for patients with focal localized disease is low, ranging from 0% to 6%; however, for patients with diffuse forms of the disease the recurrence rate ranges from 15% to 40% (van der Heijden L1, 2013). Additionally, patients with diffuse disease may experience multiple recurrences and may also have more extensive disease and poorer outcomes with surgery.

External beam radiation can be administered in select cases where surgery is not feasible. The goals of treatment are to reduce tumor-related symptoms of pain, stiffness, and immobility and to lessen the risk of recurrence. There are no systemic therapies approved for treatment of patients with PVNS or GCT-TS. Commercially marketed systemic therapies that have activity against CSFR1 have been investigated in, but do not have FDA approval for, patients with TGCT.

These include imatinib and nilotinib. In patients who received imatinib or nilotinib, reported ORR was approximately 20% and approximately 6%, respectively (Cassier PA, 2012; Gelderblom H, 2018) Neither imatinib or nilotinib have been investigated in a randomized clinical trial of patients with TGCT.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Pexidartinib is a new molecular entity and is not currently approved for marketing in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following summarizes the important clinical pre-submission regulatory activity for pexidartinib:

- July 21, 2009: Plexxikon submitted Investigational New Drug (IND) application (b) (4) containing the protocol for Study PLX108-01, a dose-finding study of PLX3397 in patients with refractory solid tumors. The IND was deemed safe to proceed on August 19, 2009; the study was initiated in October 2009. This study is ongoing and includes an expansion cohort for patients with inoperable pigmented villonodular synovitis (PVNS) and giant cell tumor of the tendon sheath (GCT-TS).
- February 14, 2014: PLX3397-HCl was granted orphan drug status (#13-4199) for the "Treatment of pigmented villonodular synovitis/giant cell tumor of tendon sheath".
- February 27, 2014: A pre-IND/end-of-phase 2 (EOP2) meeting was held to discuss the design of Trial PLX108-10 (ENLIVEN), intended to support a New Drug Application (NDA) for PLX3397 in patients with PVNS and GCT-TS. FDA made the following key points:
  - Durable objective response (DOR) of sufficient magnitude supported by reliably detected effects on clinically important patient functional status and patient reported outcomes (PROs) may serve as a basis to support approval.
  - Objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 will be the primary efficacy endpoint, and response rate according to the protocol specific Tumor Volume Score (TVS), will be assessed as a secondary endpoint.
  - PRO endpoints could provide useful supportive data if it can be shown that they reliably measure an improvement in pain or function in patients with PVNS.
  - A post-marketing study might be required to establish an optimal dose because the product may be administered chronically.
  - Given the rarity of the disease, the estimated safety database of patients treated with PLX3397 in conjunction with the safety database accumulated in clinical trials of PLX3397 in other patient populations may be sufficient to support a marketing application provided that no unusual toxicities are identified.
  - A single trial could support an application for registration if the results show a highly statistically significant effect on a measure of clinical benefit and are sufficiently robust and so compelling that it would be unethical to repeat the study in this rare disease population. FDA recommended that Plexxikon incorporate a reliable objective measure of functional improvement.

  - FDA emphasized that the results of PRO endpoints may not be interpretable if there are substantial missing data or due to inadvertent unblinding issues.

- September 29, 2014: Plexxikon submitted IND 117332 containing the ENLIVEN protocol entitled "A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumor of the Tendon Sheath." FDA deemed the IND safe to proceed on October 29, 2014.
- September 29, 2014: Plexxikon submitted a Special Protocol Assessment (SPA) request for the ENLIVEN trial. Clinical and statistical concerns pertaining to the proposed eligibility criteria, the methods of collecting and analyzing key patient reported outcomes, secondary endpoints, and the proposed statistical test for the primary efficacy analysis, were communicated to Plexxikon during a teleconference on November 4, 2014.
- November 12, 2014: A Special Protocol No Agreement letter was issued, and it included comments detailing the protocol revisions required to reach a SPA agreement.
- January 30, 2015: Plexxikon informed FDA that they would not re-submit the SPA request.
- February 10, 2015: Plexxikon transferred the legal and regulatory obligations for PLX3397 under IND 117332 to Daiichi Sankyo, Incorporated (DSI).
- June 26, 2015, FDA and DSI participated in a teleconference as part of the Office of Hematology and Oncology Products (OHOP) Preliminary Breakthrough Therapy Designation Request (BTDR) process, to discuss whether the preliminary efficacy results from patients with PVNS or GCT-TS treated in Study PLX108-01, could support a BTDR; FDA agreed that the based on the preliminary data, DSI could submit a BTDR.
- October 28, 2015: PLX3397 was granted Breakthrough Therapy Designation (BTD) for the treatment of patients with PVNS or GCT-TS where surgical resection is associated with potentially worsening functional limitation or severe morbidity. The BTD was based on an ORR of 45% (95% CI: 27,64) and median duration of response from onset of response until progression, discontinuation or data cutoff of seven months in 31 patients treated in Study PLX108-01.
- February 19, 2016: DSI submitted a request for a Type B/multidisciplinary Breakthrough Therapy meeting to obtain FDA's feedback on proposals to expedite the development program. Preliminary responses containing the following key points were sent to DSI on April 7, 2017, and the meeting subsequently was cancelled by DSI:
  - FDA agreed to the nonclinical package for a proposed NDA submission
  - FDA agreed that an NDA may be submitted based on positive data from primary safety and efficacy analyses from Trial ENLIVEN but stated that a post marketing study may be required to establish safety of chronically administered dosing
  - FDA agreed that the 120-day safety update will include safety data and analyses through data cut off that is 3 months after planned submission for all ongoing clinical trials of pexidartinib and for the ENLIVEN trial

- March 29, 2016: FDA and DSI participated in a Type B meeting to discuss topics related to the CMC development for PLX3397
- October 12, 2016: FDA placed IND 117332 on partial clinical hold and halted further enrollment into ENLIVEN due to reported serious adverse events (SAEs) of hyperbilirubinemia with concurrent liver enzyme elevation in patients with TGCT and in patients with cancer treated under other INDs.
- March 16, 2017: DSI provided a complete response to the partial clinical hold. FDA assessed the response to partial clinical hold as complete and to have satisfactorily addressed the issues (refer to Section 8.2.1 of review for details) and removed the clinical hold on April 10, 2017.
- July 24, 2017: DSI submitted a Type B meeting request to obtain the Agency's feedback on the proposal to revise the sequential hierarchy for testing of secondary efficacy endpoints in ENLIVEN (refer to Section 8.2.1 of the review for details). On September 6, 2017, FDA provided DSI with preliminary comments, and the meeting subsequently was cancelled.
- October 16, 2017: DSI submitted a Type A meeting request to discuss specific aspects of clinical pharmacology study (PL3397-A-U126) and to obtain FDA feedback on the suitability of a proposed clinical pharmacology data package to support NDA review. The meeting was denied because the information contained in the meeting request did not meet the criteria for a stalled development program. However, FDA provided a response to a question about the acceptability of enrolling patients with TGCT in the planned drug-drug interaction (DDI) study, PL3397_A_U126. FDA provided information to facilitate DSI's drug-drug interaction program.
- November 9, 2017: DSI requested a Type B meeting to discuss the clinical pharmacology program for pexidartinib for the treatment of patients with symptomatic TGCT. The meeting was held via teleconference on January 12, 2018.
- November 13, 2017: FDA placed IND 117332 on partial clinical hold and halted further enrollment into other trials across the development program for pexidartinib, due to additional reports of serious adverse events of hepatotoxicity (refer to Section 8.2.1 of the review for details). DSI provided a complete response to the partial clinical hold on December 20, 2017, that satisfactorily addressed the hold issues by revising the protocol to increase frequency of monitoring for hepatotoxicity, incorporating additional risk mitigation strategies in the protocol, and amending the informed consent and Investigator's brochure. The clinical hold was removed on January 12, 2018.
- January 12, 2018: FDA and DSI held a type B meeting via teleconference to discuss the clinical pharmacology program for pexidartinib for the treatment of patients with symptomatic TGCT.
- January 19, 2018: DSI submitted a Type B pre-New Drug Application (pNDA) meeting request to obtain guidance for a planned NDA submission for pexidartinib for the treatment of symptomatic tenosynovial giant cell tumor.
- March 20, 2018: A Type B pre-NDA meeting was held to discuss and come to agreement on the content and format of the NDA submission. The following key agreements were made:

- FDA agreed to review an NDA seeking approval for pexidartinib in an appropriate subgroup of patients with TGCT in which the likelihood of obtaining clinical benefit from pexidartinib outweighs the risks. FDA recommended that the NDA include adequate justification for the proposed restricted indication and a robust benefit: risk assessment for pexidartinib for this subgroup. FDA stated that the totality of the efficacy and safety data in the application would be reviewed and if necessary, advice from an Advisory Committee (AC) may be sought prior to taking an action on the application for pexidartinib in TGCT.
- FDA recommended that DSI also include in the NDA a discussion of why the totality of the available evidence overcomes the limitations in the collection of patient-reported outcomes (PROs) data.
- FDA agreed to the presentation of objective response rate and duration of response efficacy data according to RECIST and Tumor Volume Score (TVS) in the following groups:
  - Patients who received pexidartinib (N=61) as compared to patients who received placebo (N=59) during Part 1 of ENLVIEN;
  - Patients who initially received placebo and then crossed over to receive pexidartinib in Part 2 of ENLVIEN (N=30);
  - Patients who were initially randomized to pexidartinib for the randomized portion of the trial and who continued on the single arm Part 2 of the study (N=61)
  - Patients who were treated in the TGCT cohort of PLX108-01 (N=39);
  - FDA also requested an exploratory analyses of response rate and DOR that pools the 91 patients treated with pexidartinib in ENLIVEN with the 39 patients who received pexidartinib in PLX108-01.
- FDA agreed with DSI's general proposal for evaluating the clinical outcomes data from ENLIVEN; however, FDA requested confirmation that the following analyses will be conducted and included in the Summary of Clinical Efficacy (SCE) (or Integrated Summary of Efficacy if appropriate):
  - a comparison of the mean change from baseline for range of motion, PROMIS, and worst stiffness and worst pain assessments between all patients treated with pexidartinib versus placebo during the randomized portion (Part1) of ENLIVEN
  - a comparison of the mean change from baseline for range of motion, PROMIS, and worst stiffness and worst pain measures between the patients treated during the randomized portion of ENLIVEN who had a valid baseline and at least one post-baseline assessment
  - associations between tumor response rate and range of motion, PROMIS, and worst stiffness and worst pain endpoints to demonstrate that tumor shrinkage correlates with improvement in clinical outcomes
  - a sensitivity analysis that addresses the missing PRO and range of motion data on both arms of Part 1 of ENLIVEN

    - a thorough discussion of the actual clinical benefit of improved ROM in individual patients based upon the specific joint involved and the extent of impairment at baseline

- FDA agreed to the submission of a separate PRO report in Module 5.3.5.3 to support the use of the selected PRO measures in ENLIVEN but stated that it is unlikely that labeling claims can be made if there is significant missing data even if the tools are validated for the study population.
- FDA agreed with the submission of individual patient efficacy narratives for patients treated during ENLIVEN. These narratives should provide the patient's best response to pexidartinib (if any) and discuss any correlative improvements observed in the patient's disease-related symptoms and functional status. If the patient is considered to have had clinical benefit during treatment with pexidartinib, include examples of this benefit (e.g., ability to ambulate following tumor shrinkage during treatment with study drug). Include available and relevant photographic assessments in the narratives.
- FDA agreed with the proposal to submit available photographic data from Studies PLX108-01 and ENLIVEN as supportive evidence of the clinical benefit provided with pexidartinib.
- DSI stated that the following datasets for both PLX108-01 and ENLIVEN would be submitted:
    - SDTM and ADaM datasets for the March 2017 data cut
    - ADaM datasets for the Jan 31, 2018 data cut
- FDA agreed with DSI's plan to pool the safety data from Studies PLX108-01 and ENLIVEN to provide the primary integrated safety analyses for the Summary of Clinical Safety (SCS) and to pool safety data from patients with non-TGCT solid tumor malignancies who received single agent pexidartinib across the pexidartinib development program to conduct supportive safety analyses. Safety analyses from Study PLX108-05 (AML trial) should also be included, though these data need not be pooled with the solid tumor data. FDA stated that there may be additional requests for exploratory analyses of pooled data across both the TGCT and cancer populations that have been exposed to pexidartinib for specific safety signals that are observed during the review of the NDA.
- FDA requested side-by-side summary tables to present key safety information from all patients with TGCT, non-TGCT solid tumors, and AML treated with pexidartinib, regardless of dose.
- With regard to the risk for hepatotoxicity with pexidartinib, FDA stated that DSI should include in the SCS a thoughtful assessment of this risk that discusses the mechanism of liver injury, ways to mitigate risk for patients, and how this toxicity impacts the overall benefit: risk assessment for pexidartinib for the intended population.
- FDA stated that DSI should provide summary tables that list all patients in the TGCT development program and all patients in the non-TGCT pexidartinib program who

experienced elevation of transaminases and elevation of bilirubin concurrent with or following transaminitis. The tables should include subject identification (ID), diagnosis, risk factors, concomitant medications, pexidartinib dose, time of initial event, presenting symptoms, peak laboratory values, duration of transaminitis and hyperbilirubinemia in days, actions taken with study drug, other medical interventions (e.g., hospitalization, liver biopsy, etc.), and whether there was resolution. DSI should also submit copies of all liver biopsy reports with hyperlinks in the respective patient narratives.

- FDA agreed with DSI's plan to include the narrative portion of the ISS in Module 2.7.4 with a hyperlink to the tables, listings, and figures of the integrated analyses of pooled data located in Module 5 if there is sufficient space to provide a robust and thoughtful discussion of the integrated safety data that permits a thorough assessment of the risks and benefits of pexidartinib in the proposed population. Summary tables of key results from the pooled analyses (with footnotes and hyperlinks to the relevant Module 5 tables/listings) should be included in Module 2 to support the relevant text discussions in the SCS.
- DSI will provide safety narratives for the following events:
  - Deaths during treatment or within 30 days of treatment discontinuation
  - Deaths after 30 days of treatment discontinuation reported as related to pexidartinib
  - SAEs
  - Discontinuations due to AEs, excluding disease progression
  - AEs judged to be of special interest
  - Events meeting liver function test signature criteria of transaminases increase with hyperbilirubinemia
- FDA stated that a full review of the proposed REMS will be made during review of the NDA. At the time of submission, DSI will include the REMS Supporting Document, relevant prescriber certification, and training materials as well as any patient materials that will support the REMS. The Agency will review the prescriber training program in the proposed REMS. FDA will also review the language in the labeling and whether this information is sufficient to communicate the risk.
- DSI stated that clinical study reports (CSRs) for all completed studies will be included in the NDA submission. The CSRs for the two studies conducted in patients with TGCT (PLX108-01 and ENLIVEN) are based on locked datasets with a clinical cut-off of March 3, 2017, and March 27, 2017, respectively. To provide more mature data for the NDA, an additional cut of the study data will be performed with a clinical cut-off of January 31, 2018.These data will be locked and select tables, listings, and figures will be generated and included in the CSRs by amendment.
- Since a draft Table of Contents (TOC) was not included in the meeting package for the pre-NDA meeting, FDA agreed to review the TOC as a follow-up submission after the pre-NDA meeting.

The following summarizes the post submission regulatory activity for pexidartinib:

- On December 3, 2018, the final module of NDA 211810 was received.
- On January 16, 2019, a teleconference was held between FDA and Daiichi Sankyo where FDA informed Daiichi Sankyo that NDA 211810 would be presented to an Oncology Drug Advisory Committee (ODAC). The issues that will be discussed at ODAC are the assessment of the clinical benefit and the characterization of hepatotoxicity.
- On January 31, 2019, FDA designated the review of the application as a priority review. FDA issued a "Filing Review Issues Identified" letter. The letter stated that during filing review of NDA application, FDA stated that the application would be referred to the ODAC to discuss the following potential review issues:
  - The risk-benefit profile in the indicated population and the identification of the population in whom the potential risks of serious hepatotoxicity are outweighed by the benefits and possible measures,
  - The interpretability and reliability of the patient-reported outcomes data, given the extent of missing data and the consequent mid-protocol reordering of key trial endpoints.
- On February 26, 2019, FDA issued a "Proprietary Name Request - Conditionally Acceptable" letter, stating that the proposed proprietary name, Turalio, was found to be conditionally acceptable.
- On March 15, 2019, FDA and Daiichi Sankyo held a mid-cycle communication. FDA provided an update on the status of the review and communicated significant issues arising from the review. FDA stated the following concerns:
  - Review of data to characterize the risk of hepatotoxicity, including both short-term and long-term risks to patients, is ongoing. Additional information will be requested to evaluate these risks.
  - Development of a risk mitigation plan to ensure safe use postmarket and to obtain information to enable further characterization of hepatotoxicity in the postmarket setting is ongoing.
  - Impact of missing data for clinical outcome assessments (COA) and the interpretation of the estimated treatment effect with respect to each COA instrument is under review.
  - The evidence to support Daiichi's proposed contraindication of pexidartinib in all patients with pre-existing mild hepatic impairment is under review. A potential PMR to be conducted in patients enrolled in ongoing clinical trials is being considered to assess the risk benefit profile of pexidartinib in patients with pre-existing moderate hepatic impairment.
  - Pexidartinib exposure is increased with a high-fat meal, compared to the fasted condition. As pexidartinib is recommended to be administered under a fasted condition, twice daily, there is a significant safety concern in patients who may not comply with this fasting condition. A PMR to assess the effect of a low-fat meal on pexidartinib will be issued. This PMR will be designed to determine the

recommended lower dose of pexidartinib under fed conditions which matches exposure under the current fasted conditions.

- On April 25, 2019, FDA sent Daiichi Sankyo an information request in order to address the proposed REMs. In this information request FDA request that Daiichi Sankyo modify the REMS goals and add a patient registry to the REMs in order to further characterize the risk of acute chronic, and irreversible hepatotoxicity. On May 14, 2019, Daiichi Sankyo responded and agreed to the modification of REMs goals as well as the addition of the patient registry.
- May 2, 2019: A late cycle meeting was held to provide updates on the status of the review.
- May 14, 2019: FDA held on Oncologic Drugs Advisory Committee meeting to discuss whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatoxicity.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI review team determined that the data from the ENLIVEN trial appear reliable based on available information from the inspections of one domestic and two foreign clinical sites. These sites were selected for inspection based upon being the sites with the highest enrollment in ENLIVEN.

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).

GCP violations were observed during the inspection of the Clinical Investigator, Dr. Hans Gelderblom, M.D. These were 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 patients revealed multiple deficiencies as follows:

- 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.
- Laboratory safety and pharmacokinetic samples were routinely reported as collected at the nearest 5-minute interval, rather than the actual time.
- Source documents for all patients indicated that the timing of all study medication dosing occurred in multiples of 5 minutes.

The OSI review team determined that these violations 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). Refer to the Clinical Inspections Summary by Dr. Homayouni). Please see Section 8.1.2 for reviewer assessment of potential impact of these deficiencies.

4.2. Product Quality and Clinical Microbiology

From the chemistry, manufacturing, and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this application.

Based on the provided stability data, a 30-month expiration dating period is granted for Turalio (pexidartinib) capsules, 200 mg when stored at 20 - 25ºC (68 - 77ºF); with excursions permitted to 15 - 30ºC (59 - 86ºF) [see USP controlled room temperature. Refer to the CMC review for full details.

4.3. Devices and Companion Diagnostic Issues

Not relevant to this NDA submission.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Pexidartinib is a small molecule tyrosine kinase inhibitor of the 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 (FLT3-ITD); its established pharmacologic class is kinase inhibitor.

In an in vitro assay, pexidartinib inhibited the catalytic activity of CSF1R, KIT, and FLT3 with IC_{50} values of 0.017, 0.12, and 0.16 µmol/L, respectively. Pexidartinib did not induce biologically relevant off target activity in vitro against any other kinases in a 226-kinase panel or across a panel (n=71) of receptors, ion channels, transporters, and enzymes. In human cells, pexidartinib inhibited the phosphorylation of CSF-stimulated CSF1R and constitutively active FTL3-ITD with IC_{50} values of 0.007 and 0.026 µmol/L, respectively, but did not significantly inhibit phosphorylation of wild-type FLT3 in human cells. Pexidartinib induced in vitro cell growth inhibition in 6 different cells lines dependent on CSF1R, KIT, or FLT3-ITD. In an in vivo model in which injection of CSFR1 signaling-dependent cells results in splenomegaly, pexidartinib inhibited splenomegaly by 79%, compared to the vehicle control.

The Applicant conducted stand-alone GLP-compliant safety pharmacology studies in rats and dogs to assess the effects of pexidartinib on the central nervous system, respiratory function, and the cardiovascular system. There were no pexidartinib-related adverse effects on the central nervous system or respiratory function following a single dose up to 200 mg/kg. Pexidartinib inhibited the hERG potassium channel with an IC_{50}=0.7 µM, suggesting some potential for QTc prolongation; however, there were no effects on QTc or other electrocardiogram parameters in in vivo animal studies and no evidence of QT prolongation occurring in humans at the 800 mg dose, likely due to the high protein binding of pexidartinib in human plasma (C_{max}=8625 ng/mL, 20 µM, with 99.8% protein binding; free C_{max} ~40 nM). Up to 3 µM of pexidartinib did not prolong cardiac action potential repolarization or induce any significant changes to cardiac parameters in isolated rabbit Purkinje fibers. Pexidartinib inhibited the human cardiac L-type calcium channel (hCav1.2-β2-α2δ) stably expressed in Chinese Hamster Ovary (CHO) cells (IC_{50}=0.2 µM); this inhibition may be related to the in vivo animal finding of transient pexidartinib-related reductions of 6.0, 11.0, or 10.0 mmHg in mean arterial pulse pressure in male dogs at doses of 50, 300, or 1000 mg/kg, respectively.

To assess its safety, the Applicant conducted GLP-compliant toxicology studies of daily oral pexidartinib of up to six months in Sprague Dawley rats and up to nine months in Beagle dogs. In both species major target organs included the reproductive organs of both sexes and the kidney. In the rat, the liver and lymph/hematopoietic compartments as well as connective fibers in the skin and gastrointestinal (GI) tract were additional target organs.

In the six-month study in rats, treatment with pexidartinib at 60 mg/kg daily (approximately 1.6 times the clinical exposure of 154930 ng·h/mL [estimated AUC_{24} from the 77465 AUC_{12} cited in the label] at the recommended human dose of 800 mg daily) resulted in the death of 3 main

study animals due to treatment-related immunocompromise. In the liver, hemosiderin deposition and necrotizing inflammation with increased levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) occurred at doses ≥20 mg/kg (approximately 0.6 times the clinical exposure at 800 mg). Additionally, biliary cysts and increased gamma-glutamyl transferase (GGT) levels occurred in female rats at 60 mg/kg. The liver is a major target organ clinically, with frequent elevations in transaminases, including serious ones (refer to Section 8.3 of the review for details). In the kidney, rats had evidence of chronic progressive nephropathy at doses ≥20 mg/kg. Pexidartinib-related observations on the lymph/hematopoietic compartments include lymphoid depletion of the thymus with decreased thymus weight and lymphocyte counts and lymphoid hyperplasia with lymph node enlargement and increases in neutrophils and large unstained cells (LUC). Pexidartinib-related minimal to severe vascular inflammation compatible with polyarteritis nodosa and characterized by medial hypertrophy of arterioles and arteries, fibrinoid necrosis of the vessel walls and a mixed inflammatory cell infiltration also occurred in males dosed at 60 mg/kg. At doses ≥20 mg/kg there were frequent findings of myxomatous changes in the skin that ranged from mild to moderate; similar changes occurred in the tongue and cecum at the 60 mg/kg high dose level. In the 2-year rat carcinogenicity study there were also findings of alterations in the tunica intima of the aorta. Clinical signs associated with pexidartinib treatment in all rat studies included swollen facial area, forelimbs, hindlimbs, and/or ventral neck, and dried red material around eyes. Edema, including peri-orbital edema is a common clinical reaction as well. With the exception of edema, all findings in rats were partially to fully reversible within the recovery period. Finally, at doses ≥60 mg/kg (approximately 1.6 times the exposure in humans at the 800 mg dose) there were dose-dependent findings of minimal to moderate subphyseal or cortical hyperostosis (increased bone growth) and physeal hypertrophy in the femur that correlated with decreased systemic phosphate levels. These changes were consistent with the role of CSFR1 in osteoclast development and activity.

In the 9-month dog study, there were no test article related deaths. Exposures in dogs at the highest tested dose of 100 mg/kg were approximately 0.3 times the human exposure at the 800 mg dose. Clinical observations in animals treated ≥30 mg/kg (~ 0.15 times the clinical exposure at 800 mg) included loss of hair and skin pigmentation on various body surfaces (face, forelimbs, hindlimbs, dorsal trunk), clear discharge from the eye(s), and emesis that persisted during the 16-week recovery period. Hair color changes are a frequent clinical reaction as well.

In humans, the most abundant metabolite of pexidartinib is a result of its N-glucuronidation to ZAAD-1006a. This metabolite did not inhibit the activity of CSF1R, KIT, or FLT3 at relevant concentrations; however, the Applicant did not assess any additional potential off-target effects of this metabolite, which occurs at levels that exceed those of the parent compound in humans. This deficiency resulted in a PMC for additional in vitro screening assays for ZAAD-1006a. In the repeat-dose toxicology studies in rats and dogs, systemic exposure of ZAAD-1006a was not assessed, and therefore its toxicological potential was not evaluated. Based on single dose studies showing high levels of ZAAD-1006a in monkeys but not in rats, mice, or dogs, the Applicant conducted an additional GLP-compliant, 13-week, repeat-dose toxicity study of pexidartinib in cynomolgus monkeys with a four-week recovery period. In this study, systemic exposure of ZAAD-1006a was at least 60-fold higher than exposure to pexidartinib after 91 days

of dosing and exposures were higher than those seen clinically. There were no test-article related toxicities in animals at any dose level in this study.

Pexidartinib was not mutagenic in the in vitro bacterial reverse mutation (Ames) test or clastogenic in either the in vitro chromosomal aberrations assay in peripheral human lymphocytes or the in vivo bone marrow micronucleus assay in rats. The Applicant also conducted a two-year (104-week) carcinogenicity study in rats and a 26-week carcinogenicity study in transgenic mice. Pexidartinib was negative for carcinogenicity in these studies.

To assess pexidartinib effects on fertility, the Applicant mated male rats treated with pexidartinib (4, 10, 40 mg/kg) orally once daily (63 days prior to mating until the day of mating) with female rats administered pexidartinib (4, 10, 40 mg/kg) orally once daily starting 14 days prior to mating until Gestation Day (GD) 7. At the high dose level of 40 mg/kg (approximately 1.3 times the clinical exposure of pexidartinib at the 800 mg dose), rats displayed decreases in fertility. In males, lower epididymal and testicular weights with corresponding macroscopic findings occurred at doses ≥10 mg/kg/day (~0.3 times the clinical exposure), accompanied by clear reductions in sperm production and motility at 40 mg/kg. These findings were consistent with findings in the 6-month toxicology study in rats of germ cell depletion of the testes and hypospermia and cellular debris in the epididymis at doses ≥20 mg/kg (~0.6 times the human exposure at the 800 mg dose) as well as with germ cell depletion in the testes and hypospermia in the epididymides with lower organ weights in dogs at doses ≥30 mg/kg (~0.15 times the human exposure at the 800 mg dose). In females administered 40 mg/kg pexidartinib, findings included increases in pre-and post-implantation loss and decreases in viable embryos. These changes were consistent with ovarian findings in the 6-month rat study of necrosis of corpora lutea, decreases in retained antral follicles, pigment deposition within the interstitium, and increases in both luteal cysts and hemorrhage of corpora lutea. In addition, pexidartinib treatment in female dogs in the 9-month study resulted in atrophy of the cervix with lower uterus/cervix weights. Findings in both males and females are consistent with literature reports of decreased fertility in CSF1 or CSFR1 knockout mice of both sexes (Cohen PE, 1999). The suboptimal study design in which both sexes received pexidartinib prior to mating makes clear attribution of the reduced fertility by sex impossible. Despite this deficiency, the histopathological findings in both male and female animals coupled with reduced pregnancy are adequate to warn patients about the potential risk of reduced fertility with pexidartinib and additional individual fertility studies would not mitigate the compelling histopathological findings from the existing data. The label includes advice for providers to alert both male and female patients taking pexidartinib of the potential for at least transient decreases in fertility.

The Applicant conducted embryo-fetal development studies in rats and rabbits. At the dose of 40 mg/kg (approximately equal to the exposure at the 800 mg clinical dose), there was a modest increase in early resorptions and post implantation loss in rats. Pexidartinib-related fetal malformations and variations including localized fetal edema, absent kidney and ureter, abnormalities of the reproductive tract, and decreased skeletal ossification also occurred at 40 mg/kg in rats. In pregnant rabbits, there was increased post-implantation loss and abortion, as well as decreases in the number of viable fetuses at 60 mg/kg/day (~0.8 times the exposure at the 800 mg clinical dose). Fetal malformations (absent kidney or ureter, misshapen or

malpositioned kidney, rib abnormality, and accessory skull bones) also occurred at 60 mg/kg. In a pre-and postnatal development study, female rats received pexidartinib once daily from GD 6 to lactation day (LD) 20 at doses up to 10 mg/kg/day (approximately 0.3 times the exposure at the 800 mg clinical dose). In this study, there were no treatment related effects observed in the F0 generation dams, the F1 generation, or the F2 generation.

Based on data from the embryo-fetal development studies and the drug's mechanism of action, the prescribing information includes a warning for embryo-fetal risk. The label also advises females of reproductive potential to use contraception for at least 30 days after the last dose of TURALIO and males with female partners of reproductive potential to use contraception for at least one week after the final dose, consistent with currently recommended timeframes for contraception for non-genotoxic but teratogenic drugs in each sex. No studies were conducted or required to investigate the presence of pexidartinib in milk. Because many drugs are secreted in milk, the label includes a warning not to breastfeed during treatment with TURALIO for one week after the final dose, based on the half-life of the drug.

There are no outstanding issues from a pharmacology/toxicology perspective that would prevent the approval of TURALIO for the treatment of adult patients with symptomatic tenosynovial giant cell tumors (TGCT) associated with severe morbidity or functional limitations which is not amenable to improvement with surgery.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary Pharmacology

The Applicant utilized a Z'-LYTE^{TM} assay to assess the in vitro inhibitory activity of pexidartinib against a panel of 226 kinases including colony stimulating factor 1 receptor (CSF1R), KIT proto-oncogene receptor tyrosine kinase (KIT), and FMS-like tyrosine kinase 3 (FLT3; Study DRN-108-030). The Z'-LYTE^{TM} assay employs a fluorescence-based, coupled-enzyme format based on the differential sensitivity of phosphorylated and non-phosphorylated peptides to proteolytic cleavage. Kinase inhibition increases the cleavage of substrates and releases fluorescent quenching, leading to higher fluorescent signals. As detailed in Table 1, pexidartinib demonstrated in vitro inhibitory activity against CSF1R, KIT, and FLT3 at concentrations as low as 29 nM. Pexidartinib did not cause significant inhibition of any other kinases at the 29 nM concentration.

Table 1. In Vitro Inhibition by Pexidartinib

Kinase	% Inhibition	
	0.029 µmol/L Pexidartinib	1.0 µmol/L Pexidartinib
CSF1R	72	92
KIT	35	54
FLT3	80	61

CSF1R = colony stimulating factor 1 receptor; FLT3 = FMS-like tyrosine kinase 3; KIT = KIT proto-oncogene receptor tyrosine kinase.

Source: Applicant Figure reproduced from Study DRN-108-030.

Using an AlphaScreen™ assay, the Applicant confirmed that pexidartinib inhibits the catalytic activity of CSF1R, KIT, and FLT3 (Study DRN-108-083). The AlphaScreen™ assay uses an anti-phosphotyrosine antibody conjugated to an acceptor bead, to detect phosphorylation of a biotinylated peptide product immobilized to a platform by a streptavidin conjugated donor bead. Phosphorylation of a peptide results in an increase in the chemiluminescent signal caused by the close proximity of donor and acceptor beads. Pexidartinib inhibited the catalytic activity of CSF1R, KIT, and FLT3 with IC_{50} values of 17, 12, and 160 nM, respectively (Table 2). Pexidartinib did not inhibit other tested kinases at likely clinically achievable free concentrations of pexidartinib (~40 nM based on a C_{max} of 8625 ng/mL and ≥99% protein binding).

Table 2. In Vitro Biochemical IC_{50s} for Pexidartinib

Tyrosine Kinase	Average IC_{50} (µmol/L)	Average Ki (µmol/L)
CSF1R	0.017	0.00189
KIT	0.012	0.00203
FLT3	0.16	NC
KDR	0.21	NC
LCK	0.86	NC
FLT1	0.88	NC
TRKC	0.89	NC
TRKA	1.7	NC
BTK	31	NC

BTK = Bruton tyrosine kinase; CSF1R =colony stimulating factor 1 receptor; FLT1 = FMS-like tyrosine kinase 1; FLT3 = FMS-like tyrosine kinase 3; IC_{50} = concentration of drug producing 50% inhibition; KDR = kinase insert domain receptor; Ki = inhibition constant; KIT = KIT proto-oncogene receptor tyrosine kinase; LCK = LCK proto-oncogene, Src family tyrosine kinase; NC = not calculated; TRKA = neurotrophic receptor tyrosine kinase 1; TRKC = neurotrophic receptor tyrosine kinase 3.

Source: Applicant Figure reproduced from Study DRN-108-083

The Applicant also assessed the ability of pexidartinib to inhibit phosphorylation of the CSFR1 and FLT3 receptor tyrosine kinases (Study DRN-108-101). Briefly, a human acute myeloid leukemia cell line expressing CSF1R (THP-1), a human B cell precursor leukemia cell line expressing wild-type FLT3 (RS4;11), and a human acute monocytic leukemia cell line that harbors a homozygous internal tandem duplication mutation of the FLT3 gene (MV-4-11), were each incubated with pexidartinib or vehicle control for one hour. THP-1 and RS4;11 cells were then stimulated with either CSF-1 or the FLT3 ligand to induce autophosphorylation. Since the internal tandem duplication mutation in MV-4-11 results in constitutive activation of FLT3, MV-4-11 cells did not require stimulation. To quantify phosphorylation of tyrosines, the Applicant utilized enzyme-linked immunosorbent assay. As shown in Table 3, pexidartinib inhibited the phosphorylation of CSF1R and mutated FLT3 with IC_{50} values of 0.007 and 0.026 µmol/L,

respectively. Pexidartinib did not significantly inhibit the phosphorylation of wild-type FLT3 at concentrations likely to be clinically relevant.

Table 3. Effect of Pexidartinib on the Phosphorylation of Receptor Tyrosine Kinases

Cell Line	Description	ELISA (Stimulation)	IC_{50} Values (µmol/L)
THP-1	Human AML cell line expressing CSF1R	Phospho-CSF1R (CSF-1)	0.0068
RS4;11	Human B cell precursor leukemia cell line expressing wild-type FLT3	Phospho-FLT3 (FLT3 ligand)	1.5
MV-4-11	Human acute monocytic leukemia cell line that harbors a homozygous ITD mutation of the FLT3 gene and expresses the constitutively activated FLT3-ITD receptor tyrosine kinase	Phospho-FLT3 (no stimulation)	0.026

AML = acute myelocytic leukemia; CSF-1 = colony stimulating factor 1; CSF1R = colony stimulating factor 1 receptor; ELISA = enzyme-linked immunosorbent assay; FLT3 = FMS-like tyrosine kinase 3; IC_{50} = concentration of drug producing 50% inhibition; ITD = internal tandem duplication.

Source: Applicant Figure reproduced from Study DRN-108-101

The Applicant evaluated the ability of pexidartinib to inhibit the growth of cells dependent on CSF1R, KIT, or FLT3 with an internal duplication mutation (FLT3-ITD) using 6 cell lines, as described in Table 4 (Study DRN-108-076). Cells were incubated with pexidartinib or vehicle control for 3 days and evaluated using the ATPlite 1step luminescence assay which tests the viability of cells by quantification of ATP present in cell culture. Pexidartinib inhibited growth in all cell lines tested.

Table 4. Pexidartinib-Induced Growth Inhibition in Various Cell Lines

Cell Lines	Description	Average IC_{50} (µmol/L)
CSF1R cell lines		
BCR-FMS/Ba/F3	Engineered cell line created by introduction of CSF1R fusion constructs that render the cells dependent on the introduced kinase for growth	0.010
Bac1.2F5 (stimulated with CSF-1)	SV40 immortalized murine macrophage cell line dependent upon the CSF1R ligand CSF-1 for proliferation	0.22
M-NFS-60 (stimulated with CSF-1)	Murine myelogenous leukemia cell line that is growth responsive to IL-3 and M-CSF (the CSF1R ligand, CSF-1)	0.44
KIT Cell Lines		
BCR-KIT/Ba/F3	Engineered cell line created by introduction of KIT fusion constructs that render the cells dependent on the introduced kinase for growth	0.22
M-07e (stimulated with SCF)	Human acute megakaryoblastic leukemia cell line expressing endogenous KIT and reliant upon the addition of the KIT ligand SCF for growth	0.099
FLT3 Cell Lines		
MV-4-11	Human acute monocytic leukemia cell line that harbors a homozygous ITD mutation of the FLT3 gene and expresses the constitutively activated FLT3-ITD receptor tyrosine kinase	0.15

Ba/F3 = murine IL-3-dependent pro-B cell line; BCR = breakpoint cluster region; CSF-1 = colony stimulating factor 1; CSF1R = colony stimulating factor 1 receptor; FLT3 = FMS-like tyrosine kinase 3; FMS = feline McDonough sarcoma; IC_{50} = concentration of drug producing 50% inhibition; IL = interleukin; ITD = internal tandem duplication; KIT = KIT proto-oncogene receptor tyrosine kinase; M-CSF = macrophage colony stimulating factor 1; SCF = stem cell factor; SV40 = Simian virus 40.

Source: Applicant Figure reproduced from Study DRN-108-076

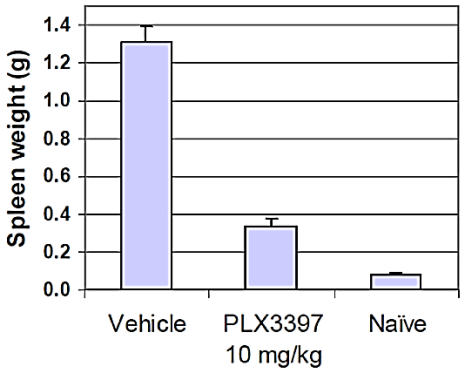
In humans, the most abundant metabolite of pexidartinib involves its N-glucuronidation to ZAAD-1006a. The Applicant examined the ability of ZAAD-1006a to inhibit the catalytic activity of CSF1R, KIT, and FLT3 using the Z'-LYTE™ assay method, as previously described. ZAAD-1006a inhibited the activity of CSF1R, KIT, and FLT3 with IC_{50} values of 6, 10, and >50 µmol/L, respectively (Study CQ16-H0098-R02). The Applicant also utilized a LanthaScreen™ Eu kinase assay that is based on displacement of a tracer to measure the ability of pexidartinib or ZAAD-1006a to inhibit FLT3 with an internal tandem duplication mutation (FLT-ITD; Study CQ16-

H0098-R02). Pexidartinib and ZAAD-1006a inhibited FLT-ITD with IC_{50} values of ~0.04 µmol/L and 7 µmol/L, respectively.

In Vivo Studies

BaF3-FMS cells are IL-3 dependent Ba/F3 murine cells engineered to express CSF1R. Signaling through CSF1R allows the cells to survive without IL-3; however, these cells become apoptotic when exposed to an CSF1R inhibitor. When injected into the tail veins of nude mice, the Ba/F3-FMS cells travel to the spleen and proliferate causing marked splenomegaly. Using this mouse model, the Applicant assessed the ability of pexidartinib to inhibit CSF1R signaling dependent cells in vivo (Study DRN-108-060). Female nu/nu mice (n=4-5) were injected with Ba/F3-FMS cells into their tail veins. After a 10-day incubation period, animals were received 10 mg/kg of pexidartinib or vehicle control, orally once daily, for a week. Spleen weights were measured 4 hours after the last dose. As shown in Figure 2, pexidartinib inhibited splenomegaly by 79%, compared to vehicle control.

Figure 2. Pexidartinib-Induced Inhibition of Splenomegaly in Mice



Source: Applicant Figure reproduced from Study PF-00299804-Pharm-001

Secondary Pharmacology

Pexidartinib (10 µmol/L) did not induce off target activity when evaluated across a panel (n=71) of receptors, ion channels, transporters, and enzymes in a NovaScreen™ assay (Study DRN-108-035).

Safety Pharmacology

The Applicant conducted stand-alone GLP-compliant safety pharmacology of pexidartinib in rats and dogs to assess its effects on the central nervous system, respiratory function, and the cardiovascular system.

To evaluate the effect of pexidartinib on the central nervous system, female Crl:CD®(SD) rats (6/dose group) received a single oral dose of 0, 20, 60, or 200 mg/kg of pexidartinib followed by assessment in a functional observational battery (FOB) up to 24 hours post-dose (Study DRN-108-037). There were no pexidartinib-related effects on FOB parameters following a single dose up to 200 mg/kg.

To evaluate the effect of pexidartinib on respiratory function, female Sprague-Dawley rats (8/dose group) were administered a single oral dose of 0, 20, 60, or 200 mg/kg of pexidartinib and monitored for at least 6 hours post-dose using head-out plethysmography (Study DRN-108-038). There were no pexidartinib-related effects on tidal volume, minute volume, or respiratory rate following a single dose up to 200 mg/kg.

The Applicant used a modified Latin square crossover design that included a 7-day washout period between doses to evaluate the effect of pexidartinib on the cardiovascular system in telemetered male Beagle dogs (4/dose group) administered single oral doses of 0, 50, 300, or 1000 mg/kg of pexidartinib (Study DRN-108-039). Cardiovascular data was obtained from each animal for up to 25 hours post-dose on Days 1, 8, 15, and 22. On Day 29, plasma drug concentrations were measured up to 24 hours post-dose in 50 and 1000 mg/kg animals. Clinical signs and body weights were also evaluated. Adverse clinical signs consisted of dose-responsive emesis at doses ≥300 mg/kg. Pexidartinib induced 6.0, 11.0, or 10.0 mmHg reductions in mean arterial pulse pressure up to 7 hours post-dose in animals given 50, 300, or 1000 mg/kg, respectively. There were no pexidartinib-related effects on electrocardiogram parameters (heart rate, PR, QT, QTc, and QRS intervals).

The Applicant further assessed the effect of pexidartinib on cardiovascular endpoints in an in vitro assay using human ether-à-go-go related gene (hERG) potassium channel stably expressed in HEK293 cells (human embryonic kidney cell type; Study DRN-108-036). Pexidartinib inhibited hERG signaling with an IC_{50} of 0.7 µM, suggesting some potential for QTc prolongation.

The Applicant also examined the in vitro effect of pexidartinib on cardiac action potentials in isolated rabbit Purkinje fibers (Study DRN-108-089). Pexidartinib was added sequentially to Purkinje fiber preparations (4 fibers/concentration) at 2 stimulus intervals (basic cycle lengths of 0.5 and 1 second). The Applicant measured the effect of pexidartinib on the action potential duration at 60% repolarization (APD60) and 90% repolarization (APD90), resting membrane potential, action potential amplitude, and the maximum rate of rise of the action potential upstroke (Vmax). Up to 3 µM of pexidartinib did not prolong action potential repolarization or induce any significant changes to cardiac parameters in isolated rabbit Purkinje fibers. The positive control (50 µM of dl-sotalol) produced a statistically significant ($p<0.05$) prolongation of action potential duration, validating the test system.

Finally, the Applicant measured the effect of pexidartinib on human cardiac L-type calcium channel (hCav1.2-β2-α2δ) stably expressed in Chinese Hamster Ovary (CHO) cells (Study EXP-13-AC2037). The IC_{50} for the inhibitory effect of pexidartinib on hCav1.2 calcium current was 0.2 µM. This inhibition occurred at concentrations that were modestly higher than the approximate amount of free pexidartinib at the human dose of 800 mg (~40 nM based on a total C_{max} of 8625 ng/mL and 99.8% protein binding), but that may contribute to the transient decrease in blood pressure observed at high dose levels in the single dose dog telemetry study.

5.4. ADME/PK

Table 5. Nonclinical Pharmacokinetic Findings

Type of Study	Major Findings
Absorption	
Pharmacokinetics, Absorption, Distribution, Metabolism, and Excretion of ^{14}C-PLX3397 Following a Single Oral Dose to Rats; Study No. EXP-14-AD6143	Male Sprague Dawley rats were orally administered a single 10 mg/kg dose of radiolabeled (^{14}C) pexidartinib. C_{max} (ng/mL): 2670 (~4 hours post-dose) AUC (ng.h/mL): 39400 $T_{1/2}$ (hours): 29
The Pharmacokinetics of PLX3397 Following a Single Oral Dose (30 or 80 mpk) or Intravenous Dose (1 mpk) in Male and Female Beagle Dogs; Study No. DRN-108-025	Beagle dogs were administered a single oral dose of 30 or 80 mg/kg of pexidartinib formulated as a capsule ((b) (4)% w/w pexidartinib hydrochloride, (b) (4)% w/w (b) (4)% w/w (b) (4)% w/w (b) (4)). Exposure levels were less than dose-proportional due to increased capsule load. C_{max} (ng/mL): 2980 (30 mg/kg; LD; 1802 (80 mg/kg; HD) AUC (ng.h/mL): 31501 (LD); 19261 (HD) $T_{1/2}$ (hours): 23 (LD); 8 (HD) Bioavailability: 81% (LD); 12% (HD) Beagle dogs were administered a single intravenous infusion of pexidartinib at a dose of 1 mg/kg. C_{max} (ng/mL): 1170 AUC (ng.h/mL): 2153 $T_{1/2}$ (hours): 2
Distribution	
Plasma Protein-Binding Determinations for PLX-3397; Study No. DRN-108-102	The in vitro protein binding of pexidartinib was assessed in male mice, rat, dog, and human plasma at concentrations of 2, 10, and 75 µM. At the highest concentration, the mean protein binding was 99.8% in mice, 98.3% in rats, 99.7% in dogs, and 99.8% in humans, with similar results at lower concentrations.
Quantitative Whole-Body Autoradiography of Rats Following Oral Administration of ^{14}C-PLX3397; Study No. 8326670	Radiolabeled (^{14}C) pexidartinib was orally administered to Long-Evans rats at a dose of 10 mg/kg. Pexidartinib was present in the blood up to the last sampling time of 336 hours post-dose. C_{max} in blood was 8 hours; C_{max} in CNS tissues was 1-8 hours. Pexidartinib was present in most tissues through 24 hours. Approximately 70% of all tissues were devoid of pexidartinib 72 hours post-dose. Tissues with the highest exposure (C_{max}) to pexidartinib were the uveal tract, liver, pancreas, Harderian gland, and the entire eye. At the last sampling time of 336 hours post-dose, pexidartinib was still present in the eye including the uveal tract.

Type of Study	Major Findings
Metabolism	
Assessment of PLX3397 Metabolites Generated by Incubation with Human, Sprague-Dawley Rat, and Beagle Dog Hepatocytes; Study No. DRN-108-043	The primary metabolites of pexidartinib after incubation with human liver microsomes were two oxidized metabolites, one di-oxidized metabolite, one N-dealkylated metabolite, and four N-glucuronide metabolites (A-D). Among the four N-glucuronide metabolites, metabolites C and D were detected in rat liver microsomes, but none were detected in dog liver microsomes. Except for two of the N-glucuronide metabolites (A and B), all human metabolites were detected after pexidartinib incubation with rat and dog liver microsomes.
Excretion	
Pharmacokinetics, Absorption, Distribution, Metabolism, and Excretion of ^{14}C-PLX3397 Following a Single Oral Dose to Rats; Study No. EXP-14-AD6143	Bile duct-intact and bile duct-cannulated male Sprague Dawley rats were orally administered a single 10 mg/kg dose of radiolabeled (^{14}C) pexidartinib. In bile duct-intact rats, excretion was through feces (64%) and urine (29%). In bile duct-cannulated rats, excretion was through bile (52%), feces (24%), and urine (19%).
TK data from general toxicology studies	Refer to Section 5.5.1
TK data from reproductive toxicology studies	Refer to Section 5.5.4

5.5. Toxicology

5.5.1. General Toxicology

A 6-month oral (gavage) toxicity study of PLX3397 with a 16-week recovery period in Sprague Dawley rats/Study (b) (4)-578139

- Treatment with pexidartinib resulted in death of animals at the high dose (60 mg/kg/day)
- Target organs of toxicity included liver, male and female reproductive compartment, kidney, lymph/hematopoietic compartments

Conducting laboratory and location: (b) (4)
GLP compliance: Yes

Table 6. Methods of Study (b) (4)-578139

Study Method	Details
Dose and frequency of dosing:	0.5, 4, 20, 60 mg/kg once daily
Route of administration:	Oral gavage
Formulation/vehicle:	PLX3397 Test Article blend (b) (4)% PLX3397-HCL (w/w), (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4) in deionized water
Species/strain:	Sprague Dawley rat
Number/sex/group:	20/sex: main study, 10/sex: recovery (control and high dose)
Age:	7 weeks
Satellite groups/unique design:	TK groups: 3/sex/control, 9/sex/treatment
Deviation from study protocol affecting interpretation of results:	No

Table 7. Observations and Results of Study (b) (4)-578139: Changes From Control

Parameters	Major Findings
Mortality	*Main* 60 mg/kg: 2 males (Day 41, 150), cause of death-suppurative inflammation of the joint due to bacterial infection and 1 female (Day 49), cause of death- pulmonary thrombosis with bacterial colonies, secondary to test-article related immunocompromised state. An additional 4 males, cause of death lung hemorrhage and septicemia due to gavage accident (Day 19, 46, 86, 150). The septicemia due to gavage accident was likely secondary to pexidartinib-related immunocompromise. *Recovery* 60 mg/kg: 1 male (Day 254) cause of death renal secondary hyperparathyroidism due to glomerulosclerosis
Clinical signs	*Main* 20 mg/kg females: swollen hindlimbs, facial area, and/or ventral neck 60 mg/kg: swollen facial area, forelimbs, hindlimbs, and/or ventral neck, rales, labored respiration, reddened hindlimbs, dried red material around eyes, exophthalmos of eyes *Recovery* 60 mg/kg: swollen facial area, forelimbs, hindlimbs, and/or ventral neck, dried red material around eyes
Body weights	*Main* 60 mg/kg: females +9.4% *Recovery* 60 mg/kg males: -14.9%
Ophthalmoscopy	Unremarkable, pre-dose and Week 25

Parameters | **Major Findings**

Hematology

Main toxicities were decreased white blood cell (WBC) counts at all doses and signs of regenerative anemia at ≥20 mg/kg

Percent Differences in Mean Values vs. Concurrent Controls

Sex		Males				Females			
Dose (mg/kg/day)		0.5	4	20	60	0.5	4	20	60
WBC	Week 12		-16.2	-26.6	-20.7	-24		-20.7	
	Week 26		-22	-26.6	-25.1				
Lymphocytes	Week 12	-11.2	-16.9	-31	-37.3	-28.5		-28.8	-19.1
	Week 26	-11.9	-20.6	-35.7	-39.3			-21.2	-25.6
Neutrophil	Week 12				104.7	13	29	50.7	179.7
	Week 26							69.6	107.6
LUC	Week 12			80	60		20		80
	Week 26				66.7			33.3	66.7
RBC	Week 12			-13.9	-28.8			-13.9	-37.7
	Week 26			-18.3	-42.9			-17.2	-40.6
% Retic.	Week 12				38.9				111.8
	Week 26	11.8		29.4	100			26.7	173.3
HDW	Week 12				27.2			12.7	49.3
	Week 26			12.4	28.5			28.3	47.3
Platelets	Week 12			14.3	50			15	72.3
	Week 26				48.7			21.1	73.6

Left blank = no findings
There were no findings in the recovery animals

Clinical chemistry

Increased ALT and AST at doses ≥20 mg/kg

Percent Differences in Mean Values vs. Concurrent Controls

Sex		Males				Females			
Dose (mg/kg/day)		0.5	4	20	60	0.5	4	20	60
Globulin	Week 12			18.5	37			17.2	34.5
	Week 26			17.9	28.6			12.9	29
	Week 42				10				
Total Protein	Week 12			14.7	20.6			10.3	11.5
	Week 26			10.3	11.8				
A/G	Week 12				-14.3				-26.2
	Week 26				-22.7			-10.2	-29.9
	Week 42				-15				-11.9
ALT	Week 12			117.5	252.5			67.4	190.7
	Week 26							91.2	117.5
AST	Week 12		110	165	256			143	234
	Week 26							87.7	102.6
GGT	Week 12				60.7				255.6
	Week 26				425				633.3
Phosphorous	Week 12								-10.8
	Week 26				-22.6				-15.8
	Week 42								-15.5
Cholesterol	Week 12				44.1			28.8	46.6
	Week 26				67.9			39.3	84.5
Total Bilirubin	Week 12								-80
	Week 26			-25	-75			-40	-90
	Week 42				-100				-11.1
Glucose	Week 26								-10.9

Left blank = no findings

Urinalysis

Main
60 mg/kg: +57%/+167% urine urobilinogen (M/F), increase in urine protein (semi-quantitative analysis)

There were no findings in the recovery animals

Parameters | **Major Findings**

Gross pathology

Sex	Male				Female			
Dose (mg/kg/day)	0.5	4	20	60	0.5	4	20	60
# Main	20	20	20	20	20	20	20	20
Ovaries								
Cyst						5	2	4
Testes								
Soft			8	18				
Epididymides								
Small			1	15				
Lymph node, mandibular								
Enlarged			8	12			5	19
Paws								
Swollen				2				3
Pituitary								
Pale		1	2	1			1	1
Skin								
Swollen				1				2
Thymus								
Small	3	3	7	6				
Clitoral gland								
Green/enlarged								2
Kidney								
Depressed area(s)								5
Pale								6
Liver								
Cyst								4
Lymph node, axillary								
Enlarged								4
Salivary gland								
Edematous				1				4

Left blank = no findings
There were no findings in the recovery animals

Organ weights

Increases in adrenal and liver weight at the high dose
Dose-dependent decreases in male reproductive organs, and thymus
Percent Differences in Mean Organ Weight (grams) vs. Concurrent Controls

Sex		Male				Female			
Dose (mg/kg/day)		0.5	4	20	60	0.5	4	20	60
Adrenal	Week 26				48.2			21.2	25
Liver	Week 26								26.3
Kidneys	Week 26				9.8				25.2
Pituitary	Week 26								-24.9
Spleen	Week 26		-22.9	-23.8					48.1
Thymus	Week 26		-21.4	-36.1	-47.6			-18	-38.4
Thyroid/parathyroid	Week 26	14	22.6	18.3	25.8				23.7
Epididymides	Week 26			-23.6	-45.3				
	Week 42				-29.9				
Seminal vesicle	Week 26				-17				
Testes	Week 26		-10.3	-32.6	-61.8				
	Week 42				-40.6				
Ovaries/oviducts	Week 26								31.7

Left blank = no findings
Results were similar relative to body and brain weight

Parameters	Major Findings
Histopathology Adequate battery: Yes	See Table 8 for details Minimal to moderate myxomatous change in many tissues at ≥20 mg/kg, including the superficial dermis and subcutaneous tissue of the skin, the fatty tissue associated with the mammary gland, serosa of the glandular stomach, submucosa of the cecum, and the interfiber connective tissue of the tongue. Myxomatous change was characterized by deposition of pale blue fibrillar or finely beaded material. The material was rarely associated with inflammatory cell infiltration. Minimal to severe vascular inflammation in two 60 mg/kg/day group males. Vascular inflammation was compatible with polyarteritis nodosa, characterized by medial hypertrophy of arterioles and arteries, fibrinoid necrosis of the vessel walls and a mixed inflammatory cell infiltration. In the 2 animals, vascular inflammation affected multiple tissues including the epididymides, kidney, mesentery, glandular stomach, rectum and vas deferens. Vascular inflammation was also present in 3 early death 60 mg/kg/day males, and 1 scheduled necropsy control male. Additional major target organs were the male and female reproductive organs, liver, bone marrow, and kidney
Toxicokinetics	There was minimal drug accumulation (accumulation ratios ranged from approximately 0.6-2.3) Exposure generally increased in a dose-dependent manner Exposure was similar between sexes

Day	Dose (mg/kg/day)			
Parameter	**0.5**	**4**	**20**	**60**
Day 0				
C_{max} (ng/mL)	133	1360	8170	16900
AUC_{0-24} (ng·h/mL)	1170	11900	84000	250000
T_{max} (h)	3	3	4	5
Day 86				
C_{max} (ng/mL)	170	1690	7130	11200
AUC_{0-24} (ng·h/mL)	1680	16600	88700	173000
T_{max} (h)	3	3	2	6
Day 181				
C_{max} (ng/mL)	182	1830	7730	14800
AUC_{0-24} (ng·h/mL)	1860	19100	93000	251000
T_{max} (h)	4	3	3	4

Table 8. Pexidartinib-Related Microscopic Findings in Rats

Sex		**Male**					**Female**				
Dose (mg/kg/day)		**0**	**0.5**	**4**	**20**	**60**	**0**	**0.5**	**4**	**20**	**60**
# Main, # Recovery		**20, 8**	**20**	**20**	**20**	**20, 4**	**20, 10**	**20**	**20**	**20**	**20, 9**
Bone marrow, femur											
Depletion, generalized	Minimal	1	4	9	4	1					
	Mild			6	8	7	2			4	1
	Moderate			1	3	8					
Bone marrow, sternum											
Depletion, generalized	Minimal		1	1		2	1				1
	Mild			2	6	9				3	
	Moderate				1	7				1	
Cecum											
Myxomatous change	Minimal										1
	Mild					3					14

Sex		**Male**					**Female**				
Dose (mg/kg/day)		**0**	**0.5**	**4**	**20**	**60**	**0**	**0.5**	**4**	**20**	**60**
# Main, # Recovery		**20, 8**	**20**	**20**	**20**	**20, 4**	**20, 10**	**20**	**20**	**20**	**20, 9**
	Moderate					1					1
Kidney											
Nephropathy, chronic progressive	Minimal	4	3	1	2	3		1	1	6	2, 3
	Mild	3, 2	2	7	9	10, 1	0, 1	1	1	3	5, 3
	Moderate	1			4	6, 3	0, 1			3	11, 3
Liver											
Inflammation, necrotizing	Minimal	1, 1			1					2	2
	Mild	1			1	0, 1				4	7, 5
	Moderate	0, 1					1				
	Severe	1									
Hypertrophy, hepato-cellular, centrilobular	Minimal					1					2
	Mild	1				14				4	9
Pigment	Minimal					7				6	14
	Mild					3					4
Hyperplasia, bile duct	Minimal							1		3	3
Cyst, biliary	Present							1			5
Lymph node, axillary											
Hyperplasia, lymphoid	Mild	1	1	2	1	3			2	10	7
	Moderate										1
Lymph node, mandibular											
Hyperplasia, lymphoid	Minimal									2	
	Mild	2	1	3	7	8	1		2	7	12
	Moderate				1	5				1	5
Ovaries											
Cyst, luteal	Present						1	3	2	1	9
Decreased number corpora lutea	Mild								1		1
	Moderate						1	4	2	1	
	Severe						7	3	4	6	13
Hemorrhage, corpora lutea	Minimal									1	3
	Mild										5
	Moderate										5
Necrosis, corpora lutea	Minimal							1		3	
	Mild							1	2	1	3
	Moderate									1	
Pigment	Minimal										2
	Mild										11
Retained antral follicles	Present						7	7	7	7	1
Paws											
Inflammation	Mild					2					
	Moderate							1			3
Pituitary											
Castration cells	Mild					13, 1					
	Moderate					1					
Skin											
Myxomatous change	Minimal				18	4				13	4
	Mild				2	13				7	12
	Moderate					2				0	4

Sex		**Male**					**Female**				
Dose (mg/kg/day)		**0**	**0.5**	**4**	**20**	**60**	**0**	**0.5**	**4**	**20**	**60**
# Main, # Recovery		**20, 8**	**20**	**20**	**20**	**20, 4**	**20, 10**	**20**	**20**	**20**	**20, 9**
Spleen											
Pigment increased	Minimal									2	
	Mild				16	18	1		11	15	8
	Moderate					1					
Systemic lesion											
Inflammation, vascular	Present	1				2					
Thymus											
Depletion, lymphoid	Minimal			1				1		2	
	Mild	1	1	10	13	9	4	4	4	7	12
	Moderate		1		1	7				1	4
	Severe					1					
Testes											
Depletion, germ cell	Minimal				7						
	Mild				9	0, 2					
	Moderate				1	3					
	Severe					16, 2					
Epididymis											
Cellular debris	Mild				1	3, 2					
	Moderate					15, 2					
Hypospermia	Minimal				1						
	Mild				3						
	Moderate					2					
	Severe					16					
Thyroid gland											
Hypertrophy, follicular cell	Minimal			1						1	2
	Mild	8	1	9	9	2			1	6	12
	Moderate					1					
Tongue											
Myxomatous change	Mild					8					13
	Moderate					10					6

A 9-month oral (gavage) toxicity study of PLX3397 with a 16-week recovery period in Beagle dogs/Study (b) (4)-578140

- There were no pexidartinib-related deaths in this study
- Target organs of toxicity include the reproductive compartment of both sexes

Conducting laboratory and location: (b) (4)

Table 9. Methods of Study (b) (4)-578140

Study Method	Details
Dose and frequency of dosing:	1, 6, 30, 100 mg/kg once daily
Route of administration:	Oral gavage
Formulation/vehicle:	PLX3397 Test Article blend (b) (4)% PLX3397-HCL (w/w) (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4) in deionized water
Species/strain:	Beagle dog
Number/sex/group:	4/sex: main study; 2/sex: recovery
Age:	10-11 months
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	No

Table 10. Observations and Results of Study (b) (4)-578140: Changes From Control

Parameters	Major Findings
Mortality	All animals survived to scheduled necropsy
Clinical signs	*Main* ≥30 mg/kg: loss of hair pigmentation (face, forelimbs, hindlimbs, dorsal trunk), loss of skin pigmentation on the facial area, clear discharge from eyes, and emesis *Recovery* ≥30 mg/kg: loss of hair pigmentation (face, forelimbs, hindlimbs, dorsal trunk), loss of skin pigmentation on the facial area, clear discharge from eyes
Body weights	Unremarkable, evaluated twice daily
Ophthalmoscopy	Unremarkable, evaluated pre-dose and Week 38
ECG	Unremarkable, evaluated pre-dose and Week 38
Hematology	Evaluated at Weeks 12, 39 and recovery (Week 55) Decreases in RBC Percent Differences in Mean Values vs. Concurrent Controls

Sex		Males				Females			
Dose (mg/kg/day)		1	6	30	100	1	6	30	100
RBC	Week 12			-11.2	-25.7			-16.5	-12.7
HGB	Week 12			-10.7	-23.9			-14.9	-13
HCT	Week 12			-10.1	-22.3			-13.6	

Left blank = no findings

Clinical chemistry

Percent Differences in Mean Values vs. Concurrent Controls

Sex		Males				Females			
Dose (mg/kg/day)		1	6	30	100	1	6	30	100
Total protein	Week 12				12.1				
	Week 39				15.3				
Globulin	Week 12				22.2				
	Week 39		10.3		24.1				
AST	Week 12	10.3	34.5	20.7	79.3			83.3	40
	Week 39			22.6	71	11.5	15.4	73.1	69.2
SDH	Week 12								
	Week 39	33.3	33.3	100	100				

Left blank = no findings
There were no findings in the recovery animals

Urinalysis	Unremarkable, evaluated pre-dose, Week 12, Week 39, Week 55
Gross pathology	Unremarkable

Parameters | **Major Findings**

Organ weights

Percent Differences in Mean Organ Weight (grams) vs. Concurrent Controls

Sex		Male				Female			
Dose (mg/kg/day)		1	6	30	100	1	6	30	100
Thymus	Week 39	-26	-67.6	-71	-56.8		-62.4	-54.7	-56.2
Testes	Week 39			-36.7	-43.3				
Epididymides	Week 39		-9.8	-6.3	-18.7				
Ovary/oviduct	Week 39						-28	-23.7	-18
Uterus/cervix	Week 39						-62.4	-54.7	-56.2

Left blank = no findings
Results were similar relative to body and brain weight

Histopathology
Adequate battery: Yes

Sex		Male					Female				
Dose (mg/kg/day)		0	1	6	30	100	0	1	6	30	100
# Main, # Recovery		4, 2	4	4, 2	4, 2	4, 2	4, 2	4	4, 2	4, 2	4, 2
Epididymis											
Hypospermia	Marked				4						
	Severe					4					
Testes											
Depletion, germ cell	Minimal					0, 1					
	Moderate				1						
	Marked				1	4					
	Severe				2						
Hyperplasia, Leydig cell	Minimal				1	2					
	Mild				1	2					
Liver											
Pigment	Minimal								1	1, 1	
	Mild									1	2
Spleen											
Pigment	Minimal	1	1	3	1	2	1		1		
	Mild		1	1	1			1		2	4
Ovary											
Decreased number, follicles	Mild								1		1
	Moderate							1		1	2
Oviduct											
Atrophy	Mild								1		
	Moderate							1	1		2
Uterus											
Atrophy	Mild								1	1	
	Moderate							1	1	1	3
Estrous	Anestrus						0	1	3	2	3
	Diestrus						2	2	0	2	1
	Proestrus						2	1	0	0	0
	Estrus						0	0	0	0	0
	Immaturity						0	0	1	0	0
Cervix											
Atrophy	Moderate							1			1

Left blank = no findings

Parameters	Major Findings
Toxicokinetics	There did not appear to be drug accumulation (accumulation ratios ranged from approximately 0.166-8.5) Exposure increase was less than dose-proportional with no evidence of a significant increase in long-term exposure at doses >30 mg/kg Exposure was similar between sexes

Day	Dose (mg/kg/day)			
Parameter	**1**	**6**	**30**	**100**
Day 0				
C_{max} (ng/mL)	445	801	3320	4070
AUC_{last} (ng·h/mL)	1050	3870	23600	48600
T_{max} (h)	1.6	1.6	6.2	6.5
Day 84				
C_{max} (ng/mL)	178	862	1800	2660
AUC_{last} (ng·h/mL)	671	4730	14200	23400
T_{max} (h)	1.3	2.2	2	2.4
Day 272				
C_{max} (ng/mL)	214	689	2730	2710
AUC_{last} (ng·h/mL)	887	4000	21600	22500
T_{max} (h)	1.1	1.8	1.9	2.5

Repeated dose toxicity study in monkeys treated orally with PLX3397 for 3 months followed by a 1-month recovery period/Study (b) (4) 315-576

- There were no test-article related mortalities
- There were no test-article related changes
- Systemic exposure to ZAAD-1006a was at least 60-fold higher than exposure to pexidartinib after 91 days of dosing; pexidartinib exposure was approximately 0.06x times the human exposure at the highest tested dose of 100 mg/kg

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 11. Methods of Study (b) (4) 315-576

Study Method	Details
Dose and frequency of dosing:	1, 10, 100 mg/kg once daily
Route of administration:	Oral, intragastrically using a disposable catheter and syringe
Formulation/vehicle:	PLX3397 Test Article blend (b) (4)% PLX3397-HCL (w/w), (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4)
Species/strain:	Cynomolgus monkey
Number/sex/group:	3/sex/group
Age:	3-5 years
Satellite groups/unique design:	2/sex/recovery group
Deviation from study protocol affecting interpretation of results:	No

Table 12. Observations and Results of Study (b) (4) 315-576: Changes From Control

Parameters	Major Findings
Mortality	Unremarkable, observed twice daily
Clinical signs	Unremarkable, observed twice daily
Body weights	Unremarkable, weighed once weekly
Ophthalmoscopy	Unremarkable, evaluated on Week 4 and 13
ECG	Unremarkable, evaluated on Week 4 and 13
Hematology	Unremarkable, evaluated on Week 4 and 13
Clinical chemistry	Unremarkable, evaluated on Week 4 and 13
Urinalysis	Unremarkable, evaluated on Week 4 and 13
Gross pathology	Unremarkable, evaluated at the end of the dosing period
Organ weights	Unremarkable, evaluated at the end of the dosing period
Histopathology Adequate battery: Yes	Unremarkable, evaluated at the end of the dosing period
Toxicokinetics	Exposure increased with dose There were no apparent gender differences in exposure Systemic exposure to ZAAD-1006a was much higher (~63-1000 fold after 91 days) compared to pexidartinib Summary TK parameters of PLX3397 and ZAAD-1006a in cynomolgus monkeys

Dose* (mg/kg/day)	Day	Sex	PLX3397			ZAAD-1006a		
			Cmax (ng/mL)	Tmax (h)	AUC_{0-24h} (ng·h/mL)	Cmax (ng/mL)	Tmax (h)	AUC_{0-24h} (ng·h/mL)
1	1	M	8.00	1.0	8.00	2960	1.0	10300
		F	8.80	NC	15.7	2930	1.0	16300
	14	M	38.9	1.0	229	3050	1.0	16300
		F	0.00	NC	0.00	2360	1.3	13600
	91	M	7.77	1.0	7.77	2900	1.0	10200
		F	0.00	NC	0.00	3180	1.0	14700
10	1	M	83.9	2.2	444	9410	2.2	88500
		F	71.0	2.5	670	7440	2.8	106000
	14	M	84.4	2.6	445	11500	2.4	117000
		F	72.5	1.8	422	9920	1.4	91800
	91	M	107	1.0	486	14000	1.2	109000
		F	94.6	1.8	541	7960	1.8	87800
100	1	M	444	4.8	5190	13800	4.2	239000
		F	1750	5.8	18300	35700	5.8	506000
	14	M	393	3.6	4130	20200	2.6	315000
		F	713	3.6	5800	29600	3.4	387000
	91	M	679	2.8	5550	24500	1.4	351000
		F	543	2.8	4400	26800	3.0	389000

*: As PLX3397 free form, M: Male, F: Female, NC: Not calculated

(Applicant table reproduced from Study (b) (4) 315-576)

General Toxicology; Additional Studies

The Applicant conducted 28-day and 13-week GLP-compliant, repeat-dose toxicity studies in Sprague Dawley rats and Beagle dogs that included daily oral dosing of pexidartinib at doses at or below those explored in the 6- and 9-month studies. These studies did not identify additional toxicology findings not observed in the longer-term studies.

In an additional 14-day exploratory tolerability study in Sprague Dawley rats, 5 animals/sex received pexidartinib daily at doses of 50, 300, and 1000 mg/kg. A mid-dose female and high dose male were found dead prior to dosing on Day 4 and following dosing on Day 5,

respectively. These deaths as well as clinical signs of severe toxicity (lethargy, prostration, raspy breathing, hunched posture, cold to touch) led to euthanasia of all animals at doses >50 mg/kg by Day 6. Toxicology findings in this study that were not described in the 6-month study included decreased body weights at the mid and high doses, as well findings in the heart and forestomach. In the heart of rats given 300 and 1000 mg/kg, acute or subacute inflammation characterized by the presence of neutrophilic or histiocytic inflammatory cell infiltration between necrotic individual cardiac myocytes and ranging from minimal to moderate severity was present in the left ventricular apical myocardium of most animals. In the stomach, mild to moderate hyperplasia of nonglandular epithelium was accompanied by mild to marked hyperkeratosis. Finally, at doses ≥60 mg/kg (approximately 3 times higher than the human exposure at the 800 mg dose), there were dose-dependent findings of minimal to moderate subphyseal or cortical hyperostosis (increased bone growth) and physeal hypertrophy in the femur; these findings correlated with decreased systemic phosphate levels.

5.5.2. Genetic Toxicology

5.5.2.1. In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Bacterial Reverse Mutation Assay/Study AC14GH.503.BTL

Key Study Findings:

- PLX3397-HCl was negative for mutagenic activity in the strains tested with and without S9 activation
- Standard positive controls confirm the sensitivity and validity of the assay

GLP compliance: Yes
Test system: Salmonella strains TA98, TA100, TA1535 and TA1537 and E. coli strain WP2 uvrA
Study is valid: Yes

5.5.2.2. In Vitro Assays in Mammalian Cells

In Vitro Mammalian Chromosome Aberration Test/Study AC14GH.341.BTL

Key Study Findings:

- PLX3397-HCl was negative for the induction of structural and numerical chromosome aberrations in both non-activated and S9-activated test systems
- Standard positive controls confirm the sensitivity and validity of the assay

GLP compliance: Yes
Test system: human peripheral blood lymphocytes
Study is valid: Yes

5.5.2.3. In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Mouse Bone Marrow Erythrocyte Micronucleus Test Following Oral Administration of PLX339-HCl/Study AC14GH.123.BTL

Key Study Findings:

- PLX3397-HCl was negative for induction of structural and numerical chromosome aberrations in the bone marrow polychromatic erythrocytes of mice
- Standard positive controls confirm the sensitivity and validity of the assay

GLP compliance: Yes
Test system: Male and female ICR mice (bone marrow polychromatic erythrocytes)
Study is valid: Yes

5.5.3. Carcinogenicity

The Applicant conducted a two-year (104-week) carcinogenicity study with pexidartinib in rats and a 26-week carcinogenicity study in rasH2 transgenic mice (See Appendix 19.3 for full review).

Animals treated with pexidartinib did not show statistically significant increases in neoplastic lesions compared to control treated animals. Pexidartinib-related non-neoplastic findings included chronic progressive nephropathy, increased mast cells of the mesenteric lymph nodes, increased follicular colloid of the thyroid, and testicular degeneration in rats. Deposits of mucosubstance in the connective tissues of multiple organs also occurred in rats, including in the skin, and the tongue. There were also alterations in rats in the tunica intima of the aorta. In mice, pexidartinib-related non-neoplastic findings included decreased cellularity of the bone marrow, mucinous degeneration and subcutaneous mineralization of the skin, hemosiderin pigmentation in the spleen, and testicular degeneration.

5.5.4. Reproductive and Developmental Toxicology

5.5.4.1. Fertility and Early Embryonic Development

An oral (gavage) study of fertility and early embryonic development to implantation of PLX3397 in rats/Study AN14-C0113-R01

Key Study Findings

- Reductions in spermatogenic parameters occurred at 40 mg/kg/day and adverse macroscopic findings and lower epididymal and testicular weights occurred at ≥10 mg/kg/day
- A reduction in viable embryos and an increase in pre-implantation loss and early resorption occurred at 40 mg/kg/day
- The exposures at 10 (males) and 40 (females) mg/kg/day were approximately 0.5 and 2 times the human clinical exposure based on AUC at the recommended human dose of 800 mg, respectively

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 13. Methods of Study AN14-C0113-R01

Study Method	Details
Dose and frequency of dosing:	4, 10, 40 mg/kg; once daily dosing starting 63 days prior to mating until the day evidence of mating was present in males and 14 days prior to mating until Gestation Day (GD) 7 in females
Route of administration:	Oral gavage
Formulation/vehicle:	PLX3397 Test Article blend (b) (4)% PLX3397-HCL (w/w), (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4) in deionized water
Species/strain:	Sprague Dawley rat
Number/sex/group:	25/sex/group
Satellite groups:	8/sex/group for toxicokinetic evaluation
Study design:	Females treated with pexidartinib were cohabitated 1:1 with treated males until evidence of mating was present (GD 0). Necropsy of males occurred on the day that evidence of mating was present, and necropsy of females occurred on GD 15.
Deviation from study protocol affecting interpretation of results:	No

Table 14 Observations and Results of Study AN14-C0113-R01

Parameters	Major Findings							
Mortality	Unremarkable							
Clinical signs	40 mg/kg: slightly lower mean male and female fertility and copulation indices compared to controls							
	Sex	**Male**				**Female**		
	Dose (mg/kg/day)	**0**	**4**	**10**	**40**	**0**	**4**	**10**	**40**
	Copulation index (%)	100	100	100	88				
	Conception index (%)					100	100	100	88
	Fertility index (%)	100	100	100	88	100	100	100	88
Body weights	Unremarkable							

Parameters	Major Findings
Necropsy findings	Organ Weights No changes were observed in females Percent Differences in Mean Values vs. Concurrent Controls, absolute weight

		Male		
Dose (mg/kg)		**4**	**10**	**40**
Epididymis	Right		-8.3	-26.7
	Left		-7	-26.3
Testis	Right		-13.5	-45.5
	Left		-12.9	-45.5
Cauda epididymis	Right			-26.6
	Left			-24.4

Gross Pathology

	Male			
Dose (mg/kg)	**0**	**4**	**10**	**40**
# Examined	**25**	25	25	25
Epididymis				
Small			3	15
Lymph node, mandibular				
Enlarged				5
Testis				
Small			3	19
Soft				12

Reproductive changes

Males

Percent Differences in Mean Values vs. Concurrent Controls

	Male		
Dose (mg/kg)	**4**	**10**	**40**
Sperm production rate			-37
Motile sperm production			-11
Cauda epididymal sperm concentration			-55
Cauda testicular sperm concentration			-37

Females

	Female			
Dose (mg/kg)	**0**	**4**	**10**	**40**
Number gravid	**25**	**25**	**25**	**22**
Pre-implantation loss (Total)	26	30	22	58
Early resorptions (Total)	18	20	28	47
Viable embryos (Total)	344	354	349	255

Parameters	Major Findings
Toxicokinetics	Blood was collected at the start of dose administration (study Day 0 for males and Day 49 for females) and following a minimum of 9 weeks dose administration for males and GD 7 for females. The AUC exposures in rats at doses of 4, 10, and 40 mg/kg were approximately 0.2x, 0.5x, and 2x those achieved in patients given the 800 mg daily dose of pexidartinib.

	Males			Females		
Dose (mg/kg/day)	**4**	**10**	**40**	**4**	**10**	**40**
	Day 0			Day 49*		
C_{max} (ng/mL)	796	2280	9280	2040	4750	14700
AUC_{last} (ng·h/mL)	8640	20500	115000	17300	49300	202000
	Week 9			GD 7		
C_{max} (ng/mL)	1070	2950	10500	1270	3040	14800
AUC_{last} (ng·h/mL)	12000	42600	132000	13900	35300	199000

*first day of dosing in females

5.5.4.2. Embryo-Fetal Development

An oral (gavage) study of the effects of PLX3397 on embryo-fetal development in rats/Study (b) (4)-578054

Key Study Findings

- Pexidartinib-related fetal malformations (localized fetal edema, absent kidney and ureter, abnormalities of the reproductive tract, decreased skeletal ossification) were noted at 40 mg/kg
- The maternal exposure at 40 mg/kg/day was approximately 2 times the human clinical exposure based on AUC at the recommended human dose of 800 mg

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 15. Methods of Study (b) (4)-578054

Study Method	Details
Dose and frequency of dosing:	4, 10, and 40 mg/kg once daily from Gestation Day (GD) 6 to 17
Route of administration:	Oral gavage
Formulation/vehicle:	PLX3397 Test Article blend (b) (4)% PLX3397-HCL (w/w), (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4) in deionized water
Species/strain:	Sprague Dawley rat
Number/sex/group:	25 females/group
Satellite groups:	4 females/group for toxicokinetics
Study design:	Female rats were bred naturally, and mating day was designated GD 0. Presumed pregnant females were assigned to groups and administered treatment daily on GDs 6-17. Rats were euthanized on GD 20.
Deviation from study protocol affecting interpretation of results:	No

Table 16. Observations and Results of Study (b) (4)-578054

Parameters	Major Findings
Mortality	Unremarkable
Clinical signs	Unremarkable
Body weights	Unremarkable
Necropsy findings Maternal Necropsy Data	Macroscopic Findings: 40 mg/kg: 4 animals with white areas on 1-3 placentae; 1 animal also had dark red areas on the same placenta. Cesarean Section Findings:

	Female			
Dose (mg/kg)	**0**	**4**	**10**	**40**
Number gravid	**25**	**25**	**24**	**23**
Viable fetuses (%)	96.7	97.1	95.7	91.4
Mean early resorptions (%)	3.3	2.9	4	8.2
Pre-implantation loss (%)	5	5.2	7.7	9.2
Post-implantation loss (%)	3.3	2.9	4.3	8.6

Necropsy findings
Offspring

Dose (mg/kg)	**0**	**4**	**10**	**40**
Females gravid	**25**	**25**	**24**	**23**
Fetuses available for evaluation	**358**	**375**	**354**	**337**
Fetuses with malformations	**2**	**1**	**3**	**320**
External malformations				
Localized fetal edema (neck, thorax, abdomen)				317
Omphalocele			1	
Gastroschisis	1			
Visceral malformations				
Kidney and ureter absent				26
Kidney, misshapen				2
Uterus, portion absent				9
Uterus, thin				3
Ovary, absent				1
Skeletal malformations				
Sternebrae 5 and/or 6 unossified	4	2	10	42
Reduced ossification of the skull				13
Cervical centrum #1 ossified	71	41	35	3
Stermebrae malaligned	1	2		10

Parameters	Major Findings
Toxicokinetics	The AUC exposures in female rats at doses of 4, 10, and 40 mg/kg were approximately 0.2x, 0.5x, and 2x those achieved in patients given the 800 mg daily dose of pexidartinib.

Maternal exposure on GD17: Females

	Dose (mg/kg/day)		
Parameter	**4**	**10**	**40**
C_{max} (ng/mL)	1219	3825	10008
AUC_{last} (ng·h/mL)	15503	41872	145372
T_{max} (h)	1	2	4
$T_{1/2}$ (H)	4.2	4.4	5.5

An oral (gavage) study of the effects of PLX3397 on embryo/fetal development in rabbits/Study (b) (4)-578135

Key Study Findings

- Increased post-implantation loss and abortion, and decreases in the number of viable fetuses at 60 mg/kg/day
- Fetal malformations (absent kidney or ureter, misshapen or malpositioned kidney, rib abnormality, and accessory skull bones) at 60 mg/kg
- The maternal exposure at 60 mg/kg/day was approximately 1.6 times the human clinical exposure based on AUC at the recommended human dose of 800 mg

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 17. Methods of Study (b) (4)-578135

Dose and frequency of dosing:	6, 20, and 60 mg/kg once daily from Gestation Day (GD) 7 to 20
Route of administration:	Oral gavage
Formulation/vehicle:	PLX3397 Test Article blend [(b) (4)% PLX3397-HCL (w/w), (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4) in deionized water
Species/strain:	New Zealand White rabbit
Number/sex/group:	22 females/group
Satellite groups:	4 females/group for toxicokinetics
Study design:	Female rabbits were time-mated and received by the conducting laboratory on GD 2, 3, or 4. Pregnant females were assigned to groups and administered treatment daily on GDs 7-20. Rabbits were euthanized on GD 29.
Deviation from study protocol affecting interpretation of results:	No

Table 18. Observations and Results of Study (b) (4)-578135

Parameters	Major Findings
Mortality	20 mg/kg TK group: 1 animal was found dead on GD 15. Necropsy findings indicated possible intubation error. 60 mg/kg TK group: 1 animal was euthanized following CNS-related observations and labored respiration at the time of receiving the first dose. The death was not considered to be test article related.
Clinical signs	60 mg/kg: 2 females aborted on GD 25 and 26
Body weights	Unremarkable
Necropsy findings Maternal Necropsy Data	Macroscopic findings 60 mg/kg: 1 animal with cystic oviducts Cesarean Section Findings:

	Female			
Dose (mg/kg)	**0**	**6**	**20**	**60**
Number gravid	**22**	**22**	**22**	**22**
Viable fetuses	176	186	173	95.4
Postimplantation loss	13	8	8	25
Early resorptions	8	4	5	6
Late resorptions	5	3	3	19

Necropsy findings
Offspring

Dose (mg/kg)	0	6	20	60
Females gravid	**22**	**22**	**22**	**22**
Fetuses available for evaluation	**176**	**186**	**180**	**173**
Fetuses with malformations	3	5	6	33
Visceral malformations				
Kidney and ureter absent				21
Kidneys, rudimentary				3
Ureter, absent				3
Kidneys, malpositioned				2
Kidneys, misshapen				2
Skeletal malformations				
Rib anomaly				7
Accessory skull bone	1		3	20

Toxicokinetics

The AUC exposures in female rabbits at doses of 6, 20, and 60 mg/kg were approximately 0.3x, 0.7x, and 1.6x those achieved in patients at the 800 mg daily dose of pexidartinib.

Maternal exposure on GD20

	Females		
Dose (mg/kg/day)	**6**	**20**	**60**
C_{max} (ng/mL)	1950	4730	9760
AUC_{0-24} (ng·h/mL)	21700	54000	121000
T_{max} (h)	3	2	3

5.5.4.3. Prenatal and Postnatal Development

An oral (gavage) study of the effects of PLX3397 on pre- and postnatal development, including maternal function in rats/Study (b) (4)-147041

Key Study Findings

- There were no test article-related findings at any dose level in any generation
- The maternal exposure at the NOAEL of 10 mg/kg/day was approximately 0.5 times the human clinical exposure based on AUC at the recommended human dose of 800 mg

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 19. Methods of Study (b) (4)-147041

Study Method	Details
Dose and frequency of dosing:	1, 4, and 10 mg/kg, once daily from Gestation Day (GD) 6 to Lactation Day (LD) 20 for a total of 36-38 doses
Route of administration:	Oral gavage
Formulation/vehicle:	PLX3397 Test Article blend (b) (4)% PLX3397-HCL (w/w), (b) (4)% Poloxmer 407 (w/w)]/ (b) (4)% (b) (4) in deionized water
Species/strain:	Sprague Dawley rat
Number/sex/group:	25 females/group
Satellite groups:	8 females/group, toxicokinetics
Study design:	Pregnant females (F0 dams) were administered pexidartinib once daily from GD 6 through LD 20; females were allowed to deliver the F1 litters and rear the F1 pups to weaning on LD/postnatal day (PND) 21 to evaluate the effects on the F0 dams and F1 generation pups through weaning; standardization of litter size (culling) to 8 pups/litter (4/sex when possible), occurred on PND 4; F1 pups were evaluated for attainment of developmental landmarks, motor activity, auditory startle response, and learning and memory assessment, and F1 parent animals were assessed for copulation rate, fertility rate, and implantation rate. Measurement of the number of live F2 embryos and mortality of the F2 embryos was performed on GD 15
Deviation from study protocol affecting interpretation of results:	No

Table 20. Observations and Results of Study (b) (4)-147041

Generation	Major Findings
F0 Dams	Unremarkable
F1 Generation	Unremarkable
F2 Generation	Unremarkable
Toxicokinetics	PK results from F0 Dams

Day	Dose (mg/kg/day)		
Parameter	1	4	10
GD 6			
C_{max} (ng/mL)	314	1460	4400
AUC_{last} (ng·h/mL)	2970	15700	46400
LD 20			
C_{max} (ng/mL)	229	1550	4090
AUC_{last} (ng·h/mL)	2100	13500	35500

5.5.5. Other Toxicology Studies

5.5.5.1. Phototoxicity

In vitro 3T3 NRU Phototoxicity Test with PLX3397/Study (b) (4)397-002

The Applicant evaluated the phototoxic potential of pexidartinib using an in vitro 3T3 NRU phototoxicity test in Balb/c 3T3 mouse fibroblasts. Cultured Balb/c 3T3 cells were seeded into two 96-well plates and treated with pexidartinib at concentrations of 0.949, 1.33, 1.86, 2.60, 3.64, 5.10, and 7.14 µg/mL, based on the results of a dose-range finding test. Following a 1 hour incubation, one of the plates was exposed to UVA irradiation (5 J/cm2). Cell viability was determined by neutral red extraction from cells. Vehicle (dimethyl sulfoxide) and chlorpromazine hydrochloride were used as the negative and positive controls, respectively.

The absorbance of the negative control, the cell viability of the irradiated negative control, the mean absorbance of the negative control, and the photo irradiation factor of the positive control met the acceptance criteria. In cells treated with pexidartinib, an IC_{50} could not be determined because cell viability remained close to 100% at the highest concentration, both with and without irradiation (97.5% and 99.2%, respectively). The mean photo effect of pexidartinib was -0.021. Pexidartinib was negative for phototoxic potential in this study.

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Team Leader

6. Clinical Pharmacology

6.1. Executive Summary

The NDA includes clinical pharmacology data from single-dose pharmacokinetic (PK) studies in male and female healthy subjects and from multiple-dose PK studies in patients with solid tumors or TGCT. Studies conducted include drug-drug interaction (DDI) studies, assessment of pexidartinib ADME, and studies to assess the effects of food and acid reducing agents, and the effects of hepatic and renal impairment on the PK of pexidartinib. In addition, exposure-response (E-R) analyses for efficacy and safety, population PK (popPK) analyses, physiologic-based pharmacokinetic modeling (PBPK), and assessment of the potential for QT/QTc interval prolongation, were included in the NDA. FDA's review evaluated the acceptability of the proposed dosing regimen in relation to efficacy and safety, as well as dosage adjustments for DDIs and for renal and hepatic impairment.

The proposed clinical dosage is 800 mg/day as 400 mg taken twice daily (BID) on an empty stomach (at least 1 hour before or 2 hours after a meal). This initial dosing regimen was selected based on the safety and tolerability data obtained from the first-in-human phase 1 dose-escalation Study PLX108-01; this study evaluated pexidartinib in patients with solid tumors at doses ranging from of 200 mg/day to 1200 mg/day (600 mg BID). The 1000 mg/day dosage (400 mg in the morning and 600 mg in the evening), was selected as the MTD and the Recommended Phase 2 Dose (RP2D). In the randomized placebo-controlled trial PLX108-10 (ENLIVEN), patients received pexidartinib 1000 mg/day (400 mg in the morning and 600 mg in the evening) for the first 2 weeks, followed by 800 mg/day (400 mg BID). The primary evidence of efficacy supporting the proposed 800 mg/day dosage (400 mg BID) is based on the overall response rate (ORR) in Part 1 of ENLIVEN being comparable to that in patients enrolled in Part 2, where all patients in the placebo arm were eligible to receive open-label pexidartinib at 800 mg/day (400 mg BID). A comparison of 1000 mg for 2 weeks followed by 400 mg BID, versus a starting dose of 800 mg (400 mg BID), showed no apparent difference in the probability of ORR between the two regimens in ENLIVEN. The observed efficacy and exposure-response (E-R) relationships between pexidartinib exposure and liver enzyme elevations (AST, ALT and total bilirubin) support the proposed dosing regimen of 400 mg BID.

Recommendations

The Office of Clinical Pharmacology concludes that NDA 211810 is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Table 21. Recommendations and Comments on Review Issues

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	The primary evidence of effectiveness in the indicated population comes from Study PLX108-10 (ENLIVEN). Refer to Section 7 for further details.
General dosing instructions	The proposed dosing regimen is 400 mg BID on an empty stomach (at least 1 hour before or 2 hours after a meal or snack). This dosing regimen is supported by the clinically significant improvement in ORR and an acceptable safety profile observed in ENLIVEN.
Dosing in patient subgroups: hepatic and renal impairment	*Specific Populations* *Hepatic Impairment:* Based on NCI-ODWG criteria, the exposure to pexidartinib (geometric mean $AUC_{0\text{-}inf}$) was similar in healthy volunteers with mild hepatic impairment and healthy volunteers with normal hepatic function. No dosage adjustment is necessary in patients with mild hepatic impairment. There is insufficient information to assess the effect of moderate hepatic impairment (n=2) on pexidartinib exposure. The review team recommends a PMR to evaluate the effect of moderate hepatic impairment on pexidartinib exposure. Patients with severe hepatic impairment have not been studied. *Renal Impairment:* A dedicated study showed that healthy volunteers with mild (CL_{CR}=60-89 mL/ min), moderate (CL_{CR}=30-59 mL/min) and severe (CL_{CR}=15-29 mL/min) renal impairment (RI) had a 65%, 30% and 32% higher exposure (geometric mean $AUC_{0\text{-}inf}$) to pexidartinib, respectively, compared to healthy volunteers with normal renal function (CL_{CR} ≥90 mL/ min). healthy volunteers with end stage renal disease (ESRD) on or off dialysis had similar pexidartinib exposure to subjects with normal renal function. Based on the popPK analysis using clinical data, patients with mild (n=67) and moderate RI (n=9) (CL_{CR}=30 - 89 mL/min) had approximately 30% higher exposure, compared to patients with normal renal function (n=299). Based on the popPK analysis results and dedicated study results in patients with severe RI, the total daily dose of pexidartinib should be reduced to 600 mg (1 x 200 mg capsule in the morning and 2 x 200 mg capsules in the evening) in patients with mild-to-severe renal impairment (CL_{CR}=15 - 89 mL/min as estimated by Cockcroft-Gault) to match exposure to that in patients with normal renal function. The dose reduction is supported by the observed increased risk of liver enzyme elevations with increased exposure observed at the 1000 mg/day pexidartinib dosage. (b) (4)
Dosing in patient subgroups: effect of food	The standard FDA defined high-fat meal increased the pexidartinib geometric mean C_{max} and $AUC_{0\text{-}inf}$ by 98% and 110%, respectively, compared to fasted conditions. Pexidartinib should be administered on an empty stomach (at least 1 hour before or 2 hours after a meal or snack). Non-compliance with the fasting condition under the BID dosing regimen is a safety risk, given the exposure-response relationships for key safety endpoints. The review team recommends a PMR to evaluate the effect of a low-fat meal (400-500 Kcal) on pexidartinib exposure. The results from this study will be used to optimize the dose or dosage regimen with regard to food intake.
Dosing in patient subgroups: effect of gastric acid-lowering agents	*Proton pump inhibitors (PPIs):* Esomeprazole, a PPI, decreased the pexidartinib geometric mean C_{max} and $AUC_{0\text{-}inf}$ by 45% and 53%, respectively. The concomitant use of PPIs while taking pexidartinib should be avoided. As an alternative to PPI, pexidartinib should be administered 2 hours before or 2 hours after taking a locally acting antacid, or if using a histamine 2 (H2)-receptor antagonist, pexidartinib should be administered at least 2 hours before or 10 hours after taking an H2-receptor antagonist.

Review Issues	Recommendations and Comments
Dosing in patient subgroups: DDI potential with strong CYP34A inhibitors	Itraconazole, a strong CYP3A4 inhibitor, increased the geometric mean C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib by 48% and 73%, respectively, compared with pexidartinib alone. Concomitant use of pexidartinib with strong CYP3A inhibitors should be avoided. If concomitant use with a strong CYP3A inhibitor cannot be avoided, the pexidartinib starting dose of should be reduced from 400 mg (2 x 200 mg capsules) orally twice daily to 200 mg (1 x 200 mg capsule) orally twice daily. In patients who have had a dose reduction to a total daily dose of 600 mg (3 x 200 mg capsules) or 400 mg (2 x 200 mg capsules) due to adverse reactions and who initiate a strong CYP3A4 inhibitor, the pexidartinib total daily dose should be reduced by 200 mg (1 x 200 mg capsule). If concomitant use of a strong CYP3A inhibitor is discontinued, the pexidartinib dose should be increased (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor.
Dosing in patient subgroups: DDI potential with strong CYP34A inducers	Rifampin, a strong CYP3A4 inducer, decreased the pexidartinib geometric mean C_{max} and $AUC_{0\text{-}inf}$ by 33% and 63%, respectively, compared with pexidartinib alone. The concomitant use of strong CYP3A4 inducers with pexidartinib should be avoided, including St John's Wort.
Dosing in patient subgroups: DDI potential with UGT inhibitors	Probenecid, a known UGT inhibitor, increased the pexidartinib geometric mean $AUC_{0\text{-}inf}$ by 60% compared with pexidartinib alone with no effect noted on its C_{max}. The concomitant use of pexidartinib with UGT inhibitors should be avoided. If concomitant use with a UGT inhibitor cannot be avoided, the starting dose of pexidartinib should be reduced from 400 mg (2 x 200 mg capsules) orally twice daily to 200 mg (1 x 200 mg capsule) orally twice daily. In patients who have had a dose reduction to a total daily dose of 600 mg (3 x 200 mg capsules) or 400 mg (2 x 200 mg capsules) due to adverse reactions and who initiate a UGT inhibitor, the total daily pexidartinib dose should be reduced by 200 mg (1 x 200 mg capsule). If concomitant use of a UGT inhibitor is discontinued, the pexidartinib dose should be increased (after 3 plasma half-lives of the UGT inhibitor) to the dose that was used before starting the UGT inhibitor.
Labeling	Labeling recommendations were communicated to the Applicant. Refer to Section 10 for details.
Bridge between the to-be marketed and clinical trial formulations	The proposed commercial 200 mg capsule formulation [(b) (4) Formulation J-3397-AF] was used in ENLIVEN. This formulation is found to be equivalent to the clinical 200 mg capsule formulation (b) (4) Formulation J-3397-AF].

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The pharmacokinetics (PK) of both pexidartinib and its major circulating *N*-glucuronide metabolite, ZAAD-1006a, were assessed in male and female healthy volunteers following single oral dose range of 200 mg to 2400 mg of pexidartinib. The PK of both pexidartinib and ZAAD-1006a were assessed in patients with solid tumors at 200 mg to 900 mg once daily and at 1000 mg/day (500 mg BID) and 1200 mg/day (600 mg BID). The PK of both pexidartinib and ZAAD-1006a were also assessed in patients with TGCT at 1000 mg/day (600 mg in the morning and 400 mg in the evening) and 800 mg/day (400 mg BID).

In healthy volunteers, C_{max} and $AUC_{0\text{-}inf}$ values for pexidartinib are dose proportional over the dose range of 200 mg to 2400 mg.

In patients with TGCT, the geometric mean steady state (coefficient of variation [CV%]) C_{max} and $AUC_{0\text{-}12h}$ values for pexidartinib are 8625 ng/mL (32%) and 77465 ng·h/mL (32%), respectively, at the proposed clinical dose of 400 mg BID; the corresponding values for ZAAD-1006a are 13564 ng/mL (45%) and 137872 ng.h/mL (45%). Both pexidartinib and ZAAD-1006a accumulate upon twice daily dosing of pexidartinib [R_{ac} values are 3.6 (22%) and 4.6 (17%), respectively], which is consistent with the estimated effective $T_{1/2}$ of approximately 26 hours for both compounds.

Absorption

The median T_{max} for pexidartinib is 2.5 (range=1.5 to 8.0) hours following a single 400 mg oral dose in healthy subjects. ZAAD-1006a appears in plasma within a median T_{max} of 4.5 (range=3.0-8.0) hours after a single 400 mg oral dose of pexidartinib. Due to its low solubility and given that an intravenous (IV) formulation of pexidartinib is not available, the absolute bioavailability of pexidartinib has not been determined.

Distribution

Pexidartinib has a mean (%CV) apparent volume of distribution (Vz/F) of 187 L (27%) following a single 400 mg oral dose in healthy subjects. Both pexidartinib and ZAAD-1006a are highly bound to human plasma proteins (%PB >99%) including serum albumin and α1-acid glycoprotein and binding is independent of in vitro concentrations for both compounds.

Elimination

The mean (%CV) apparent clearance (CL/F) and terminal elimination half-life ($T_{1/2}$) of pexidartinib are 5.1 L/h (35%) and 26.7 hours (24%), respectively, following a single 400 mg oral dose in healthy subjects. ZAAD-1006a has a similar $T_{1/2}$ as for pexidartinib [mean=26.4 hours (23%)].

Metabolism: Pexidartinib is extensively metabolized in the liver by CYP3A4 to several pharmacologically inactive minor metabolites and also by UGT1A4 to the major *N*-glucuronide metabolite, ZAAD-1006a. ZAAD-1006a, the only major circulating metabolite identified in human plasma, was measured in all clinical pharmacology studies. The mean ± SD $AUC_{0\text{-}inf}$ ratio of ZAAD-1006a/pexidartinib (M/P), corrected for molecular weight [MW] of the parent (MW=418) versus metabolite (MW=594) is 110±9.7% in healthy subjects. ZAAD-1006a has minimal pharmacological activity compared to pexidartinib (355-fold lower) (See Section 5 above). Therefore, an increase or decrease in exposure of ZAAD-1006a observed in clinical pharmacology studies (e.g., renal, hepatic, DDI) is not expected to have any clinical relevance to safety or efficacy.

Excretion: Following a single 400 mg (150 µCi) oral dose of ^{14}C-pexidartinib in healthy volunteers, the majority of the radioactivity is eliminated in the feces (mean ± SD=64.8±6.8%)

with approximately one third of dose being excreted in urine (mean ± SD=27.4±6.94%) over 240 hours after dosing. No unchanged parent drug is found in urine. ZAAD-1006a is primarily eliminated in urine (10.3% of dose). A dealkylated glucuronide metabolite, represented 5.4% of the total radioactive dose, is also detected in urine.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The proposed clinical dose of pexidartinib is 400 mg BID (800 mg/day) administered orally on an empty stomach (at least 1 hour before or 2 hours after a meal or snack).

6.2.2.2. Therapeutic Individualization

Effect of Hepatic impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. A limited number of patients with moderate hepatic impairment (n=2) have been studied. Patients with severe hepatic impairment have not been studied.

Based on the Child-Pugh (C-P) classification, subjects with mild (C-P class A, 5-6 scores, n=8) and moderate (C-P class B, 7-9 scores, n=8) hepatic impairment (HI) had similar pexidartinib exposure to that in subjects with normal hepatic function (n=8 matching subject per each HI group, a total of n=16) following a single 200 mg oral dose. The geometric mean $AUC_{0\text{-}inf}$ ratio and 90% confidence intervals (90%CI) were 108% (90% CI: 74%, 160%) and 99% (90% CI: 74%, 134%) for the subjects with mild and moderate HI, respectively. Plasma protein binding of pexidartinib was more than 99% (mean %PB is 99.96%) irrespective of hepatic function at time points of 2.5 and 24 hours post dosing.

During the review of the NDA, the review team requested that DSI provide the results of a re-analysis of the PK data obtained from the above hepatic impairment study using the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria instead of Child-Pugh classification. After re-categorization using the NCI-ODWG criteria, there were 6 subjects in the mild HI B1 (total bilirubin ≤ ULN and ALT/AST > ULN) group, 1 subject in the mild HI B2 (total bilirubin >1.0-1.5x ULN and ALT/AST: Any) group and 23 subjects with normal hepatic function. Only 2 subjects the moderate HI were in the dataset. Based on NCI-ODWG criteria, subjects with mild HI B1 had a 16% higher geometric mean $AUC_{0\text{-}inf}$ for pexidartinib than subjects with normal hepatic function following a single 200 mg oral dose of pexidartinib.

Because of the limited data in subjects with moderated HI (n=2), the effect of moderate HI on pexidartinib exposure is not known. The review team recommends a PMR to evaluate pexidartinib in subjects with moderate HI.

(b) (4)

Effect of Renal impairment

Reduce the total daily dose to 600 mg (1 x 200 mg capsule in the morning and 2 x 200 mg capsules in the evening) in patients with mild-to severe renal impairment (CL_{CR}=15 - 89 mL/min as estimated by Cockcroft-Gault) to match exposure to that in patients with normal renal function.

In a dedicated study, subjects with mild (creatinine clearance [CL_{CR}]=60-89 mL/min), moderate (CL_{CR}=30-59 mL/min) and severe (CL_{CR}=15-29 mL/min) renal impairment had 65%, 30% and 32% higher geometric mean $AUC_{0\text{-}inf}$ for pexidartinib, respectively, than subjects with normal renal function (CL_{CR} ≥90 mL/min) following a single 200 mg oral dose of pexidartinib (N=8 per each group). The CL_{CR} was estimated using the Cockcroft-Gault Formula. Subjects with end stage renal disease (ESRD) on and off dialysis, had comparable pexidartinib exposure to subjects with normal renal function. Plasma protein binding of pexidartinib is high (mean %PB=99.96) irrespective of renal function at time points of 2.5, 6.5 and 24 hours post dosing. The dialysis clearance of pexidartinib is not known but because of high protein binding, it can be predicted that the drug may not cross the dialysis membrane and thus may have a low dialysis clearance.

Based on a popPK analysis of clinical data, patients with mild (n=67, CL_{CR}=89 to 60 mL/min) had approximately 30% higher exposure to pexidartinib than in patients with normal renal function (n=299, CL_{CR} ≥90 mL/min). FDA recommends that the total daily dose of pexidartinib be reduced to 600 mg (1 x 200 mg capsule in the morning and 2 x 200 mg capsules in the evening) in patients with mild to severe RI (CL_{CR}=15 to 89 mL/min). The 20% dose reduction (600 mg/day) is

supported by the observed increased risk of liver enzyme elevations with increased exposure observed at the 1000 mg/day pexidartinib dosage.

Effect of UGT1A4 polymorphisms

An analysis of PK data from healthy subjects suggests that pexidartinib exposure is approximately 19% higher in *UGT1A4*2* variant allele carriers and approximately 11% higher in *UGT1A4*3* variant allele carriers compared to wild-type subjects. The clinical relevance of these changes in pexidartinib exposure is unclear and no dosage adjustment is recommended based on *UGT1A4* genotype.

6.2.2.3. Food Interaction and Drug-Drug Interactions (DDIs):

Effect of food and of gastric acid reducing agents

- *A high-fat meal increases pexidartinib exposure 2-fold. Administer TURALIO an empty stomach (at least 1 hour before or 2 hours after a meal or snack). Non-compliance with fasting condition within the BID dosing regimen is a safety concern, given the potential 2-fold increase in exposure with food and exposure-response relationships with key adverse events. The effect of a low-fat meal on pexidartinib exposure is not known. A PMR will be issued to assess the effect of low-fat (400 - 500 Kcal) meal on pexidartinib exposure in order to further optimize administration or dosage with regard to food intake.*
- *Avoid the concomitant use of PPIs while taking TURALIO. As an alternative to PPI, administer TURALIO 2 hours before or 2 hours after taking a locally acting antacid, or if using a histamine 2 (H2)-receptor antagonist, administer TURALIO at least 2 hours before or 10 hours after taking an H2-receptor antagonist.*

Effect of Food

Healthy volunteers who exposed to what FDA defines as a high-fat meal (i.e., 800 – 1000 Kcal), had increased geometric mean C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib by 98% and 110%, respectively, compared to fasted conditions.

Effect of Proton Pump Inhibitors (PPIs): Esomeprazole, a PPI, decreased the geometric mean C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib by 45% and 53%, respectively, compared to administration of pexidartinib alone, in healthy volunteers.

DDI Potential

- *Avoid concomitant use of TURALIO with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the starting dose of TURALIO from 400 mg (2 x 200 mg capsules) orally twice daily to 200 mg (1 x 200 mg capsule) orally twice daily. In patients who have had a dose reduction to a total daily dose of 600 mg (3 x 200 mg capsules) or 400 mg (2 x 200 mg capsules) due to adverse reactions and who initiate a strong CYP3A4 inhibitor, reduce the total daily TURALIO dose by 200 mg (1 x 200 mg capsule). If concomitant use of a strong CYP3A inhibitor is discontinued, increase the TURALIO dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor. Avoid the concomitant use of strong CYP3A4 inducers with TURALIO, including St John's Wort.*
- *Avoid concomitant use of TURALIO with UGT inhibitors. If concomitant use with a UGT inhibitor cannot be avoided, reduce the starting dose of TURALIO from 400 mg (2 x 200 mg capsules) orally twice daily to 200 mg (1 x 200 mg capsule) orally twice daily. In patients who have had a dose reduction to a total daily dose of 600 mg (3 x 200 mg capsules) or 400 mg (2 x 200 mg capsules) due to adverse reactions and who initiate a UGT inhibitor, reduce the total daily TURALIO dose by 200 mg (1 x 200 mg capsule). If concomitant use of a UGT inhibitor is discontinued, increase the TURALIO dose (after 3 plasma half-lives of the UGT inhibitor) to the dose that was used before starting the UGT inhibitor.*

Strong CYP3A4 Inhibitors*:* In healthy volunteers, itraconazole, a strong CYP3A4 inhibitor (200 mg loading dose then 200 mg once daily for 15 days) increased the geometric mean $AUC_{0\text{-}inf}$ and C_{max} of pexidartinib by 73% and 48%, respectively, compared to pexidartinib alone (600 mg single dose).

***Moderate CYP3A4 inhibitors*:** The effect of a moderate CYP3A4 inhibitor on pexidartinib exposure has not been studied. The review team recommends a PMR to assess the effect of a moderate CYP3A4 inhibitor on pexidartinib exposure.

Strong CYP3A4 Inducers: In healthy volunteers, rifampin, a strong CYP3A4 inducer (600 mg once daily for 10 days) reduced the geometric mean $AUC_{0\text{-}inf}$ and C_{max} of pexidartinib by 63% and 33%, respectively, compared to pexidartinib alone (600 mg single dose).

UGT Inhibitors*:* In healthy volunteers, probenecid, a known UGT inhibitor (500 mg four times a day) increased the geometric mean $AUC_{0\text{-}inf}$ of pexidartinib by 60% compared to pexidartinib alone (600 mg single dose) with no effect noted on its C_{max}.

6.2.2.4. Outstanding Issues

The outstanding issues will be addressed by the proposed postmarketing studies. The review team recommends:

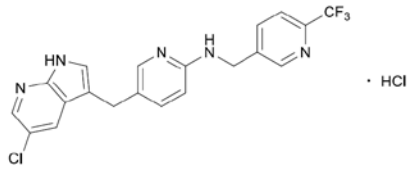
- PMRs to assess:
  - The effect of moderate hepatic impairment on pexidartinib exposure,
  - The effect of a low-fat meal on pexidartinib exposure,
  - The effect of a moderate CYP3A4 inhibitor on pexidartinib exposure
  - The effect of a moderate CYP3A4 inducer on pexidartinib exposure
- PMC to submit the complete study report and data files for the ongoing clinical drug interaction study (PL3397-A-U126) to assess the effect of pexidartinib on midazolam, a sensitive CYP3A substrate and tolbutamide, a sensitive CYP2C9 substrate.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The general overview of pexidartinib ADME and clinical PK information are presented in the table below.

Table 22. Pharmacokinetic Characteristics of Pexidartinib

<table>
<tr><td colspan="3">PHYSICOCHEMICAL PROPERTIES</td></tr>
<tr><td>Chemical structure and molecular formula & weight</td><td>Pexidaritinib (PLX3397)
 
· HCl</td><td>Molecular formula: $C_{20}H_{15}ClF_3N_5$•HCl
Molecular weight: 454 Daltons (free base: 418 Daltons)</td></tr>
<tr><td>Aqueous solubility</td><td colspan="2">The solubility of pexidartinib HCl decreases with increasing pH. The solubility of pexidartinib HCl in various pH solutions is provided in the Applicant's table below.
Table 1.2: Solubility of Pexidartinib Hydrochloride at Equilibrium Concentrations in Aqueous Solutions of Different pH at 37°C
<table>
<tr><th>Media</th><th>pH[a]</th><th>Solubility (mg/mL)</th></tr>
<tr><td>Water</td><td>2.42</td><td>0.29</td></tr>
<tr><td>0.1N HCl</td><td>1.1</td><td>2.451</td></tr>
<tr><td>0.01N HCl</td><td>1.9</td><td>1.1</td></tr>
<tr><td>pH 3.0 Diluted McIlvaine buffer</td><td>2.5</td><td>0.13</td></tr>
<tr><td>pH 4.0 Diluted McIlvaine buffer</td><td>3.3</td><td>0.018</td></tr>
<tr><td>pH 7.5 Diluted McIlvaine buffer</td><td>7.0</td><td>0.000051</td></tr>
</table>
[a] pH of solution reached at equilibrium concentration after addition of pexidartinib HCl.
Pexidartinib drug substance is considered a low solubility compound as its solubility over the pH range of 1.0–6.5 is all less than the value of dose/250 ml (3.2 mg/mL). Pexidartinib is has a high-permeability (18 to 32 × 10^{-6} cm/sec). Based on the low solubility and high permeability data, pexidartinib is categorized as a BCS class II compound.</td></tr>
<tr><td colspan="3">PHARMACOLOGY</td></tr>
</table>

Mechanism of action	Pexidartinib is a small molecule inhibitor that targets the colony stimulating factor 1 receptor (CSF1R). This receptor is also known as feline McDonough sarcoma (FMS) kinase. Pexidartinib also inhibits the KIT proto-oncogene receptor tyrosine kinase (KIT) and FMS-like tyrosine kinase 3 (FLT3) harboring an internal tandem duplication mutation (FLT3-ITD). The IC_{50} values for pexidartinib against recombinant human CSF1R, KIT and FLT3 were 0.017 µM, 0.012 µM, and 0.16 µM, respectively. Mean steady-state pexidartinib C_{max}=8625 ng/mL (20 µM) at 400 mg BID dose. The IC_{50} values for ZAAD-1006a against recombinant human CSF1R, FLT3, and KIT were 6.04 µM, 10.3 µM, and >50 µM, respectively. Mean state-state ZAAD-1006a C_{max}=13564 ng/mL (22 µM) at 400 mg BID pexidartinib dose. The IC_{50} values for pexidartinib and ZAAD-1006a against recombinant human FLT3-ITD were 0.038 µM and 7.3 µM, respectively (state-state C_{max} is 20 µM and 22 µM, respectively, at 400 mg BID pexidartinib dose).
Active moiety	Pexidartinib and its major circulating inactive *N*-glucuronide metabolite, ZAAD-1006a.
QT/QTc prolongation	A thorough QT study evaluated the effect of pexidartinib on the Fridericia's corrected QT interval (QTcF) in 36 healthy volunteers after either pexidartinib (1800 mg single dose), a matching placebo or moxifloxacin (400 mg single dose) (Study PL3397-A-U125). According to the QTc-IRT review, no clinically relevant effects were observed on the QTc interval at pexidartinib exposure twice the mean maximum exposure determined at the proposed clinical dose (400 mg BID). The change-from-baseline QTcF (ΔQTcF) was mostly negative after dosing with pexidartinib and placebo. The largest upper bound of the 90% confidence interval was 4.8 ms at 48 hours after dosing.

GENERAL INFORMATION	
Bioanalytical assay	A validated liquid chromatography with tandem mass spectrometry detection (LC-MS/MS) assay was used to measure the concentrations of pexidartinib and ZAAD-1006a in human plasma, urine, plasma dialysate samples in clinical pharmacology studies of this NDA (See Appendix 19.4).
Patient PK versus healthy volunteers PK	Based on the population PK (popPK) analysis, healthy volunteers (n=159) had a 21% lower $AUC_{0\text{-}24h,ss}$ (95% CI: -25%, -16%) than patients with solid tumors and TGCT (n=216). This difference in pexidartinib exposure is not clinically relevant.
Steady-state exposure at the proposed dosing regimen	Based on the popPK analysis, the geometric mean steady state $C_{max.ss}$ and $AUC_{0\text{-}12h}$ values for pexidartinib are 8625 ng/mL (32%) and 77465 ng·h/mL (32%), respectively, following a 400 mg BID oral dose. The geometric mean steady state (CV%) $C_{max,ss}$ and $AUC_{0\text{-}12h}$ values for ZAAD-1006a, the major circulating *N*-glucuronide metabolite of pexidartinib, are 13564 ng/mL (45%) and 137872 ng.h/mL (45%).
Minimal effective dose or exposure	The proposed dose is 800 mg/day (400 mg BID). Pexidartinib demonstrated dose-dependent inhibition of its CSF1R target as shown by the exposure-dependent increase in plasma CSF-1 concentrations at once daily doses ranging from 100 mg to 2000 mg. The lowest effective dose level is 800 mg/day at which the predicted steady state C_{max} is higher than the EC_{50} (8625 ng/mL versus 4430 ng/mL). Doses less than 800 mg/day were less effective in inhibiting the CSF1R target.
Maximum tolerated dose or exposure	Based on the dose-limiting toxicity data from the first-in-human phase 1 Study PLX108-01 in patients with solid tumors at doses of ranging from 200-1200 mg/day, the Applicant declared the 1000 mg/day (500 mg BID) dose to be the MTD and the recommended phase 2 dose (RP2D). This dose was used in the extension cohorts of Study PLX108-01 in patients with TGCT and other tumors types and also was initially used in Part 1 of ENLIVEN in TGCT patients.
Dose proportionality	Pexidartinib C_{max} and $AUC_{0\text{-}inf}$ are dose-proportional over the single doses of 200-2400 mg in healthy volunteers (combined data from Studies PL3397-A-U117 and PL3397-A-U121). ZAAD-1006a C_{max} and $AUC_{0\text{-}inf}$ are dose-proportional over the single doses of 200-600 mg of pexidartinib in healthy volunteers.
Accumulation	Both pexidartinib and ZAAD-1006a accumulate upon BID dosing of pexidartinib [mean (%CV) R_{ac}=3.6 (22%) and 4.6 (17%), respectively] based on the popPK analysis.
Variability	Inter-patient variability (CV%) is 32% for both $C_{max,ss}$ and $AUC_{0\text{-}12h}$.

ABSORPTION

Bioavailability/Bio-equivalence

The relative bioavailability of the proposed commercial 200 mg capsule formulation [known as Formulation J-3397-AF (b) (4) Treatment B] and the clinical 200 mg capsule formulation [known as Formulation J-3397-AF (b) (4) (b) (4) Treatment A] was assessed in 36 healthy volunteers following a single 600 mg oral pexidartinib dose (Study PL3397-A-U116). Both formulations were found to be equivalent (see Applicant's table below).

PK Parameter	Geometric LS Means[a]		Ratio of Geometric LS Means Treatment B/ Treatment A (%)	90% CI for Ratio (%)
	Treatment A Pexidartinib 600 mg J-3397-AF (Pre-Optimized) (n = 36)	Treatment B Pexidartinib 600 mg J-3397-AF (Optimized) (n = 36)		
Cmax (ng/mL)	6406	6804	106.22	96.67, 116.71
AUCinf (ng·h/mL)	103,294	109,436	105.95	98.74, 113.68

Source: Module 5.3.1.2, PL3397-A-U116 CSR, Table 9.2.

The proposed commercial 200 mg capsule formulation was also used in ENLIVEN study.

T_{max}

Median (range) T_{max} for pexidartinib is 2.5 (range=1.5 to 8.0) hours following a single 400 mg oral dose in healthy volunteers (Study PL3397-A-U117).

Effect of food

GM Ratio C_{max} (90% CI)	GM Ratio $AUC_{0\text{-}inf}$ (90% CI)	Median (range) T_{MAX}
198 [176, 222]	210 [192, 232]	5.5 (4.0 - 10) hours (Fed) 2.5 (1.5 - 5) hours (Fasted)

Following a single 400 mg dose in 29 healthy volunteers, an FDA standard high-fat and high-calorie meal (800-1000 Kcal) increased mean C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib by 98% and 110%, respectively, compared to fasted conditions (Study PL3397-A-U114). The clinical 200 mg capsule formulation (Formulation J-3397-AF (b) (4)) was used in the study which is equivalent to the commercial formulation (Formulation J-3397-AF (b) (4)), see above). It is recommended that pexidartinib be taken on an empty stomach (at least 1 hour before or 2 hours after a meal).

Effect of esomeprazole, a PPI

GM Ratio C_{max} (90% CI)	GM Ratio $AUC_{0\text{-}inf}$ (90% CI)	Median (range) T_{MAX}
45 [37, 56]	53 [47, 59]	2 (1.5-4) hours (+ esomeprazole 3 (1.5 -4.5) hours (alone)

Following a single 600 mg dose in 16 healthy volunteers, esomeprazole, a PPI, decreased mean C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib by 45% and 53%, respectively, compared to administration of pexidartinib alone (Study PL3397-A-U120).

DISTRIBUTION

Apparent volume of distribution (Vz/F)

Pexidartinib is widely distributed throughout the body with a mean (%CV) Vz/F of 187 L (27%) following a single 400 mg oral dose in 18 healthy volunteers (Study PL3397-A-U117).

Protein Binding

Pexidartinib is highly bound to human plasma proteins (99.8% at 10 µM and 99.9% at 75 µM (Study PLX-018). Pexidartinib binds to both human serum albumin (HSA) and to alpha-1 acid glycoprotein (AAG), 99.9% and 89.9%, respectively (Study CYP1187-R3). ZAAD-1006a is also highly bound to human plasma proteins; plasma protein binding of ZAAD-1006a at 3, 10 and 30 µM ranged from 99.4% to 99.5% (Study CB150294). The binding of ZAAD-1006a to HSA and AAG is 99.4% and 23.3%, respectively (Study CB171779).

ELIMINATION	
Elimination terminal half-life ($T_{1/2}$) and apparent clearance (Cl/F)	The mean (%CV) $T_{1/2}$ and Cl/F of pexidartinib are 26.7 hours (24%) and 5.1 L/h (35%), respectively, after a single 400 mg oral dose in 18 healthy subjects (Study PL3397-A-U117). The mean $T_{1/2}$ for ZAAD-1006a, the major circulating metabolite, is similar to that for pexidartinib [26.4 hours (23%)] indicating formation rate-limited kinetics of ZAAD-1006a.
Metabolism	Pexidartinib is extensively metabolized by CYP3A4 (76% decrease) and UGT1A4 (25% decrease) (Study XT154103). Overall, twelve minor metabolites were observed in incubations with CYP3A4. The most abundant metabolite (21%) was proposed to be a combination of di-oxygenation and hydrogenation. Two radiolabeled glucuronide metabolites (U1 and U2, 15.1% and 6.8%, respectively) were observed only in incubations with recombinant human UGT1A4 and U2 was identified as ZAAD-1006a (*N*-glucuronide metabolite).
Excretion	Following a single 400 mg (150 µCi) oral dose of [^{14}C]-pexidartinib as a suspension) in 8 male healthy volunteers, the total recovery of radioactivity in urine and feces was mean ± SD=92.2±2.7% (Study PL3397-A-U115). The majority of the radioactivity is eliminated in feces (mean ± SD=64.8±6.8%) with approximately one third (mean ± SD=27.4±6.9%) in urine over 240 hours post-dose. Only one major metabolite of pexidartinib, *N*-glucuronide metabolite (ZAAD-1006a) is detected in human plasma. ZAAD-1006a appeared rapidly in the plasma with a median T_{max} of 3.0 (2.5 - 4.5) hours. The mean ± SD $AUC_{0\text{-}inf}$ ratio of ZAAD-1006a/pexidartinib (M/P), corrected for molecular weight [MW] of the parent (MW=418) versus metabolite (MW=594, is 110±9.7%). The most abundant radioactive component in urine is the inactive metabolite, ZAAD-1006a, accounting for 10.3% of the administered pexidartinib dose. A dealkylated glucuronide metabolite is detected in urine accounting 5.4% of the administered dose. Unchanged pexidartinib was not detected in urine. Unchanged pexidartinib is the major radioactive component detected in feces, representing 44% of the administered dose.
DDIs	
In vitro DDIs	CYP450/UGT Enzymes Pexidartinib is a substrate for both CYP3A4 and UGT1A4. It is an inhibitor of CYP 2B6, 2C8, 2C9, 2C19 & CYP3A4 with estimated IC_{50} values of 9.3 µM for CYP2B6, 7.9 µM for CYP2C8, 3.7 µM for CYP2C9, 9.3 µM for CYP2C19 and 16.7 µM for CYP3A4 (testosterone). Mean $C_{max,ss}$ is 8625 ng/mL (20 µM, MW=417 free base) at the 400 mg BID dose. Pexidartinib is an inhibitor of UGT 1A1, 1A4 & 2B7 with IC_{50} values of 6.9, 22, and 26 µM, respectively. Pexidartinib is an inducer of CYP 3A4 and 2B6. The induction of CYP3A4 enzyme (3.9 times) was lower than the mRNA increase (65 times), indicating possible time-dependent inhibition. Transporters Pexidartinib is not a substrate of P-gp, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, OATP2B1, SMVT, BCRP or BSEP Pexidartinib is not an inhibitor of BSEP, SMVT, OCT1, OCT2, OAT1, or OAT3 Pexidartinib is an inhibitor of MATE1, MATE2-K, OATP1B1, OATP1B3, OATP2B1 & P-gp and to a lesser extent, BCRP.

In vivo DDIs	*Effect of strong CYP3A4 inhibitors on pexidartinib:* Itraconazole, a strong CYP3A4 inhibitor, increased the geometric mean (GM) $AUC_{0\text{-}inf}$ of pexidartinib by 73% [GM ratio=173% (90% CI: 160, 186)] and its C_{max} by 48% [GM ratio=148% (90% CI: 128, 172)] compared to pexidartinib alone in 16 healthy volunteers (Study PL3397-A-U118).
	Effect of strong CYP3A4 inducers on pexidartinib: Rifampin, a strong CYP34A inducer, decreased geometric mean $AUC_{0\text{-}inf}$ of pexidartinib by 63% [GM ratio 37% (90% CI: 30, 45)] and its C_{max} by 33% [GM ratio 67% (90% CI: 53, 85)] compared to pexidartinib alone in 16 healthy volunteers (Study PL3397-A-U119).
	Effect of UGT inhibitors on pexidartinib: Probenecid, a known UGT inhibitor, increased geometric mean $AUC_{0\text{-}inf}$ of pexidartinib by 60% [GM ratio 160% (90% CI: 143, 178)] with no effect noted on its C_{max} (only 5% increase) compared to pexidartinib alone in 15 healthy volunteers (Study PL3397-A-U122).
	Effect of pexidartinib on omeprazole: Coadministration of pexidartinib decreased the geometric mean C_{max} and $AUC_{0\text{-}inf}$ of omeprazole (a CYP2C19 substrate) by 37% and 17%, respectively, compared to omeprazole alone in 19 healthy volunteers (Study PL3397-A-U127).
	Effect of pexidartinib on digoxin: Coadministration of pexidartinib increased the geometric mean C_{max} of digoxin (a P-gp substrate) by 32% with no effect on its $AUC_{0\text{-}inf}$ (only 9% increase) compared to digoxin alone in 19 healthy volunteers (Study PL3397-A-U127).

6.3.2. Clinical Pharmacology Questions

6.3.2.1. Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The clinical pharmacology information along with the efficacy results from ENLIVEN study provided adequate support for evidence of effectiveness of pexidartinib in the proposed TGCT indication. The primary efficacy endpoint was ORR, defined as the proportion of patients who achieved a complete response (CR) or partial response (PR) at the Week 25 Visit. The ORR was significantly higher at Week 25 (39%) following pexidartinib treatment than that observed for placebo (0%).

The PK of both pexidartinib and ZAAD-1006a was determined at the proposed clinical dose of 400 mg BID of pexidartinib in patients with TGCT (ENLIVEN and PLX108-01). Table 23 below summarizes the single-dose and steady-state exposure parameters (C_{max} and $AUC_{0\text{-}12h}$) for pexidartinib and ZAAD-1006a.

Table 23. Predicated Exposure in TGCT Patients

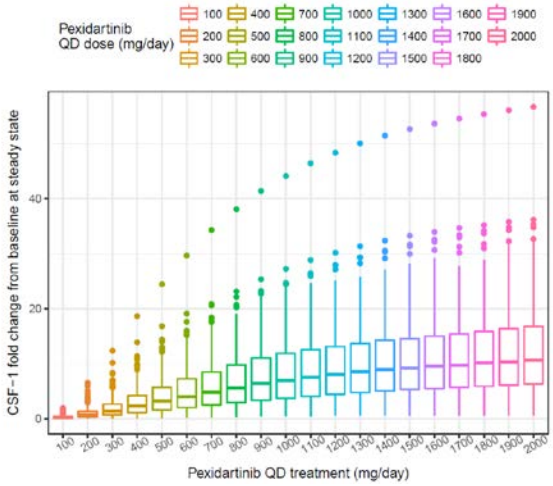
PK Parameter*	Pexidartinib (N=216)	ZAAD-1006a (N=84)
$AUC_{0\text{-}12h}$ (ng·h/mL)		
Day 1	21529 (25%)	30602 (45%)
Day 28	77465 (32%)	137872 (45%)
C_{max} (ng/mL)		
Day 1	3524 (31%)	4194 (52%)
Day 28	8625 (32%)	13564 (45%)
Accumulation ratio (R_{ac})	3.6 (22%)	4.6 (17%)

* Geometric Mean (%CV)

Source: Reviewer generated table – Summary of Clinical Pharmacology Studies

Pexidartinib demonstrated a dose-dependent inhibition of its CSF1R target as shown by the dose-dependent increase in plasma CSF-1 concentrations, a PD biomarker (Figure 3). At the 800 mg/day dose, the predicted pexidartinib steady state C_{max} is higher than the EC_{50} of CSF1R inhibition (8625 ng/mL versus 4430 ng/mL) and therefore, the response was closer to E_{max} at 800 mg/day dose. In addition, lower doses of pexidartinib had less effect on CSF-1 concentrations suggesting less effective inhibition of CSF1R.

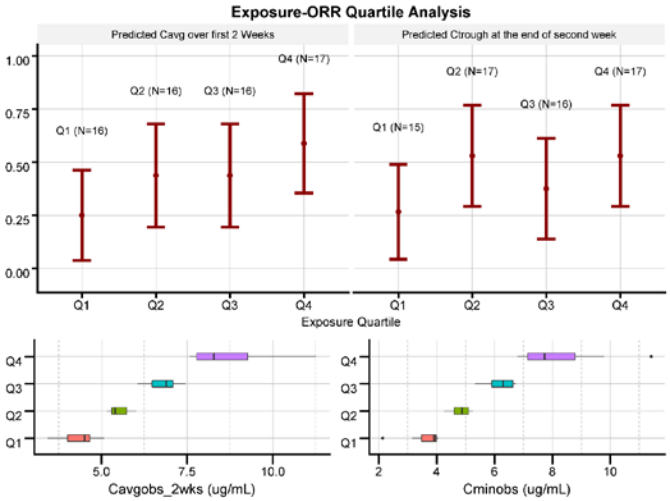
Figure 3. Simulated CSF-1 Change by Dose



Source: Summary of Clinical Pharmacology Studies

Exposure-response analyses were conducted by the Applicant to explore the relationship between exposure of pexidartinib and efficacy in patients who received pexidartinib. Overall, there appears to be a positive trend of exposure-response relationship for ORR with shallow slope. However, caution should be taken when interpreting this relationship as it was based on a small sample size with one dosing regimen (Figure 4).

Figure 4. Relationship Between Pexidartinib Exposure and ORR in TGCT Patients



Source: Reviewer's Analysis based on "ds 0102resp.xpt"

6.3.2.2. Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of 400 mg BID (total 800 mg/day) appears acceptable for the proposed TGCT patient population. The selection of this dosing regimen was based upon the safety and tolerability data obtained from the first-in-human phase 1 Study PLX108-01. In the dose-escalation portion of this study, 41 patients with solid tumors were treated at pexidartinib doses of 200 mg/day (n=3), 300 mg/day (n=6), 400 mg/day (n=6), 600 mg/day (n=6), 900 mg/day (n=7), 1000 mg/day (given as 500 mg BID) (n=7) and 1200 mg (n=6) (given as 600 mg BID). Six out of 41 patients (14.6%) experienced a total of nine dose-limiting toxicities (DLTs) as seen in the following Table 24 below:

Table 24. DTLs Observed by Dose Level (Study PLX108-01)

Dose Level (mg/day)	Total N/ Dose Level	N with DTLs	DLTs
300	6	1	INR increased and hematuria
600	6	2	Decreased lymphocyte count and hyponatremia
1000	7	1	Increased AST
1200	6	2	One patient: Increased AST Other patient: Anemia, neutropenia & syncope

Source: Reviewer generated table – DTL data from Study PLX108-01

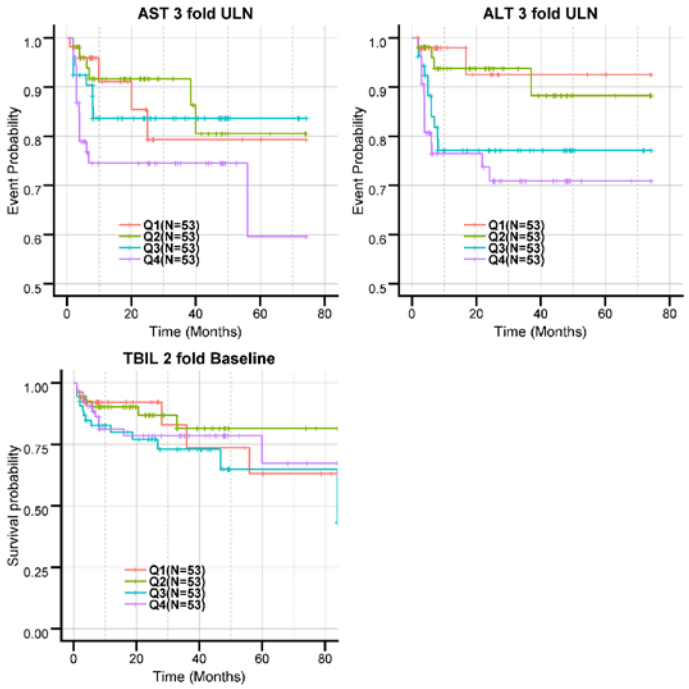
The Applicant declared the 1000 mg/day (administered as 500 mg BID) dose to be the MTD and the RP2D and this dose was used in the Extension Cohort portion of this study in patients with various tumor types including TGCT. In Part 1 of ENLIVEN, the 1000 mg/day dose (600 mg in the morning and 400 mg in the evening) was administered for the first 2 weeks. Subsequently, after the two weeks, the dose was reduced to 800 mg/day (400 mg BID) because of the incidence of liver enzyme elevations (AST and ALT). At this 800 mg/day dose, ENLIVEN met its primary efficacy endpoint by demonstrating that response rate for pexidartinib arm (39%) was significantly higher than that in the placebo arm (0%).

The studied dose in 59 patients who received pexidartinib in Part 1 of Study PLX108-01 is 1000 mg total daily dose for the first 2 weeks followed by 400 mg BID for the remaining period. Thirty placebo-treated patients switched over to the proposed pexidartinib regimen of 400 mg BID in Part 2 of ENLIVEN. In the 30 patients who crossed over from placebo, the rate of complete or partial response achieved (53.3%) is comparable to the rate in the treatment group in Part 1 (52.5%). This provides the primary evidence in support of the proposed clinical dose of 800 mg/day (400 mg BID).

Exposure-safety analyses were performed to investigate whether the adverse events related to hepatic function (hepatic enzyme elevations) could be attributed to the variability in pexidartinib exposure. Graphical quartile analyses suggest higher pexidartinib concentrations during the first week of dosing were associated with faster onset and higher incidence of elevated ALT (three-fold ULN) and AST (three-fold ULN) (Figure 5). Statistically significant relationships were found between average pexidartinib concentration during the first week and elevated ALT (three-fold ULN) and AST (three-fold ULN) but not for total bilirubin (TBIL) (two-fold baseline). Exposure-safety relationship for ALT and AST elevation support the dose reduction due to adverse events.

At the pexidartinib dose of 800 mg/day (400 mg BID), the mean steady-state C_{max} concentration is 8625 ng/mL (20 µM), which exceeds the IC_{50} for inhibition of CSF1R, KIT and FLT3 (0.017 µM, 0.012 µM, and 0.16 µM, respectively).

Figure 5. Relationship Between Pexidartinib Exposure and Hepatotoxicity



Source: Reviewer's Analysis based on "ds 0102aette.xpt"," adlbtgct.xpt" and "adlbntgc.xpt"

6.3.2.3. Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

6.3.2.3.1. Effect of Hepatic Impairment

No dosage adjustment is necessary in patients with mild hepatic impairment. A limited number of patients with moderate hepatic impairment has been studied (n=2). Patients with severe hepatic impairment have not been studied.

The effect of hepatic impairment on the exposure of pexidartinib and its major circulating *N*-glucuronide metabolite, ZAAD-1006a was evaluated in a single-dose, parallel-group study in 32 healthy volunteers (Study PL3397-A-U123). Volunteers were categorized into the following hepatic groups according to the Child-Pugh classification into the following groups:

- Mild (Child-Pugh class A: Score 5 – 6) (n=8)
- Moderate (Child-Pugh class B: Score 7 – 9) (n=8)
- Normal hepatic function (n=8 for each of the hepatic group, total N=16)

The study did not enroll subjects with severe hepatic impairment (Child-Pugh class C, Score 10 - 15). Subjects ranged in age from 40 to 65 years. The majority of the volunteers were males (87.5%) and Whites (87.5%). Refer to the Applicant's table below.

Table 25. Demographic Characteristics by Hepatic Impairment Category

Demographic or Baseline Characteristic[a]	Mild HI (N=8)	Healthy Matched to Mild HI (N=8)	Moderate HI (N=8)	Healthy Matched to Moderate HI (N=8)	Overall (N=32)
Age at Informed Consent (y)					
n	8	8	8	8	32
Mean	56.6	55.1	56.9	56.3	56.2
Standard Deviation	4.50	6.17	5.96	7.96	6.00
Median	58.0	54.5	58.0	57.5	56.5
Minimum	49	45	49	47	45
Maximum	61	64	64	65	65
Age Group					
>40 to ≤65	8 (100%)	8 (100%)	8 (100%)	8 (100%)	32 (100%)
Sex					
Male	7 (87.5%)	7 (87.5%)	7 (87.5%)	7 (87.5%)	28 (87.5%)

All volunteers received a single 200 mg oral dose of pexidartinib after an overnight fast of 10 hours. A summary of PK parameters for both pexidartinib and ZAAD-1006a by hepatic group is presented in Table 26 and Table 27, respectively. Results of the statistical analysis of group comparisons is presented for pexidartinib in Table 28.

Table 26. Geometric Mean (%CV) PK Parameters for Pexidartinib

Parameter	Mild HI (n=8)	Normal Hepatic Function (n=8)	Moderate HI (n=8)	Normal Hepatic Function (n=8)
C_{max} (ng/mL)	1449 (65%)	1654 (66%)	1566 (81%)	1722 (64%)
T_{max} (h)[+]	1.5 (1.0-2.5)	2.25 (1.5-6.0)	2.5 (1.0-4.0)	2.0 (1.5-2.5)
$AUC_{0\text{-last}}$ (ng·h/mL)	29010 (37%)	26809 (53%)	29777 (28%)	30534 (36%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	29988 (37%)	27641 (54%)	31211 (29%)	31340 (36%)
$T_{1/2}$ (h)[++]	29.3±11.4	27.6±10.1	24.1±4.9	27.7±7.6
CL/F (L/h)	6.7 (36%)	7.1 (54%)	6.4 (29%)	6.4 (36%)
V_z/F (L)	264 (50%)	272 (43%)	219 (36%)	247 (29%)

[+] Median (range) [++] Arithmetic mean
Source: Reviewer generated table – PK data from PL3397-A-U123

Table 27. Summary of Statistical Analysis for Pexidartinib by Hepatic Group

Parameter	Mild HI	Normal hepatic Function	Ratio (%)* (Mild/Normal)	90% CI
C_{max} (ng/mL)	1449	1654	87	(52, 148)
$AUC_{0\text{-inf}}$ (ng·h/mL)	29988	27641	108	(74, 159)
Parameter	**Moderate HI**	**Normal hepatic Function**	**Ratio (%)* (Moderate/Normal)**	**90% CI**
C_{max} (ng/mL)	1566	1722	91	(51, 161)
$AUC_{0\text{-inf}}$ (ng·h/mL)	31211	31340	99	(74, 134)

[*]Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from PL3397-A-U123

Table 28. Geometric Mean (%CV) PK Parameters for ZAAD-1006a

Parameter	Mild HI (n=8)	Normal Hepatic Function (n=8)	Moderate HI (n=8)	Normal Hepatic Function (n=8)
C_{max} (ng/mL)	1457 (58%)	1575 (58%)	1519 (88%)	1498 (53%)
T_{max} (h)+	4.75 (2.5-10)	3.0 (2.5-6.0)	4.5 (2.5-10)	3.7 (2.5-10)
$AUC_{0\text{-last}}$ (ng·h/mL)	57189 (43%)	41619 (64%)	61789 (46%)	45432 (33%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	59037 (44%)	42809 (64%)	66879 (45%)	46441 (33%)
M/P Ratio (%)++	142±33	119±54	155±63	109±34

+ Median (range) ++ Arithmetic mean
Source: Reviewer generated table – PK data from PL3397-A-U123

Based on the Child-Pugh (C-P) classification, Subjects with mild (C-P class A, 5-6 scores) and moderate (C-P class B, 7-9 scores) hepatic impairment (HI) had a similar pexidartinib exposure (C_{max}, $AUC_{0\text{-inf}}$) to that for subjects with normal hepatic function following a single 200 mg oral dose of pexidartinib. The mean $AUC_{0\text{-inf}}$ of the major *N*-glucuronide circulating metabolite, ZAAD-1006a, was 37% and 44% higher in subjects with mild and moderate HI, respectively, than in subjects with normal hepatic function. Mean C_{max} of ZAAD-1006a was comparable between each of mild and moderate HI groups with the normal group. Plasma protein binding of pexidartinib was more than 99% (mean %PB=99.96%) irrespective of hepatic function in all study groups at time points of 2.5 and 24 hours post dosing. The mean M/P molar ratio (corrected for molecular weight) was 19% and 42% higher in the mild and moderate groups, respectively, than in the normal group. The increased exposure of ZAAD-1006a is not expected to have any clinical relevance to safety (based on preclinical toxicology data from a monkey study) or efficacy.

An FDA's Information Request (IR) was sent on 2/8/2019 requesting the Applicant to re-analyze the PK data obtained from the above hepatic impairment study using the National Cancer Institute-Organ Dysfunction Working Group (NCI-ODWG) criteria below instead of Child-Pugh classification.

Table 29. NCI-ODWG Classification of Hepatic Function Status

Hepatic Function Groups	Total Bilirubin	ALT or AST
Normal		
Mild	B1: ≤ ULN B2: > 1-1.5 × ULN	B1: > ULN B2: Any
Moderate	> 1.5-3 × ULN	Any
Severe	> 3 × ULN	Any

Table was adapted from Mansfield et al.[1]
Abbreviations: ALT = alanine amino transferase; AST = aspartate amino transferase; ULN = upper limit of normal

After re-categorization using the NCI-ODWG criteria, there were 6 subjects in the mild HI B1 (total bilirubin ≤ ULN and ALT/AST > ULN) group, 1 subject in the mild HI B2 (total bilirubin >1.0-1.5x ULN and ALT/AST: Any) group and 23 subjects with normal hepatic function. Only 2 subjects the moderate HI were in the dataset as seen in Table 30 below.

Table 30. Comparison Between the Child-Pugh and NCI-ODWG Criteria

Subject ID	Child-Pugh classification	NCI-ODWG Criteria
(b) (6)	Mild	Normal
	Mild	Mild HI B1
	Mild	Normal
	Mild	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Moderate	Mild HI B1
	Moderate	Moderate
	Moderate	Mild HI B1
	Moderate	Moderate
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Mild	Normal
	Mild	Normal
	Mild	Mild HI B1
	Mild	Mild HI B1
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Moderate	Mild HI B2
	Moderate	Mild HI B1
	Moderate	Normal
	Moderate	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal
	Normal	Normal

Source: Reviewer generated table – PK data submitted in the IR dated 2/28/2018

A summary of PK parameters for both pexidartinib and ZAAD-1006a by hepatic group is presented in Table 31 and Table 32, respectively. No statistical analysis comparisons were performed due to the limited number of subjects per group (n=6 mild HI B1, n=1 for mild HI B2 group and n=2 for moderate HI group) compared to the normal group (n=23).

Table 31. Geometric Mean (%CV) for Pexidartinib by Hepatic Group

Parameter	Mild HI B1 N=6)	Mild HI B2 (n=1)	Moderate HI (N=2)	Normal Hepatic Function (n=23)
C_{max} (ng/mL)	1942 (42%)	(1740)	(546, 3340)	1531 (60%)
T_{max} (h)[+]	2.5 (1.5-4.0)	(2.0)	(2.5, 4.0)	1.5 (1.0-6.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	32663 (20%)	(28800)	(19859, 46750)	28000 (40%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	33735 (20%)	(29500)	(20195, 47112)	28965 (41%)
$T_{1/2}$ (h)[++]	29.0±10.7	(28.6)	(20.4, 19.32)	27.4±8.6

[+] Median (range) [++] Arithmetic mean

Source: Reviewer generated table – PK data submitted in the IR dated 2/28/2018

Table 32. Geometric Mean (%CV) for ZADD-1006a by Hepatic Group

Parameter	Mild HI B1 (n=6)	Mild HI B2 (n=1)	Moderate HI (n=2)	Normal Hepatic Function (n=23)
C_{max} (ng/mL)	2108 (62%)	(888)	(685, 3350)	1418 (61%)
T_{max} (h)[+]	4.7 (4.-10)	(4.5)	(10, 4.5)	4.0 (2.5-10)
$AUC_{0\text{-}last}$ (ng·h/mL)	83542 (17%)	(61119)	(35775, 114809)	43426(46%)
$AUC_{0\text{-}inf}$ (ng·h/mL)	85757 (16%)	(62739)	(36353, 115220)	44810 (46%)
M/P Ratio (%)[++]	186±52	(149)	(127, 173)	118±44

[+] Median (range) [++] Arithmetic mean

Source: Reviewer generated table – PK data submitted in the IR dated 2/28/2018

Based on NCI-ODWG criteria, subjects with mild HI B1 had comparable pexidartinib exposure to that in subjects with normal hepatic function; geometric mean $AUC_{0\text{-}inf}$ and C_{max} Increased by 16% and 27%, respectively, compared to subjects with normal hepatic function. In clinical trials, pexidartinib was found to cause hepatotoxic adverse reactions (elevations in ALT and AST) at the proposed clinical dose of 400 mg BID.

Following a single 200 mg dose of pexidartinib, the geometric mean $AUC_{0\text{-}inf}$ for ZAAD-1006a was 90% and 48%, respectively higher in subjects with mild HI B1 than that in subjects with normal hepatic function. The mean M/P molar ratio (corrected for molecular weight) was 58% higher in the mild HI group than in the normal group. The increased exposure of ZAAD-1006a is not expected to have any clinical relevance to safety (based on preclinical toxicology data from a monkey study) or efficacy.

Because of the limited data for subjects with moderated HI (n=2), no conclusion could be made for this population and a PMR will be issued to evaluate the effect of moderate hepatic impairment on pexidartinib exposure.

6.3.2.3.2. Effect of Renal Impairment

Reduce the total daily dose of TURALIO to 600 mg 1 x 200 mg capsule in the morning and 2 x 200 mg capsules in the evening) in patients with mild-to-severe renal impairment (CL_{CR}=15 - 89 mL/min as estimated by Cockcroft-Gault) to match exposure to that in patients with normal renal function.

The effect of renal impairment on the exposure of pexidartinib and ZAAD-1006a was evaluated in a single-dose, parallel-group study in 40 healthy volunteers (Study PL3397-A-U124). Volunteers were categorized into the following renal groups based on their creatinine clearance (CL_{CR}) values (as estimated using the Cockcroft-Gault formula):

- **Group 1:** Normal renal function: CL_{CR} ≥90 mL/min (n=8)
- **Group 2:** Mild renal impairment: CL_{CR}=60 - 89 mL/min (n=8)
- **Group 3:** Moderate renal impairment: CL_{CR}=30 - 59 mL/min (n=8)
- **Group 4:** Severe renal impairment: CL_{CR}=15-29 mL/min (n=8)
- **Group 5:** ESRD (CL_{CR} ≤15 mL/min): Subjects requiring hemodialysis (8 subjects were randomized to receive pexidartinib in two sequences either followed by the 4-hour hemodialysis session [On dialysis, sequence A] OR approximately 12-24 hours between hemodialysis sessions [off dialysis, sequence B]). Following administration of pexidartinib, the next hemodialysis session did not occur until the 48 hours.

There were 26 males and 14 females in the study with a mean (SD) age of 61.8 (11.34) years. Most subjects were Not Hispanic or Latino (21 [52.5%]) and either White (30 [75%]) or Black or African American (10 [25%]). Refer to the Applicant's table below.

Table 33. Demographic Characteristics by Renal Impairment Group

Demographic/Baseline Characteristics[a]	Group 1 (N=8)	Group 2 (N=8)	Group 3 (N=8)	Group 4 (N=8)	Group 5 (N=8)	Group 5 AB (N=4)	Group 5 BA (N=4)	Total (N=40)
Age at Informed Consent (y)[b]								
Mean (SD)	51.0 (8.83)	70.8 (5.85)	70.9 (7.38)	64.8 (7.67)	51.5 (6.37)	52.8 (5.32)	50.3 (7.89)	61.8 (11.34)
Minimum	33	59	57	51	45	47	45	33
Maximum	62	77	79	73	62	59	62	79
Sex								
Male	5 (62.5)	3 (37.5)	5 (62.5)	5 (62.5)	8 (100)	4 (100)	4 (100)	26 (65.0)
Female	3 (37.5)	5 (62.5)	3 (37.5)	3 (37.5)	0	0	0	14 (35.0)
Weight (kg)								
Mean (SD)	80.35 (11.497)	75.69 (14.063)	81.38 (16.311)	78.44 (13.207)	80.56 (13.769)	83.03 (16.796)	78.10 (12.003)	79.28 (13.288)

All volunteers received a single 200 mg oral dose of pexidartinib after an overnight fast of 10 hours. A summary of PK parameters for both pexidartinib and ZAAD-1006a by renal group is presented in Table 34 and Table 35, respectively. Results of the statistical analysis of group comparisons is presented for pexidartinib in Table 36.

Table 34. Geometric Mean (%CV) PK Parameters for Pexidartinib by Renal Group

Parameter	Normal	Mild	Moderate	Severe	ESRD (On Dialysis)	ESRD (Off Dialysis)
N	8	8	8	7*	8	
CL_{CR} (mL/min)+	150 (90-218)	67 (60-80)	48 (30-53)	21 (10-28)	13 (12-15) 12 (11-13)	
C_{max} (ng/mL)	1743 (48%)	2589 (25%)	1932 (62%)	2136 (29%)	1812 (47%)	1703 (42%)
T_{max} (h)+	1.5 (1.0-3.0)	1.75 (1.0-2.5)	1.75 (1.5-2.5)	2.5 (1.0-4.5)	2.2 (1.5-6.5)	2.2 (1.0-5.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	34599 (44%)	55287 (40%)	44497 (38%)	44383 (60%)	29969 (37%)	37211 (41%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	35455 (45%)	58447 (44%)	46318 (39%)	46814 (54%)	30668 (37%)	37406 (42%)
$T_{1/2}$ (h)++	29.6±6.8	36.3±10.5	36.4±7.3	36.5±13	26.6±8.2	26.1±8.1
CL/F (L/h)	5.9 (45%)	3.2 (44%)	4.5 (39%)	4.3 (54%)	6.5 (37%)	6.5 (42%)
V_z/F (L)	246 (24%)	165 (29%)	234 (40%)	211 (24%)	243 (32%)	238 (33%)

+ Median (range) ++ Arithmetic mean
* Missed $AUC_{0\text{-inf}}$ value for Subject (b) (6) CL_{CR}=11.1 mL/min, 63-y-old Black or African American female
Source: Reviewer generated table – PK data from Study PL3397-A-U124

Table 35. Statistical Summary of Pexidartinib by Renal Group

Parameter	Normal	Mild	Moderate	Severe	ESRD (On Dialysis)	ESRD (Off Dialysis)
C_{max} (ng/mL)	1743	2589	1932	2136	1812	1703
Ratio (%)*		148	111	122	106	98
(90% CI)		(111, 199)	(83, 148)	(92, 164)	(80, 141)	(73, 130)
$AUC_{0\text{-}inf}$ (ng·h/mL)	35455	58447	46318	46814	30668	37406
Ratio (%)*		165	131	132	91	105
(90% CI)		(118, 231)	(94, 182)	(102, 203)	(69, 119)	(75, 149)

* Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U124

Table 36. Geometric Mean (%CV) PK Parameters for ZAAD-1006a by Renal Group

Parameter	Normal	Mild	Moderate	Severe	ESRD (On Dialysis)	ESRD (Off Dialysis)
N	8	8	8	8	8	
CL_{CR} (mL/min)+	149 (90-218)	67 (60-80)	48 (30-53)	21 (10-28)	13 (12-15)	
C_{max} (ng/mL)	1330 (35%)	2700 (33%)	2070 (52%)	2630 (34%)	2600 (33%)	2610 (31%)
T_{max} (h)+	2.5 (2.5-5.0)	2.75 (2.5-5.0)	3.75 (2.0-24)	3.75 (2.0-24)	6.25 (4.5-24)	9 (3.5-24)
$AUC_{0\text{-}last}$ (ng·h/mL)	42600 (43%)	84600 (40%)	99400 (34%)	117000 (91%)	112000 (64%)	109000 (91%)
$AUC_{0\text{-}inf}$ (ng·h/mL)	43600 (43%)	88300 (44%)	105000 (35%)	106000 (82%)	115000 (67%)	112000 (95%)
$T_{1/2}$ (h)++	27.3±6.1	34.0±9.05	36.4±7.3	37.6±7.5	35.0±13.2	26.9±8.2
M/P Ratio (%)++	93±18	108±39	182±86	175±60	283±114	296±170

+ Median (range) ++ Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U124

The results showed that subjects with mild (CL_{CR}=60-89 mL/min), moderate (CL_{CR}=30-59 mL/min) and severe (CRCL ≤29 mL/min) renal impairment had 65%, 30% and 32% higher geometric mean $AUC_{0\text{-}inf}$ for pexidartinib, respectively, than subjects with normal renal function (CL_{CR} ≥90 mL/min) following a single 200 mg oral dose of pexidartinib. Geometric mean C_{max} of pexidartinib was 48%, 10% and 22% higher in subjects with mild, moderate and severe renal impairment respectively, than subjects with normal renal function. Subjects with end stage renal disease (ESRD) had comparable pexidartinib exposure to that subjects with normal renal function (both on and off dialysis). Plasma protein binding of pexidartinib was more than 99% (mean %PB=99.96%) irrespective of renal function at time points of 2.5, 6.5 and 24 hours post dosing. The Applicant has not determined the dialyzability of pexidartinib through the dialysis membrane. Because pexidartinib is highly protein bound primary bound to albumin and a1-acid glycoprotein, has a large volume of distribution and is highly lipid-soluble, it can be predicted that only a small fraction of the drug is accessible for dialysis and its dialysis clearance is small. There were no obvious relationships between each of C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib; the relationships were not statistically significant (p>0.05).

Following a single 200 mg oral dose of pexidartinib, the geometric mean $AUC_{0\text{-}inf}$ of ZAAD-1006a increased by 102%, 141% and 143% in subjects with mild, moderate and severe renal impairment, respectively than subjects with normal renal function. Geometric mean C_{max} of ZAAD-1006a was 103%, 56% and 98% higher in subjects with mild, moderate and severe renal

impairment respectively, than subjects with normal renal function. Subjects with ESRD had a 164% and 157% higher mean $AUC_{0\text{-}inf}$, on and off dialysis, respectively, than subjects with normal renal function. Geometric mean C_{max} was 95% higher in ESRD subjects on and off dialysis, respectively. The mean M/P molar ratio (corrected for molecular weight) was similar between the subjects with mild renal impairment (M/P=108%) and normal subjects (M/P=93%). The mean M/P molar ratio was 95% and 88% higher in subjects with moderate and severe renal impairment, respectively, than in subjects with normal renal function. The mean M/P was 3-fold higher in ESRD subjects on dialysis and off dialysis than in normal subjects. Both C_{max} and $AUC_{0\text{-}inf}$ of ZAAD-1006a tended to decrease as CL_{CR} values increased and the relationships were statistically significant ($p<0.05$). ZAAD-1006a is primarily eliminated in urine (10.3% of dose). The increased exposure of ZAAD-1006a is not expected to have any clinical relevance to safety (based on preclinical toxicology data from a monkey study) or efficacy.

PopPK analysis was performed on the PK data from patients with TGCT and solid tumors (see table below).

Table 37. Creatinine Clearance by Renal Impairment Category

RI Group	CLCR (mL/min)	N
Normal	≥90	299
Mild RI	60-89	67

Based on a popPK analysis of clinical data, patients with mild (n=67, CL_{CR}=89 to 60 mL/min) had approximately 30% higher exposure than patients with normal renal function (n=299).

The review team recommends that the total daily dose of TURALIO be reduced to 600 mg (1 x 200 mg capsule in the morning and 2 x 200 mg capsules in the evening) in patients with mild to severe RI (CL_{CR}=15 to 89 mL/min). The 20% dose reduction (600 mg/day) is supported by the observed increased risk of liver enzyme elevations with increased exposure observed at the 1000 mg/day pexidartinib dosage.

(b) (4)

6.3.2.3.3. Effect of UGT1A4 genetic polymorphisms on pexidartinib PK

*The clinical relevance of approximately 10-20% higher pexidartinib exposure observed in UGT1A4*2 and UGT1A4*3 variant allele carriers is unclear and no dosage adjustment of pexidartinib is being recommended in patients with UGT1A4*2 or UGT1A4*3 genetic polymorphisms at this time.*

Elevations of liver transaminases and bilirubin with cases of drug induced cholestasis have been observed in pexidartinib studies. The major pexidartinib metabolite ZAAD-1006a, which has approximately 10% higher exposure than pexidartinib, is produced via N-glucuronidation of pexidartinib primarily by UGT1A4. The *UGT1A4*2* (rs6755571; allele frequency ~0-9%) and *UGT1A4*3* (rs2011425; allele frequency ~4-20%) polymorphisms are thought to have substrate-specific effects on UGT1A4 glucuronidation activity (PMIDs: 4871856, 15057901, 25492569,

22367373). The Applicant hypothesized that if liver enzyme elevations and cholestasis were related to pexidartinib or ZAAD-1006a exposure, and if *UGT1A4* genotype affects exposure, then *UGT1A4* genotype could help identify patients at increased risk of hepatotoxicity. As such, the Applicant explored the impact of *UGT1A4*2* and *UGT1A4*3* polymorphisms on pexidartinib and ZAAD-1006a PK (Study Report PL3397 PGx).

Data from 11 PK studies in healthy volunteers were pooled for the exploratory pharmaco-genomic analysis. These studies used equivalent dosage forms of pexidartinib, and had DNA collected. Participants signed an Informed Consent Form agreeing to the pharmacogenomic analysis. The C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ of pexidartinib and ZAAD-1006a were compared between genotypes of *UGT1A4 *2* (A Carriers [C/A and A/A] versus C/C ("wild-type")) and of *UGT1A4 *3* (G Carriers [T/G and G/G] versus T/T ("wild-type")) using the analysis of variance (ANOVA). Analyses were conducted for PK parameters obtained following a single 600 mg or 1800 mg dose of pexidartinib and using dose-normalized PK parameters after administration of any scheduled dose of pexidartinib.

Based on the Applicant results, the dose-normalized AUC_{inf} of pexidartinib was 19% higher in *UGT1A4*2* variant allele carriers (n=18) compared to subjects homozygous for the wild-type allele (n=214) (175 ng*hr/mL vs 147 ng*hr/mL; 90% CI for ratio 103.36, 137.68). Similarly, $AUC_{0\text{-inf}}$ of pexidartinib was 11% higher in *UGT1A4*3* variant allele carriers (n=52) compared to subjects homozygous for the wild-type allele (n=180) (161 ng*hr/mL vs 145 ng*hr/mL; 90% CI for ratio 101.47 122.17). Pexidartinib C_{max} was similar across genotypes.

The dose-normalized $AUC_{0\text{-inf}}$ of ZAAD-1006a was 56% higher in *UGT1A4*2* variant allele carriers (n=15) compared to subjects homozygous for the wild-type allele (n=152) (296 ng*hr/mL *vs* 190 ng*hr/mL; 90% CI for ratio 127.65, 191.65). Similarly, ZAAD-1006a C_{max} was 37% higher in *UGT1A4*2* variant allele carriers (n=17) compared to subjects homozygous for the wild-type allele (n=184) (10 ng/mL *vs* 7 ng/mL, 90% CI for ratio 112.18, 166.56). In contrast, $AUC_{0\text{-inf}}$ and C_{max} of ZAAD-1006a were similar across *UGT1A4*3* genotypes (G Carriers (T/G and GG) vs TT)). Results for subjects administered a single 600 mg dose were consistent with the dose-normalized results; insufficient data were available to make statistical comparisons for the 1800 mg dose.

6.3.2.3.4. Effect of Other Factors on Pexidartinib PK

The popPK analysis of PK data from 375 patients indicates that there are no clinically meaningful differences in pexidartinib exposure based on age (median=44 [18-84] years), sex (231 males/ 144 females), race (269 Whites, 84 Blacks and 22 Others) and body weight (median=79 [32, 154] kg). No dosage adjustment is recommended based on age, sex, race or bogy weight. For more details, refer to the Pharmacometrics' Review (Appendix 19).

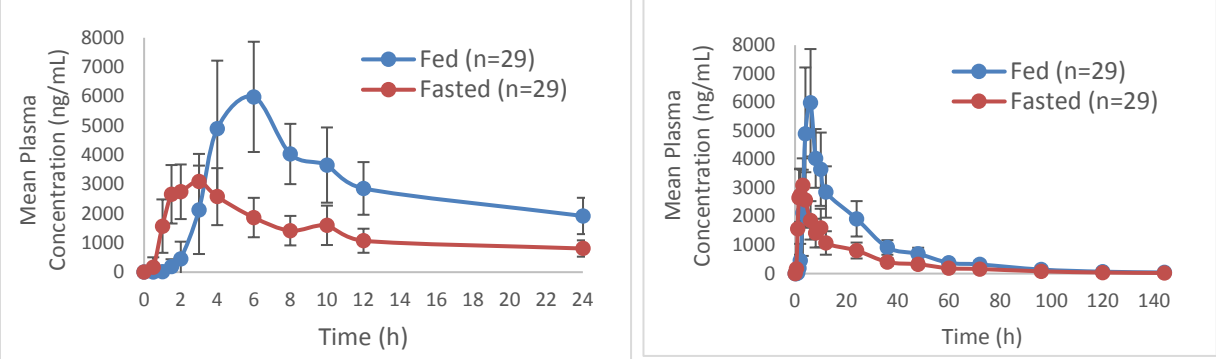
6.3.2.4. Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

6.3.2.4.1. Effect of Food

- *Pexidartinib is recommended to be taken on an empty stomach (at least 1 hour before or 2 hours after a meal or snack).*
- *Non-compliance with fasting condition within the BID dosing regimen is a safety concern, given the potential 2-fold increase in exposure with food and exposure-response relationships with key adverse events. A PMR will be issued to assess the effect of low-fat (400 - 500 Kcal) meal on pexidartinib exposure in order to further optimize administration or dosage with regard to food intake.*

The effect of food on pexidartinib exposure was evaluated in a single-dose, randomized, crossover study in 29 healthy volunteers (Study PL3397-A-U114) using the clinical Formulation J-3397-AF (b) (4) which is equivalent to the commercial formulation (Formulation J-3397-AF (b) (4)). Subjects were randomized to receive a single 400 mg dose of pexidartinib either after an overnight fast or after the standard FDA high-fat, high-calorie meal (800-1000 Kcal) with a 10-day washout period between each treatment. Figure 6 shows the arithmetic mean (SD) plasma pexidartinib concentration versus time profiles under the fed and fasted conditions over the first 24 hours after dosing and over the entire sampling period. A summary of the PK parameters of pexidartinib in the fed and fasted states is presented in Table 38. The statistical analysis for the food effect on PK parameters of pexidartinib is presented in Table 39.

Figure 6. Mean Plasma Concentration-Time Profiles With or Without Food



Source: Reviewer generated table – plasma-concentration-time data from Study PL3397-A-U114

Table 38. Geometric Mean (%CV) PK Parameters for Pexidartinib With or Without Food

Parameter	Fed (n=29)	Fasted (n=29)
C_{max} (ng/mL)	6318 (31%)	3175 (35%)
T_{max} (h)[+]	5.0 (4.0-10)	2.5 (1.5-5.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	106653 (22%)	50324 (35%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	107882 (22.5%)	51132 (32%)
$T_{1/2}$ (h)[++]	21.7±3.5	23.0±3.7

[+] Median (range) [++] Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U114

Table 39. Summary of Statistical Analysis for Food Effect

Parameter	Fed (n=29)	Fasted (n=29)	Ratio (%)* (Fed/Fasted)	90% CI
C_{max} (ng/mL)	6318	3175	198	(176, 222)
$AUC_{0\text{-}inf}$ (ng·h/mL)	107882	51132	210	(192, 232)

* Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U114

Following a single 400 mg oral dose of pexidartinib in healthy volunteers, a high-fat meal increased geometric mean C_{max} and $AUC_{0\text{-}inf}$ by 98% and 110%, respectively, and prolonged its T_{max} by 2.5 hours compared to the fasted state. Pexidartinib is recommended to be taken on an empty stomach (at least 1 hour before or 2 hours after a meal or snack).

6.3.2.4.2. Effect of Gastric Acid Reducing Agents

- *Avoid the concomitant use of PPIs while taking pexidartinib.*
- *The effect of H2-receptor antagonists on pexidartinib exposure has not been studied. Administer pexidartinib at least 2 hours before and 10 hours after taking an H2-receptor antagonist.*
- *The effect of antacids on pexidartinib exposure has not been studied. Administer pexidartinib 2 hours before or after taking an antacid.*

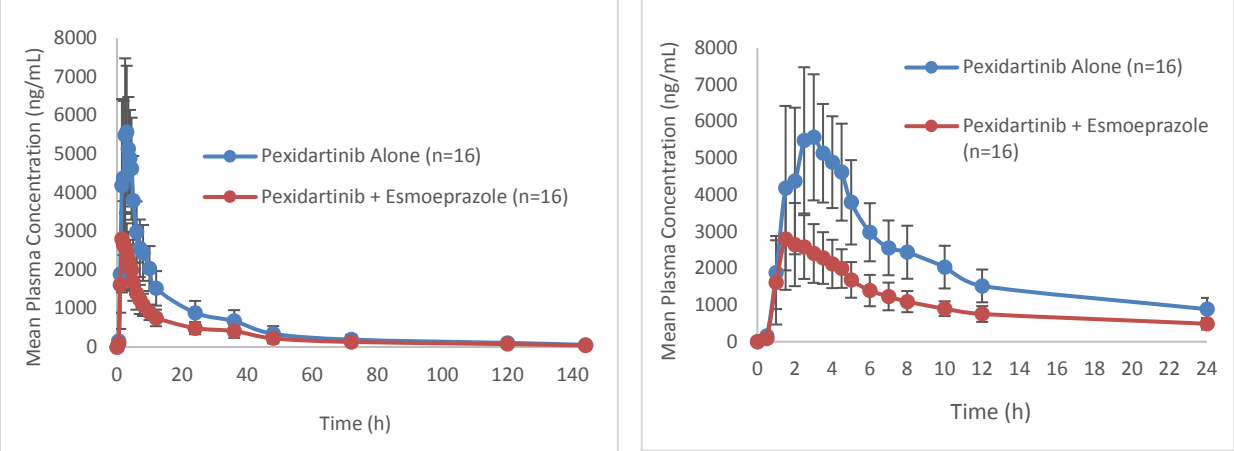
Proton Pump Inhibitors (PPIs)

The effect of esomeprazole, a PPI, on the exposure of both pexidartinib and ZAAD-1006a was evaluated in a randomized, 2-period, 2-sequence crossover study in 16 healthy subjects (Study PL3397-A-U120) using the commercial formulation (Formulation J-3397-AF (b) (4)). Subjects were randomized (1:1) to receive either of the following treatment arms with a 10-day washout period between treatments:

- Treatment A: A single 600 mg oral dose of pexidartinib following an overnight fast of 8 hours. Subjects continued to fast for at least 4 hours after pexidartinib administration.
- Treatment B: Esomeprazole 40 mg administered once daily for 4 days following overnight fast of 8 hours. On Day 5, 40 mg esomeprazole was administered in the morning 2 hours prior to a single 600 mg dose of pexidartinib. Volunteers continued to fast for at least 4 hours after pexidartinib administration.

Figure 7 shows the arithmetic mean (SD) plasma concentration versus time profiles for each of pexidartinib alone and in the presence of esomeprazole over the first 24 hours after dosing and over the entire sampling period. A summary of the PK parameters for each of pexidartinib and ZAAD-1006a alone and in presence of esomeprazole is presented in Table 40. The statistical analysis for the effect of esomeprazole on the PK parameters of each of pexidartinib and ZAAD-1006a is presented in Table 41.

Figure 7. Mean Plasma Concentration-Time Profiles With or Without Esomeprazole



Source: Reviewer generated table – plasma concentration-time data from Study PL3397-A-U120

Table 40. Geometric Mean (%CV) PK Parameters With or Without Esomeprazole

	Pexidartinib + Esomeprazole (n=16)		Pexidartinib Alone (n=16)	
Parameter	**Pexidartinib**	**ZAAD-1006a**	**Pexidartinib**	**ZAAD-1006a**
C_{max} (ng/mL)	2917 (40%)	2472 (33%)	6431 (32%)	5289 (28%)
T_{max} (h)[+]	2.0 (1.5-5)	4.25 (2.0-4.5)	3.0 (1.5-4.5)	4.25 (3.0-5.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	53589 (32%)	65409 (36%)	101998 (25%)	127291 (28%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	55378 (33%)	67646 (37%)	104389 (25%)	130366 (28%)
$T_{1/2}$ (h)[++]	26.7±8.9	26.6±7.6	25.3±7.1	25.3±6.9
M/P Ratio (%)[++]	87±14.6		87±11.6	

[+] Median (range) [++] Arithmetic mean

Source: Reviewer generated table – PK data from Study PL3397-A-U120

Table 41. Summary of Statistical Analysis for Esomeprazole Effect

Parameter	**Pexidartinib + Esomeprazole (Test) (n=16)**	**Pexidartinib Alone (Reference) (n=16)**	**Ratio (%)[*] (Test/Reference)**	**90% CI**
Pexidartinib				
C_{max} (ng/mL)	2917	6431	45	(37, 56)
$AUC_{0\text{-inf}}$ (ng·h/mL)	55378	104389	53	(47, 59)
ZAAD-1006a				
C_{max} (ng/mL)	2472	5289	47	(39, 55)
$AUC_{0\text{-inf}}$ (ng·h/mL)	67646	130366	52	(46, 58)

[*] Ratio of adjusted geometric means (test/reference)

Source: Reviewer generated table – PK data from Study PL3397-A-U120

Following a single 600 mg dose of pexidartinib in healthy subjects, the geometric mean C_{max} and $AUC_{0\text{-inf}}$ of pexidartinib decreased by 45% and 53%, respectively, when administered with esomeprazole, a PPI. The corresponding values for ZAAD-1006a are 47% and 52%, respectively. These results are consistent with decreased solubility of pexidartinib, leading to decreased bioavailability, with an increase in pH. Decreased exposure when administered with a PPI may lead to a reduced efficacy; therefore, it is recommended to avoid the concomitant use of PPIs with pexidartinib.

6.3.2.4.3. DDI Potential

Effect of Other Drugs on Pexidartinib:

- *Avoid concomitant use of TURALIO with strong CYP3A inhibitors. If concomitant use with a strong CYP3A inhibitor cannot be avoided, reduce the starting dose of TURALIO from 400 mg (2 x 200 mg capsules) orally twice daily to 200 mg (1 x 200 mg capsule) orally twice daily. In patients who have had a dose reduction to a total daily dose of 600 mg (3 x 200 mg capsules) or 400 mg (2 x 200 mg capsules) due to adverse reactions and who initiate a strong CYP3A4 inhibitor, reduce the total daily TURALIO dose by 200 mg (1 x 200 mg capsule). If concomitant use of a strong CYP3A inhibitor is discontinued, increase the TURALIO dose (after 3 plasma half-lives of the strong CYP3A inhibitor) to the dose that was used before starting the strong inhibitor. Avoid the concomitant use of strong CYP3A4 inducers with TURALIO, including St John's Wort.*
- *Avoid concomitant use of TURALIO with UGT inhibitors. If concomitant use with a UGT inhibitor cannot be avoided, reduce the starting dose of TURALIO from 400 mg (2 x 200 mg capsules) orally twice daily to 200 mg (1 x 200 mg capsule) orally twice daily. In patients who have had a dose reduction to a total daily dose of 600 mg (3 x 200 mg capsules) or 400 mg (2 x 200 mg capsules) due to adverse reactions and who initiate a UGT inhibitor, reduce the total daily TURALIO dose by 200 mg (1 x 200 mg capsule). If concomitant use of a UGT inhibitor is discontinued, increase the TURALIO dose (after 3 plasma half-lives of the UGT inhibitor) to the dose that was used before starting the UGT inhibitor.*

Effect of Strong CYP3A4 Inhibitors

Pexidartinib is metabolized by CYP3A4. The effect of itraconazole, a strong CYP3A4 inhibitor, on the exposure of each pexidartinib and ZAAD-1006a was evaluated in a 2-period, single-sequence study in 16 healthy volunteers (Study PL3397-A-U118). Volunteers received the following treatment arms with a 10-day washout period between treatments:

- Treatment A: A single 600 mg oral dose of pexidartinib on Day 1 of Period 1.
- Treatment B: Loading 200 mg dose of itraconazole administered twice on Day 1 of Period 2 followed by 200 mg once daily on Days 2 to 18, except on Day 6. On the morning of Day 6 of Period 2, a single 600 mg dose of pexidartinib was coadministered with 200 mg itraconazole.

Pexidartinib was administered following an overnight fast of at least 10 hours. A summary of the PK parameters for each of pexidartinib and ZAAD-1006a alone (n-=16) and in presence of itraconazole (n=13) is presented in Table 42. The statistical analysis for the effect of itraconazole on the PK parameters of each of pexidartinib and ZAAD-1006a is presented in Table 43 for 13 volunteers per each treatment arm. All 16 were included in the PK analysis set in Period 1 (pexidartinib alone) and 14 were included in the PK analysis set in Period 2 (pexidartinib and itraconazole). Although n=14 in the PK analysis set for Treatment B, 1 subject discontinued during Period 2 after receiving combination dosing. PK data from this subject were excluded from the analysis.

Table 42. Geometric Mean (%CV) PK Parameters With or Without Itraconazole

	Pexidartinib + Itraconazole (n=13)		Pexidartinib Alone (n=16)	
Parameter	**Pexidartinib**	**ZAAD-1006a**	**Pexidartinib**	**ZAAD-1006a**
C_{max} (ng/mL)	6308 (35%)	5858 (25%)	4137 (20%)	3818 (22%)
T_{max} (h)[+]	2.0 (1.5-4.5)	4.5 (2.5-8.0)	2.5 (1.5-4.5)	4.5 (2.0-5.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	134790 (27%)	237941 (36%)	72896 (25%)	111501 (26%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	135354 (27%)	238561 (37%)	74115 (25%)	113646 (27%)
$T_{1/2}$ (h)[++]	28.8±4.2	30.0±4.1	24.2±3.7	24.4±4.3
M/P Ratio (%)[++]	179±35.7		156±29.4	

[+] Median (range) [++] Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U118

Table 43. Summary of Statistical Analysis for Itraconazole Effect

Parameter	**Pexidartinib + Itraconazole (Test) (n=13)**	**Pexidartinib Alone (Reference) (n=13)**	**Ratio (%)[*] (Test/Reference)**	**90% CI**
Pexidartinib				
C_{max} (ng/mL)	6308	4255	148	(128, 172)
$AUC_{0\text{-inf}}$ (ng·h/mL)	135354	78240	173	(160, 186)
ZAAD-1006a				
C_{max} (ng/mL)	5858	3892	150	(129, 175)
$AUC_{0\text{-inf}}$ (ng·h/mL)	238561	121049	197	(179, 216)

[*] Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U118

Coadministration of itraconazole increased the geometric mean C_{max} and $AUC_{0\text{-inf}}$ of pexidartinib by 48% and 73%, respectively, compared to pexidartinib alone. The corresponding values for ZAAD-1006a are 50% and 97%, respectively. The mean M/P molar ratio only increased by 15% with itraconazole administration compared to pexidartinib alone. It is recommended that pexidartinib dose is reduced to 200 mg BID (400 mg/day) when it is coadministered with a strong CYP3A4 inhibitor.

Effect of Strong CYP3A4 Inducers

Pexidartinib is metabolized by CYP3A4. The effect of rifampin, a strong CYP3A4, on the exposure of each pexidartinib and ZAAD-1006a was evaluated in a 2-period, single-sequence study in 16 healthy volunteers (Study PL3397-A-U119). Volunteers received the following treatment arms with a 10-day washout period between treatments:

- Treatment A: A single 600 mg oral dose of pexidartinib on Day 1 of Period 1.
- Treatment B: Rifampin 600 mg orally once daily on Days 1 to 9 and Days 11 to 15 of Period 2. On Day 10 of Period 2, a single 600 mg oral dose of pexidartinib was coadministered with 600 mg rifampin.

Pexidartinib was administered following an overnight fast of at least 10 hours. A summary of the PK parameters for each of pexidartinib and ZAAD-1006a alone and in presence of rifampin is presented in Table 44. The statistical analysis for the effect of rifampin on the PK parameters of each of pexidartinib and ZAAD-1006a is presented in Table 45.

Table 44. Geometric Mean (%CV) PK Parameters With or Without Rifampin

	Pexidartinib + Rifampin (n=16)		Pexidartinib Alone (n=16)	
Parameter	**Pexidartinib**	**ZAAD-1006a**	**Pexidartinib**	**ZAAD-1006a**
C_{max} (ng/mL)	3304 (40%)	5942 (52%)	4924 (39%)	4384 (45%)
T_{max} (h)[+]	3.0 (1.5-4.5)	4.5 (3.0-8.0)	2.5 (1.5-4.0)	4.5 (2.5-4.5)
$AUC_{0\text{-last}}$ (ng·h/mL)	32862 (39%)	67082(36%)	91619 (36%)	118957 (41%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	33361 (39%)	67655 (52%)	91863 (36%)	122014 (41%)
$T_{1/2}$ (h)[++]	16.8±4.2	16.1±4.5	24.4±4.9	25.9±5.7
M/P Ratio (%)[++]	212±67.6		136±38.6	

[+] Median (range) [++] Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U119

Table 45. Summary of Statistical Analysis for Rifampin Effect

Parameter	**Pexidartinib + Rifampin (Test)**	**Pexidartinib Alone (Reference)**	**Ratio (%)[*] (Test/Reference)**	**90% CI**
Pexidartinib				
C_{max} (ng/mL)	3304	4924	67	(53, 85)
$AUC_{0\text{-inf}}$ (ng·h/mL)	33361	91863	37	(30, 45)
ZAAD-1006a				
C_{max} (ng/mL)	5942	4384	135	(108, 169)
$AUC_{0\text{-inf}}$ (ng·h/mL)	67655	122014	55	(46, 66)

[*] Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U119

Coadministration of rifampin decreased the geometric mean C_{max} and $AUC_{0\text{-inf}}$ of pexidartinib by 33% and 63%, respectively, compared to pexidartinib alone. Rifampin decreased the geometric mean $AUC_{0\text{-inf}}$ of ZAAD-1006a by 45% but increased its C_{max} by 35%, compared to pexidartinib alone. The mean M/P molar ratio increased by 55% with rifampin administration compared to pexidartinib alone. It is recommended that the concomitant use of strong CYP3A4 inducers with pexidartinib is to be avoided.

Effect of UGT Inhibitors

Pexidartinib is also metabolized by UGT1A4. The effect of probenecid, a known UGT inhibitor, on the exposure of each pexidartinib and ZAAD-1006a was evaluated in a randomized, 2-sequence, 2-period crossover study in 16 healthy volunteers (Study PL3397-A-U122). Volunteers were randomized (1:1) to receive either of the following treatment arms with a 17-day washout period between doses of pexidartinib as follows:

- Treatment A: A single 600 mg oral dose of pexidartinib on Day 2. Subjects fasted for at least 10 hours before pexidartinib dosing and continued to fast for at least 4 hours after pexidartinib administration.
- Treatment B: Probenecid (500 mg) administered 4 times daily (2000 mg/day) on Days 1 to 14. On Day 2, probenecid was co-administered with pexidartinib in the morning. Subjects fasted for at least 10 hours before co-administration of probenecid and pexidartinib and continued to fast for at least 4 hours after administration of the combination.

Of the 16 subjects enrolled, 15 subjects completed the study and 1 subject in Treatment B (treatment sequence BA) discontinued from the study due to a TEAE during Period 1 on Day 14. A summary of the PK parameters for each of pexidartinib and ZAAD-1006a alone and in presence of probenecid is presented in Table 46. The statistical analysis for the effect of probenecid on the PK parameters of each of pexidartinib and ZAAD-1006a is presented in Table 47.

Table 46. Geometric Mean (%CV) PK Parameters With or Without Probenecid

	Pexidartinib + Probenecid (n=16)		Pexidartinib Alone (n=15)	
Parameter	**Pexidartinib**	**ZAAD-1006a**	**Pexidartinib**	**ZAAD-1006a**
C_{max} (ng/mL)	5321 (32%)	4138 (27%)	5077 (37%)	4162 (35%)
T_{max} (h)$^{+}$	2.5 (1.5-3.5)	6.9 (3.5-12)	2.5 (1.5-4.5)	4.5 (2.5-5.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	114368(27%)	203011 (22%)	72196 (39%)	89850 (44%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	114899 (27%)	203649 (22%)	72700 (39%)	90364 (44%)
$T_{1/2}$ (h)$^{++}$	28.15±5.5	28.6±4.9	24.9±7.9	25.1±7.3
M/P Ratio (%)$^{++}$	128±31		90±22	

$^{+}$ Median (range) $^{++}$ Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U122

Table 47. Summary of Statistical Analysis for Probenecid Effect

Parameter	**Pexidartinib + Probenecid (Test) (n=16)**	**Pexidartinib Alone (Reference) (n=15)**	**Ratio (%)* (Test/Reference)**	**90% CI**
Pexidartinib				
C_{max} (ng/mL)	5324	5077	105	(92, 121)
$AUC_{0\text{-inf}}$ (ng·h/mL)	114899	71701	160	(143, 178)
ZAAD-1006a				
C_{max} (ng/mL)	4138	4162	99	(87, 113)
$AUC_{0\text{-inf}}$ (ng·h/mL)	203649	90364	225	(199, 254)

* Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U122

Coadministration of probenecid increased the geometric mean $AUC_{0\text{-inf}}$ of pexidartinib by 60% with no effect on C_{max} (a small 5% increase) compared to pexidartinib alone. The geometric mean $AUC_{0\text{-inf}}$ of ZAAD-1006a increased by 125%, again with also no effect on C_{max}, when pexidartinib was administered with probenecid. The mean M/P molar ratio increased by 42% with probenecid administration compared to pexidartinib alone. It is recommended that pexidartinib dose is reduced to 200 mg BID (400 mg/day) when it is co-administered with strong UGT1A4 inhibitors.

Effect of Pexidartinib on Other Drugs:

Effect of Pexidartinib on the Exposure of Omeprazole and Digoxin

Pexidartinib is an inhibitor of P-gp and CYP2C19. The effect of pexidartinib on the exposure of each digoxin (a P-gp substrate) and omeprazole (a CYP2C19 substrate) was evaluated in a 4-period, single-sequence study in 20 healthy volunteers (Study PL3397-A-U127). All volunteers were randomized to receive the following treatment arms:

- Treatment A: Single 40 mg oral dose of omeprazole
- Treatment B: Single 0.25 mg oral dose of digoxin
- Treatment C: Single 1800 mg oral dose of pexidartinib + Single 40 mg oral dose of omeprazole
- Treatment D: Single 1800 mg oral dose of pexidartinib + Single 0.25 mg oral dose of digoxin

Dosing in Period 1 and Period 2 (Treatment A and Treatment B, respectively) was separated by 1 day; dosing in Period 2 and Period 3 (Treatment B and Treatment C, respectively) was separated by 4 days; and dosing in Period 3 and Period 4 (Treatment C and Treatment D, respectively) was separated by 8 days (to allow wash-out of pexidartinib). Pexidartinib, omeprazole, and digoxin were administered following an overnight fast of at least 10 hours. Subjects continued to fast for at least additional 4 hours after dosing.

A summary of the PK parameters for omeprazole and its metabolite (5-hysroxy omeprazole) with or without pexidartinib is presented in Table 48. The statistical analysis for the effect of pexidartinib is presented in Table 49 and Table 50 for omeprazole and 5-hysroxy omeprazole, respectively.

Table 48. Geometric Mean (%CV) PK Parameters With or Without Pexidartinib

	Omeprazole Alone (n=19)		Omeprazole + Pexidartinib (n=19)	
Parameter	**Omeprazole**	**5-Hydroxy Omeprazole**	**Omeprazole**	**5-Hydroxy Omeprazole**
C_{max} (ng/mL)	908 (57%)	422 (39%)	570 (68%)	271 (36%)
T_{max} (h)$^{+}$	2.25 (1.0-5.0)	2.25 (1.0-5.0)	3.0 (1.5-5.0)	3.0 (1.5-5.0)
$AUC_{0\text{-last}}$ (ng·h/mL)	1727 (76%)	1091 (23%)	1336 (85%)	833 (25%)
$AUC_{0\text{-inf}}$ (ng·h/mL)	1740 (76%)	1099 (23%)	1447 (72%)	846 (23%)
$T_{1/2}$ (h)$^{++}$	1.16±0.52	0.73±0.49	1.24±0.46	0.72±0.43
M/P Ratio (%)$^{++}$	73±49		72±43	

$^{+}$ Median (range) $^{++}$ Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U127

Table 49. Summary of Statistical Analysis for Pexidartinib Effect on Omeprazole

Parameter	**Omeprazole + Pexidartinib (Test)**	**Omeprazole Alone (Reference)**	**Ratio (%)* (Test/Reference)**	**90% CI**
C_{max} (ng/mL)	570	908	63	(53, 74)
$AUC_{0\text{-inf}}$ (ng·h/mL)	1447	1740	83	(73, 94)

* Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U127

Table 50. Summary of Statistical Analysis for Pexidartinib Effect on 5-Hydroxy Omeprazole

Parameter	Omeprazole + Pexidartinib (Test)	Omeprazole Alone (Reference)	Ratio (%)* (Test/Reference)	90% CI
C_{max} (ng/mL)	271	422	64	(58, 71)
$AUC_{0\text{-}inf}$ (ng·h/mL)	846	1099	77	(71, 83)

*Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U127

Omeprazole is metabolized by CYP2C19 to form the inactive metabolite, 5-hydroxy omeprazole. Co-administration of pexidartinib decreased geometric mean C_{max} and $AUC_{0\text{-}inf}$ of omeprazole by 37% and 17%, respectively, compared to omeprazole alone. Comparable decreases in geometric mean C_{max} and $AUC_{0\text{-}inf}$ were observed for 5-hydroxy omeprazole resulting in similar M/P ratio. The observed similar M/P ratio indicates that pexidartinib had no impact on the CYP2C19 pathway. If CYP2C19 were inhibited by pexidartinib an increase in parent omeprazole exposure and decrease in metabolite exposure would have been observed. This would have resulted in decreased M/P ratio. A summary of the PK parameters for digoxin alone and in presence of pexidartinib and the statistical analysis for the effect of pexidartinib are presented in Table 51 and Table 52, respectively.

Table 51. Geometric Mean (%CV) PK Parameters With or Without Pexidartinib

Parameter	Digoxin Alone (n=19)	Digoxin + Pexidartinib (n=19)
C_{max} (ng/mL)	1.17 (28%)	1.54 (42%)
T_{max} (h)+	1.0 (0.5-3.0)	1.0 (0.5-1.5)
$AUC_{0\text{-}last}$ (ng·h/mL)	16.3 (27%)	17.6 (28%)
$AUC_{0\text{-}inf}$ (ng·h/mL)	18.3 (31%)	20.4 (34%)
$T_{1/2}$ (h)++	40.3±2.9	40.3±4.9

+ Median (range) ++ Arithmetic mean
Source: Reviewer generated table – PK data from Study PL3397-A-U127

Table 52. Summary of Statistical Analysis for Pexidartinib Effect

Parameter	Digoxin + Pexidartinib (Test) (n=19)	Digoxin Alone (Reference) (n=19)	Ratio (%)* (Test/Reference)	90% CI
C_{max} (ng/mL)	1.54	1.17	132	(118, 146)
$AUC_{0\text{-}inf}$ (ng·h/mL)	20.4	18.6	109	(99, 120)

* Ratio of adjusted geometric means (test/reference)
Source: Reviewer generated table – PK data from Study PL3397-A-U127

Co-administration of pexidartinib increased the geometric mean C_{max} of digoxin by 32% with no effect on its $AUC_{0\text{-}inf}$ (only 9%) compared to digoxin alone. The increase in digoxin C_{max} is consistent with P-gp inhibitory effect of pexidartinib in the gut.

Effect of Pexidartinib on the Exposure of Other Substrates of CYP450 Enzymes and Transporters

The perpetrator risk of pexidartinib was evaluated using PBPK modeling and simulations for the following substrates of CYPs and transporters: CYP2B6, CYP2C8, BCRP, OATP1B1, OATP1B3, MATE1, and MATE2-K.

PBPK analyses predicted that an interaction between pexidartinib and a CYP2C8 substrate (such as rosiglitazone or repaglinide) is unlikely to be clinically significant. No dose adjustment is recommended when pexidartinib is co-administered with substrates of CYP2C8 enzymes.

The Applicant's PBPK analyses were inadequate to assess pexidartinib effects on the PK of bupropion (CYP2B6 substrate), metformin (MATE1/2-K substrate), and rosuvastatin (OATP1B1/3 substrate), due to the limitations identified in the substrate PBPK models. The reader is referred to Section 19.4.3 for further information about PBPK analyses.

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7. Sources of Clinical Data and Review Strategy

Table of Clinical Studies

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Randomized Trial of Efficacy and Safety						
PLX-108-10 (ENLIVEN)/ NCT02371369	Randomized, double-blind, placebo - controlled	Pexidartinib 1000 mg/day orally × 2 weeks; followed by 800 mg/day for 25 weeks Placebo 1000 mg/day orally × 2 weeks; followed by 800 mg/day for 25 weeks After 25 weeks patients may continue at current pexidartinib dose or cross over from placebo to pexidartinib 800 mg orally daily.	Primary: ORR per RECIST v 1.1 by BIRC at week 25 Secondary: 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 as assessed by a blinded third-party clinical assessor Proportion of responders based on centrally evaluated MRI scans and tumor volume score (TVS) at Week 25 as assessed by BICR Mean change from baseline score in the Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function Scale at Week 25 as reported by the patient Mean change from baseline score in the Worst Stiffness numeric rating scale (NRS) item at Week 25 as reported by the patient Proportion of responders based on Brief Pain Inventory (BPI) Worst Pain NRS item as reported by the patient and narcotic analgesic use (BPI-30) at Week 25	120 61 randomized to pexidartinib 59 randomized to placebo 30 placebo patients crossed over to pexidartinib	Symptomatic TGCT not amenable to surgery	12 Countries Australia Canada Germany Denmark Spain France Great Britain Hungry Italy Netherlands Poland United States

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Non-randomized Trial to Support Efficacy and Safety						
PLX-108-01/ NCT01004861	First-in-human, open-label, dose-escalation, dose-expansion	Phase 1: Pexidartinib 200 mg/day to 1200 mg/day orally Phase 2: 1000 mg/day orally	Phase 1 Primary: RP2D Phase 2 Primary: ORR per RECIST v 1.1 by investigator assessment Key Secondary: Pharmacodynamic activity of pexidartinib, further evaluation of safety	132 93 with solid tumors other than TGCT 39 with TGCT	Phase 1: Solid tumors Phase 2: 6 cohorts Mucoepidermal carcinoma of the salivary gland, TGCT GIST, anaplastic thyroid carcinoma, Solid tumors with pleural or peritoneal effusions, and other solid tumors	1 Country United States (13 sites)
Sponsor Initiated Trials to Support Safety						
PL3397-A-A103/ NCT02734433	Open-label, dose-escalation, dose expansion	Pexidartinib: 600 mg/day to 1000 mg/day orally	Primary: RP2D Secondary: PK profile, PD profile, ORR, DOR, and time to response	11 patients	Solid tumors	1 Country Japan
PLX108-03/ NCT01217229	Open-label, , activity estimating	Pexidartinib: 900 mg/day orally	Primary: ORR per revised response criteria for malignancy lymphoma (Cheson 2007) Secondary: PFS, DOR, B symptom assessment, adverse events	20 patients	Refractory Hodgkin's lymphoma	1 Country United States (6 sites)

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
PLX108-04/ NCT01349036	Open-label, activity estimating	Pexidartinib: 1000 mg/day orally	Primary: 6-month PFS Secondary: ORR, DOR, OS, and safety	38 patients	Glioblastoma multiforme	1 Country United States (6 sites)
PLX108-05/ NCT01349049	Open-label, dose-escalation, dose-expansion	Pexidartinib 800 to 5000 mg daily orally	Dose escalation: RP2D Dose expansion: preliminary efficacy	90 patients	Relapsed or Refractory Flt3-ITD-positive Acute Myeloid Leukemia	1 Country United States (8 sites)
PLX108-06/ NCT01499043	Pilot study, activity estimating trial	Pexidartinib 1000 mg/day orally	Primary: adverse events	6 patients	Advanced castration-resistant prostate cancer with bone metastasis and high circulating tumor cell counts	1 Country United States (2 Sites)
PLX108-07/ NCT01525602	Open-label, dose-escalation, dose-expansion	Pexidartinib: 600 mg/day to 1600 mg/day orally Paclitaxel 80 mg/m^2 weekly IV	Dose escalation Primary: RP2D Dose expansion Primary: Safety and tolerability Secondary: ORR, DOR, PFS	68 patients	Advanced solid tumors	1 Country United States (9 Sites)

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
PLX108-08/ NCT01790503	Open-label, dose-escalation, dose-expansion	Pexidartinib: 600 mg/day to 1000 mg/day orally Temozolomide: 75 mg/m^2 weekly daily orally for 6 weeks followed by 150 mg/m^2 daily days 1-5 of a 28-day cycle. Radiation	Dose escalation Primary: RP2D Dose expansion Primary: PFS Secondary: OS, PK, safety	65 patients	Glioblastoma multiforme	1 Country United States (9 Sites)
PLX108-09/ NCT01826448	Open-label, dose escalation, dose expansion	Pexidartinib: 800 mg/day to 1000 mg/day orally Vemurafenib 720 mg BID to 960 my BID	Dose escalation Primary: RP2D Dose expansion Primary: ORR Secondary: DOR, PFS, OS	13 patients	V600-mutated BRAF unresectable or metastatic melanoma	1 Country United States
PLX108-13/ NCT02975700	Open-label, dose escalation, dose-expansion	Pexidartinib 1000 mg/day orally	Dose escalation Primary: RP2D Dose expansion Primary: ORR Secondary: DOR, PFS, OS	6 patients	Unresectable or metastatic KIT-mutated melanoma	2 Countries China South Korea
PLX108-14/ NCT02452424	Open-label, dose escalation, dose-expansion	Pexidartinib 600 mg/day to 800 mg/day orally Pembrolizumab 200 mg every 3 weeks IV	Primary: RP2D Secondary: AE profile, ORR	78 patients	Advanced solid tumors	1 Country United States (13 sites)
PLX121-01/ NCT02401815	Open-label, dose escalation, dose expansion	Pexidartinib: 600 mg/day orally PLX9486: 500 mg daily orally	Primary: safety and tolerability Secondary: PK, ORR, OS < PFS, SOR	12 patients	Advanced solid tumors	1 Country United States (6 sites)

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
Investigator Initiated Trials to Support Safety						
IST3397-001/ NCT01596751	Open-label, dose escalation, dose expansion	Dose Escalation phase: Pexidartinib 400 mg/day to 1000 mg/day orally Eribulin 1.4 mg/m^2 IV day 1 and 8 of a 21-day cycle Dose Expansions phase: Pexidartinib 800 mg/day to 1000 mg/day orally Eribulin 1.4 mg/m^2 IV day 1 and 8 of a 21-day cycle	Dose Escalation phase: Primary: MTD Secondary: Safety profile Dose expansion phase: Primary: 12-week PFS Secondary: ORR, DOR, and safety	67 patients 28 in dose escalation 39 in dose expansions	Triple negative metastatic breast cancer	1 Country United States
IST3397-002/ NCT02071940	Open-label, single-arm, activity estimating	Pexidartinib 1000 mg/day orally	Primary: 6-month PFS Secondary: ORR, OS, and safety	9 patients	Advanced Kit mutated melanoma	1 Country Great Britain
IST3397-003/ NCT02472275	Open-label, dose-escalation, dose expansion	Pexidartinib 800 mg/day orally Androgen deprivation therapy	Primary: MTD and DLTs Secondary: Effect of radiation, androgen deprivation therapy and pexidartinib on tumor associated macrophages	4 patients	Prostate Cancer	1 Country United States

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
IST3397-005/ NCT02390752	Open-label, , dose-escalation, dose-expansion	Pexidartinib 400 mg/m^2 to 800 mg/m^2 orally daily	Dose escalation: RP2D in pediatric patients Dose expansion: ORR	4 patients	Dose escalation: children (≥3 and ≤21 years of age) with recurrent or refractory solid tumors or leukemia Dose expansion: Children (≥3 and ≤30 years of age). NF1 peripheral nerve sheath tumor	1 Country United States (1 site)
IST3397-006 (I-SPY-2)/ NCT01042379	Randomized, open-label	Pexidartinib 1200 mg/day orally Paclitaxel 80 mg/m^2 weekly IV	Determine whether adding investigational agents to standard neoadjuvant paclitaxel (with or without trastuzumab), and/or doxorubicin and cyclophosphamide, increases the probability of pathologic complete response (pCR) over standard neoadjuvant chemotherapy alone	9 patients	Breast cancer	1 Country United States
IST3397-010/ NCT02584647	Open-label, dose-escalation, dose expansion	Pexidartinib 600 mg/day to 1000 mg/day orally Sirolimus: 2 mg to 6 mg day orally	Escalation: Safety profile and MTD Expansions: PFS	19 patients	Advanced unresectable sarcoma	1 Country United States

Trial /NCT #	Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
IST3397-011/ NCT02777710	Open-label, dose-escalation, dose expansion	Pexidartinib 400 mg/day to 1000 mg/day orally Durvalumab: 1500 mg every 4 weeks IV	Escalation: Safety profile and MTD Expansions: Anti-tumor activity based on Gehan design	28 patients	Advanced pancreatic and colorectal cancer	1 Country France
IST3397-015/ NCT03158103	Open-label, dose-escalation	Pexidartinib 600 mg/day orally Binimetinib: 30 mg BID orally	Primary: RP2D Secondary: MTD	3 patients	Advanced or metastatic GIST	1 Country United States

7.1. Review Strategy

7.1.1. Review Strategy

The clinical and statistical review of efficacy for pexidartinib focused on the data submitted from the primary analysis of the 120 patients that were randomized in Part I of the ENLIVEN trial.

During the review, the following issues were identified:

- Difficulty in the clinical interpretation of a statistically significant improvement in the primary endpoint of overall response rate (ORR) and the corresponding duration of response (DOR) given the disease characteristics of TGCT.
- Estimation of treatment effect size of the key secondary endpoint of range of motion (ROM), given the substantial amount of missing assessments, the variety of joints effected, and the scarcity of evidence for what constitutes a meaningful within-patient improvement for this clinically assessed outcome
- Consideration of benefit for other clinically assessed or patient reported outcomes with over 40% of patients with missing assessments.

The primary clinical review of safety for pexidartinib in the TGCT population focused on the data submitted from Part 1 of the ENLIVEN trial, specifically, the first 25 weeks of treatment, in order to allow for a comparison between the patients randomized to pexidartinib and the patients randomized to placebo. In order to better understand the safety of pexidartinib in the indicated population, a review of adverse events, laboratory assessments, and patient narratives was completed for all patients with TGCT treated with pexidartinib across the development program, which includes patients from the placebo arm in Part 1 of ENLIVEN who crossed over to receive pexidartinib in Part 2 and patients from Study PLX108-01. Finally, this safety evaluation was supported by a safety database comprised of 738 pexidartinib-treated patients enrolled in commercial- sponsored and investigator- initiated trials for whom summary safety data were provided. Safety analyses included all patients who received at least one dose of study

To assess the reliability and quality of the data, the clinical reviewer conducted random cross validation of datasets with CRF forms for ENLIVEN and PLX108-01. Datasets, clinical study reports, case report forms, case narratives, Data Monitoring Committee reports, and all supportive analyses submitted by the applicant for KEYNOTE-048 were reviewed.

8. Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. PLX108-10 (ENLIVEN)

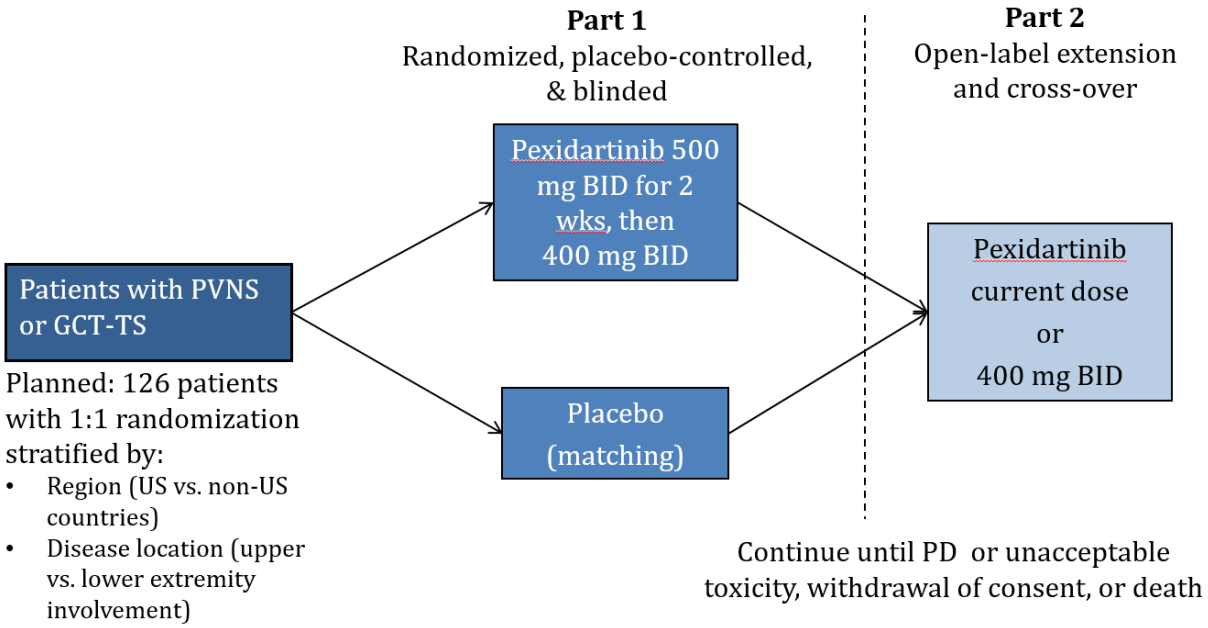
Trial Design

ENLIVEN was a randomized (1:1), 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.) and extremity involvement (upper extremity vs. lower extremity involvement). Eligible patients were randomly assigned to two treatment arms:

- Experimental: Pexidartinib 400 mg in the morning and 600 mg in the evening for 2 weeks; followed by 400 mg BID
- Control: Matching placebo BID

Figure 8 presents the study schema from ENLIVEN. Treatment continued for 24 weeks, until disease progression, unacceptable toxicity, or death. Patients who completed treatment in Part 1 were eligible to advance to Part 2, in which all patients were given the option to receive open-label pexidartinib in a long-term treatment phase for an extended period. The evaluation of efficacy for current application focuses on Part 1 of the study for efficacy and safety data.

Figure 8. ENLIVEN Study Schema



Eligibility Criteria

Inclusion criteria:

1. Age ≥18 years.
2. A 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).
3. Measurable disease as defined by RECIST 1.1 (except that a minimal size of 2 cm is required), assessed from MRI scans by a central radiologist.
4. Symptomatic disease because of active PVNS or GCT-TS, defined as one or more of the following:
    - a worst pain of at least 4 at any time during the week preceding the Screening Visit (based on scale of 0 to 10, with 10 representing “pain as bad as you can imagine”).
    - a worst stiffness of at least 4 at any time during the week preceding the Screening Visit (based on a scale of 0 to 10, with 10 representing “stiffness as bad as you can imagine”).
5. Stable prescription of analgesic regimen during the 2 weeks prior to randomization.
6. During the 2 weeks prior to randomization, at least 4 of 7 consecutive days of BPI Worst Pain NRS items and Worst Stiffness NRS items completed correctly.
7. Women of childbearing potential must have a negative serum pregnancy test within the 14-day period prior to randomization. (Where demanded by local regulations, this test may be required within 72 hours of randomization.)
8. Males and females of childbearing potential are permitted in the study so long as they consent to avoid getting their partner pregnant or becoming pregnant, respectively, by using a highly effective contraception method, as described below, throughout the study and for up to 90 days after completion. Highly effective methods of contraception include: intra-uterine device (nonhormonal or hormonal), bilateral tubal occlusion, vasectomy, sexual abstinence, or barrier methods (e.g., condom, diaphragm) used in combination with hormonal methods associated with inhibition of ovulation. Women of non-childbearing potential may be included if they are either surgically sterile or have been postmenopausal for ≥1 year. Women who have documentation of at least 12 months of spontaneous amenorrhea and have an FSH level >40 mIU/mL will be considered postmenopausal.
9. Adequate hematologic, hepatic and renal function defined by:
    - Absolute neutrophil count ≥1.5 × 10^9/L
    - Hemoglobin >10 g/dL
    - Platelet count ≥100 × 10^9/L
    - Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤1.5× ULN
    - Total bilirubin ≤1.5× ULN
    - Serum creatinine ≤1.5× ULN

10. Willingness and ability to complete the BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, and other self-assessment instruments throughout the study.
11. Willingness and ability to use an electronic diary.
12. Willingness and ability to provide written informed consent prior to any study related procedures and to comply with all study requirements.

Exclusion Criteria

Candidates with any of the following conditions or activities are ineligible for study enrollment:

1. Investigational drug use within 28 days of randomization.
2. Previous use of pexidartinib or any biologic treatment targeting CSF-1 or the CSF1R; previous use of oral tyrosine kinase inhibitors, e.g., imatinib or nilotinib, are allowed.
3. Active cancer (either concurrent or within the last year of starting study treatment) that requires therapy (e.g., surgical, chemotherapy, or radiation therapy), with the exception of adequately treated basal or squamous cell carcinoma of the skin, melanoma in-situ, carcinoma in-situ of the cervix or breast, or prostate carcinoma with a prostate-specific antigen value <0.2 ng/mL.
4. Known metastatic PVNS/GCT-TS.
5. Active or chronic infection with hepatitis C virus or hepatitis B virus or known active or chronic infection with human immunodeficiency virus.
6. Known active tuberculosis.
7. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection, or a medical or psychiatric history that, in the Investigator's opinion, would likely interfere with the person's study participation or the interpretation of his or her results.
8. Women who are breastfeeding.
9. A screening Fridericia corrected QT interval (QTcF) ≥450 ms (men) or ≥470 ms (women).
10. MRI contraindications.
11. History of hypersensitivity to any excipients in the investigational product.
12. Inability to swallow capsules.

Serious Adverse Event Definition

In ENLIVEN, adverse events were designated serious adverse events (SAEs) it they met one of the following criteria:

- Results in death
- Is life-threatening (i.e., the patient was at immediate risk of death from the adverse event as it occurred)
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in the child of a patient who was exposed to the study treatment?
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization, but when based on appropriate medical judgment, may

jeopardize the patient or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered serious adverse events.

SAEs, regardless of causality assessment, were collected for 28 days following study drug discontinuation and through the termination visit, whichever was longer. SAEs that were judged by the investigator to be related to study drug treatment were reported to the sponsor, regardless of the length of time that passed since study treatment completion.

Reviewer Comment: *This definition of SAE is in accordance with 21 CFR 312.32.*

Dose Modification and Management Guidelines

Reducing or interrupting the dose for toxicity could take place at time according to the following guidelines (Table 53 and Table 54):

Table 53. Dose Modification Guidelines for Treatment-Related Neutropenia

Toxicity Grade (CTCAE v4), Frequency	When to Hold or Stop	When and How to Restart Dosing
■ Hematologic - Grade 3 or 4 neutropenia		
1st appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L; growth factor support	If recovered to ANC $\geq 1 \times 10^9$/L in ≤ 7 days, resume at same dose. If not recovered to ANC $\geq 1 \times 10^9$/L in ≤ 7 days, reduce dose by 1 capsule.
2nd appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L; growth factor support	If recovered to ANC $\geq 1 \times 10^9$/L in ≤ 7 days, reduce dose by 1 capsule. If not recovered to ANC $\geq 1 \times 10^9$/L in ≤ 7 days, reduce dose by an additional capsule.
3rd appearance	Interrupt until ANC recovers to $\geq 1 \times 10^9$/L	If recovered to ANC $\geq 1 \times 10^9$/L in ≤ 7 days, reduce dose by 1 capsule. If not recovered to ANC $\geq 1 \times 10^9$/L in ≤ 7 days, discontinue permanently.
4th appearance	Discontinue permanently	n/a
■ Hematologic Grade 3 or 4 febrile neutropenia		
1st appearance	Interrupt until ANC and fever recover; provide growth factor support	Once resolved to ANC $\geq 1 \times 10^9$/L and T ≤ 38°C, reduce dose by 1 capsule.
2nd appearance	Interrupt until ANC and fever recover; provide growth factor support	Once resolved to ANC $\geq 1 \times 10^9$/L and T ≤ 38°C, reduce dose by an additional capsule.
3rd appearance	Discontinue permanently	n/a

ANC = absolute neutrophil count; CTCAE = Common Toxicity Criteria for Adverse Events; INR = international normalized ratio; n/a = not applicable; PLT = platelets; T = temperature

Table 54. Dose Modification Guidelines for Treatment-Related Thrombocytopenia and Non-Hematologic Toxicities

Toxicity Grade (CTCAE v4), Frequency	When to Hold or Stop	When and How to Restart Dosing
■ Hematologic - Grade 3 or 4 thrombocytopenia		
1st appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	Reintroduce at the same dose.
2nd appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	If PLT does not recover to $\geq 75 \times 10^9$/L in ≤ 7 days, reduce dose by 1 capsule.
3rd appearance	Interrupt until PLT $\geq 75 \times 10^9$/L	Reduce dose by an additional capsule.
4th appearance	Discontinue permanently	n/a
■ Non-hematologic Grade 3[a] (excluding liver function test increases [see below]): start symptomatic treatment when possible		
1st appearance	Interrupt until resolved (Grade 0-1)	If recovered in < 5 days, resume at same dose. Reduce by 1 capsule if symptoms persist for ≥ 5 days despite supportive management.
2nd appearance	Interrupt until resolved (Grade 0-1)	Reduce by an additional capsule.
3rd appearance	Discontinue permanently	n/a
■ Non-hematologic Grade 4 (excluding liver function test increases [see below]): start symptomatic treatment when possible		
1st appearance	Interrupt until resolved (Grade 0-1)	Reduce by 1 capsule.
2nd appearance	Discontinue permanently	n/a

ANC = absolute neutrophil count; CTCAE = Common Toxicity Criteria for Adverse Events; INR = international normalized ratio; n/a = not applicable; PLT = platelets

[a] Dose interruptions for Grade 2 AEs may be instituted at the discretion of the treating physician after discussion with the Sponsor's Medical Monitor or designee.

Source: ENLIVEN Protocol Version 9 dated December 17, 2017

Table 55 displays the specific dose modification guidelines for liver function abnormalities from the last version of the protocol dated December 17, 2017.

Table 55. Dose Modification Guidelines for Liver Function Abnormalities

Toxicity Grade CTCAE v4	Initial Action	Outcome	Action
ALT or AST Grade 2 (>3 to 5x ULN); no increase in bilirubin[a]	Re-check ALT and AST immediately. Hold study drug. Monitor weekly[b] 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 to 20x ULN); no increase in bilirubin[a]	Re-check ALT and AST immediately. Hold study drug. Monitor 2×/wk[2] Check for changes to medications and for symptoms.	Resolution to Grade 0-1 or baseline (no bilirubin increase) within 14 d. ALT and AST not decreasing within 14 d of holding study drug.	Restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule). *Proceed to liver evaluation*.[3] Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule). For max AST or ALT >8x ULN, consult with Medical Monitor prior to re-start.
Grade 4 ALT or AST (>20x ULN)	Discontinue treatment. Monitor 2×/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. *Proceed to liver evaluation*.[3] 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[1] with any bilirubin increase or signs of hypersensitivity	Discontinue treatment. Monitor 2×/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. *Proceed to liver evaluation*.[3] If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.
[1] Increase in bilirubin is defined as all of the following: total bilirubin > ULN, total bilirubin >20% above baseline, & direct bilirubin is > ULN. If all these conditions are met, bilirubin should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.
[2] If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.
[3] See protocol specified Liver Evaluation Guidelines below.
Source: ENLIVEN Protocol Version 9 dated December 17, 2017

Reviewer Comment: *The dose modification table included above is reproduced from the latest version of the protocol, version 9 dated December 17, 2017. The dose modification table in earlier version of the protocol included dose reductions at higher ALT, AST, and bilirubin values. In November of 2017 FDA placed IND 117332 on partial clinical hold and halted further enrollment into other trials across the development program for pexidartinib, due to reports of serious adverse events of hepatotoxicity. In December of 2017, DSI provided a complete response to the partial clinical hold addressed the hold issues by revising the protocol incorporating additional risk mitigation strategies including dose modification at lower ALT, AST and bilirubin values.*

Additional Liver Evaluation Guidelines are shown below:

Evaluation	Comments
Increase frequency of testing liver chemistries to twice per week, including INR, and continue until liver chemistries have stabilized, and then reduce to weekly until liver chemistries return to normal or baseline	Investigational treatment may be started after liver function tests recover to Grade 0 to 1 or baseline level, and in consultation with Medical Monitor
Detailed history focusing on medications and substances used: alcohol, change in medication dosages, new medications added, attention to use of acetaminophen, OTC medication use and recreational drug use. Check for change in diet or use of dietary supplements, with particular attention to dose and duration of any herbal product	Suspect medications will be discontinued or substituted for if possible
Detailed medical history and physical exam seeking new abnormalities	Evaluate abnormalities found
Full serological evaluation for hepatitis A, B, C and E (IgG and IgM). Check for autoimmune hepatitis with serological laboratory studies	If viral hepatitis or autoimmune hepatitis suggested, have subject evaluated by hepatologist
Liver ultrasound performed to evaluate liver and biliary tree	Evaluate any abnormalities found
Check history for exposure to chemical agents	Remove chemical exposure and have subject seen by hepatologist
Obtain hepatology consult if liver function continues to rise beyond 14 days	Contact Medical Monitor
We request that cases be discussed with the Medical Monitor whenever investigational product is being held for liver function test abnormality.	

Ig = Immunoglobulin; INR = international normalized ratio; OTC = over-the-counter.
Source: ENLIVEN Protocol Version 9 dated December 17, 2017

Study Endpoints

The primary endpoint of ENLIVEN was ORR at Week 25 as assessed by blinded independent central review (BICR) per RECIST v1.1. ORR was defined as the proportion of patients who achieve a complete response (CR) or partial response (PR) at Week 25.

Reviewer Comment: *As TGCT is a slow growing progressive and debilitating but non- lethal disease, the use of endpoints such as progression free survival and overall survival may not*

capture improvements in how a patient feels or functions. ORR can be used to show that these tumors have decreased in size; however, in a non-lethal disease, ORR generally requires supportive evidence of clinical benefit such as clinical outcome assessments showing improvement in pain, range of motion, and physical function.

Key secondary endpoints included Range of Motion (ROM); Patient-Reported Outcomes Measurement Information System (PROMIS®)-Physical Function items; Worst Stiffness numeric rating scale (NRS) item, and Brief Pain Inventory (BPI)-Worst Pain NRS item. These COA measures are described below.

Range of Motion (ROM)

Range of motion is a clinician-reported outcome assessment designed to assess the ROM of a single joint (i.e., planes of movement expressed in degrees). Independent and blinded third-party assessors performed this at Screening and at Weeks 13 and 25, using goniometers.

ROM was calculated as follows (expressed in percent):

Relative ROM=100 x (absolute ROM measured) / (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 comment**: The Applicant proposed a positive 6.7% threshold for what constitutes a clinically meaningful within-patient change for ROM at the knee. The normal range of motion for the knee is 150 degrees, so a 6.7% improvement corresponds to a 10 degree improvement for the knee.*

A threshold was proposed for the knee only because it is the only joint for which there is any published literature regarding range of motion and function. There is no widely used standard of improvement in ROM across joints, as impact of range of motion on a joint's function depends on the specific joint as well as the degree of impairment at baseline. Additionally, 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. The Applicant cited three studies of interventions for knee rehabilitation that were powered to detect a 5 to 15 degree improvement in ROM as clinically meaningful. None of these studies were conducted in the TGCT population.

PROMIS® Physical Function (PROMIS® PF)

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 56 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 56. 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 tying 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

Worst Stiffness NRS 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

BPI Worst Pain NRS 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.

Reviewer comment: *Patients with TGCT experience symptoms such as pain, stiffness, swelling, and impairment in range of motion, which can cause severe functional impairment. Therefore, the assessment of clinical benefit of pexidartinib may be supported by alleviation of symptomatic aspects of TGCT.*

TVS is a scoring system evaluating tumor mass and is an extension of the synovitis scale of the Rheumatoid Arthritis MRI score and Whole Organs MRI score. The ENLIVEN SAP defined the TVS criteria as follows:

- Complete response: Lesion completely gone
- Partial response: ≥50% decrease in volume score relative to baseline
- Progressive disease: ≥30% increase in volume relative to lowest score during the study
- Stable disease: Does not meet any of the prior criteria

Tumor response assessments in ENLIVEN were conducted at Screening, Week 13 (Cycle 4, Day 1) and Week 25 by magnetic resonance imaging (MRI) according to RECIST v 1.1 criteria. Tumor response assessments for PLX108-01 were conducted at baseline and every 8 weeks thereafter by MRI according to RECIST v 1.1.

Statistical Analysis Plan

The trial was designed to accrue 126 patients to provide 90% power to detect a significant difference in ORR at a two-sided alpha level of 0.05, assuming an ORR of 10% in the placebo arm and of 35% in the pexidartinib arm. There were no pre-specified interim analyses.

The primary analysis was a Fisher's exact test performed on the intent-to-treat (ITT) population, and the Wilson method was used to estimate the two-sided 95% confidence interval (CI) for ORR.

A hierarchical testing procedure was proposed to adjust for multiplicity in the hypothesis tests of the key secondary endpoints in the order listed above. The secondary analyses of ROM,

physical function, and worst stiffness were based on a mixed model for repeated measurements (MMRM) using data from visits up to Week 25. The models of change from baseline included fixed effects for treatment arm, visit, treatment arm-by-visit interaction, region (U.S. vs non-U.S.), baseline, and baseline-by-visit interaction. The analysis of ROM also accounted for joint type (knee, ankle or other). Fisher's exacts tests were used for the secondary analyses of ORR per TVS and BP1-30. A responder for BPI-30 was defined as a patient who experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and did not experience a ≥30% increase in narcotic analgesic use.

Protocol Amendments

The ENLIVEN trial protocol was amended 8 times during the study as shown in Table 57.

Table 57. Major Protocol Amendments, ENLIVEN

Version	Version Date	Major Changes	Patients Enrolled
1	Sep 18, 2014	Original protocol.	0
2	Dec 5, 2014	Modified responder definition of at least 30% reduction in the BPI worst pain NRS score. Revised testing order of secondary endpoints prior to enrolling any patients, made the clinical outcome assessment of BPI worst pain score number 1 and tumor volume score number 2.	0
3	Feb 11, 2015	Changes for clarity without significant modification to the study objectives, patient population, protocol design, or analytic plan.	0
4	Mar 25, 2016	Minor changes in eligibility criteria and schedule of assessments.	63
5	Jul 19, 2016	Patients who undergo surgical resection will not be discontinued from the study but will be discontinued from study treatment. Statistical method was amended for incorporating the provision for surgical resection. Clarification that the statistical analysis of endpoints at the end of Part 1 will be defined for the point when all randomized subjects complete or are discontinued from Part 1 with appropriate End of Part 1 follow up.	102
6	Oct 10, 2016	Response to clinical hold, protocol was placed on clinical hold when the data monitoring committee reviewed unblinded safety data and identified two cases of potential cholestatic liver injury. Updated safety information. Enrollment was stopped. Patients randomized to placebo no longer allowed to crossover to pexidartinib therapy. Patients must be reconsented to remain on trial with new hepatic safety information. The frequency of liver function testing was increased and GGT was added to the laboratory panel.	120
7	Feb 10, 2017	Revised the protocol so patients could continue on pexidartinib after Part 2 of the study ends. In previous version of the protocol patient had to enroll to another protocol for continued treatment.	120
8	Sep 11, 2017	Revised the sequential analysis hierarchy of the secondary endpoints.	120
9	Dec 15, 2017	Updated safety information for pexidartinib. Revised the dose modification criteria for pexidartinib. Increased hepatic laboratory monitoring.	120

In Protocol Version 8 (September 11, 2017), Daiichi Sankyo revised the hierarchical testing order for the secondary endpoints based on blinded assessments of the database prior to the lock and unblinding of the data, which revealed a substantial amount of missing Week 25 patient-reported outcome (PRO) assessments, specifically for BPI-30, PROMIS® Physical Function items, and Worst Stiffness NRS.

The proportion of responders based on BPI-30 was moved from position #1 to position #5 and ROM was moved from position #3 to position #1 in the hierarchy of secondary endpoints

analyses; Daiichi Sankyo considered ROM to be a clinically relevant endpoint with higher completion rate (Table 58).

Table 58. Revised Hierarchical Order of Secondary Endpoints in the ENLIVEN Trial[1,2]

	Original Protocol Version 1 (September 18, 2014)	Protocol Version 8 (September 11, 2017)
Primary	ORR per RECIST v1.1	ORR per RECIST v1.1
Key secondary	**Proportion of responders based on BPI Worst Pain NRS item and narcotic analgesic use (BPI-30)**	**Mean change from baseline in ROM**
	ORR per TVS	ORR per TVS
	Mean change from baseline in ROM	Mean change from baseline score in the PROMIS® Physical Function Scale
	Mean change from baseline score in the PROMIS® Physical Function Scale	Mean change from baseline score in the Worst Stiffness NRS item
	Mean change from baseline score in the Worst Stiffness NRS item	**Proportion of responders based on BPI Worst Pain NRS item and narcotic analgesic use (BPI-30)**

[1] All endpoints assessed at Week 25
[2] Hierarchical testing procedure to adjust for multiplicity of secondary endpoints

Reviewer Comment: *Changing the statistical analysis plan after completion of the trial is strongly discouraged due to introduction of potential bias. However, FDA acknowledged the concern regarding the statistical validity of the originally proposed hierarchical analysis given the substantial amount of missing data. The revision in hierarchy of secondary endpoints limits the interpretability of the ENLIVEN results.*

In Protocol Version 9 (December 15, 2017), Daiichi Sankyo revised the protocol to address adverse reactions that resulted in the IND being placed on clinical hold for liver toxicity. These revisions included more frequent liver test monitoring (increased to once weekly during the first 8 weeks of treatment, with more frequent assessments as needed, and implementation of more conservative toxicity management guidelines, such as the requirement to interrupt pexidartinib for ALT or AST ≥3x ULN rather than an ALT or AST >5x ULN.

8.1.2. Study Results

Data Quality and Integrity - Reviewers' Assessment

For ENLIVEN and PLX108-01, the Applicant submitted SDTM and ADAM data sets. ADAM datasets were primarily used for analysis and the key derived variable were checked. This reviewer found that the derived flags and variables with few exceptions to be correct and consistent with the define file definitions.

For the commercially sponsored trials, the applicant provided legacy data sets and summary data in the integrated summary and for the investigator-initiated trials legacy study reports were provided.

The reviewer identified the following issue with the submitted data:

- As shown in Table 64, after re-assessment of scans based on the data cutoff date of January 31, 2018, two patients who were considered responders (PR) at the time of the

NDA submission, were determined to be non-responders (SD). Similarly, one patient who was considered a non-responder (SD) at the time of the NDA submission, was deemed a responder (CR) at Week 25 based upon the January 31, 2018 data cutoff date.

The primary endpoint of the study thus changed modestly, but long-term follow-up ORR of the patients randomized to pexidartinib on ENLIVEN remained the same at 52%. The Applicant informed FDA that the change in response in these patients was due to incorporating data from later scans into image evaluation after data was unblinded. For example, viewing later scans provided additional discriminative information that improved interpretation of the Week 25 scan.

FDA determined that the rate of discordance between readers was reasonable and that the changes in response rate for the three patients were reasonable. The reviewers could not identify any other issues that questioned the integrity of the data in the submission.

Compliance with Good Clinical Practices

The Applicant stated in the NDA clinical study report for the ENLIVEN trial that the study was conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. The International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines [E6]
3. Applicable laws and regulations
4. The protocol
5. Food and Drug Administration (FDA) GCP guidelines, FDA Financial Disclosure regulations

As described briefly in Section 4.1. of the review, inspection of site NLD-0476 revealed that GCP violations had occurred. These violations were characterized as failure to maintain adequate case histories with respect to observations and data pertinent to the investigation. A review of the clinical datasets and case report forms revealed that for the 11 patients enrolled at Site ND-0476 (7 randomized to pexidartinib and 4 randomized to placebo, 2 of whom crossed over to pexidartinib at Week 25), the response rate for those treated with pexidartinib in Part 1 was 2/7 (29%) and for all patients treated with pexidartinib was 4/9 (44%). Additionally, the AE from this site were evaluated and revealed that all patients at this site experienced at least one adverse event. The most common adverse events reported in patient who received pexidartinib were fatigue (100%), hair color changes (86%), facial edema (71%), and arthralgia/myalgia. Although the OSI inspection revealed GCP violation, the trial data from this site regarding efficacy and safety appears consistent with the rest of the ENLIVEN trial and was included in the data analysis.

Reviewer Comment: *The ORR results from site NLD-0476 are unlikely to have significantly impacted the overall ORR for the ENLIVEN trial given the small numbers of patients enrolled at that site, and the even smaller number of responders.*

Financial Disclosure

The Applicant submitted a list of investigators (sNDA Section 1.3.4, Attachment 1) and FDA form 3454 certifying that all of the investigators listed in Attachment 1 had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the trial. No financial disclosures were submitted for any investigator in this sNDA. See Section 19.2 Financial Disclosure.

Patient Disposition

The data cut-off date for analysis of the ENLIVEN trial was March 27, 2017. The first patient was enrolled on May 5, 2015, and the last patient was enrolled on September 15, 2016.

Table 59 provides information on patient disposition for Part 1 of the ENLIVEN trial. The majority of patients in both the placebo arm (81%) and the pexidartinib arm (85%) completed study drug to Week 25 in Part 1 of the trial. Of those patients treated with pexidartinib, 8 patients discontinued their protocol-assigned drug for an adverse event and 1 patient withdrew consent.

Table 59. Patient Disposition for Part 1 of ENLIVEN

	Pexidartinib N=61 n (%)	**Placebo N=59 n (%)**
Completed Part 1 (25 weeks)	52 (85)	48 (81)
Discontinued prior to week 25	9 (15)	11 (19)
Adverse event	8 (13)	0
Progressive disease	0	1 (1.7)
Withdrawal of consent	1 (1.6)	6 (10)
Investigator decision	0	3 (5)
Subject noncompliance	0	1 (1.7)
Protocol deviation	0	0

Source: Reviewer generated table – summarizing subject level analysis and exposure datasets (ADSL and ADEX, March 27, 2017 data cutoff date, submitted by Applicant)

Table 60 provides information on patient disposition for Part 1 of the ENLIVEN Trial. Among the patients who received pexidartinib (n=61) or placebo (n=59) in Part 1 of the ENLIVEN trial, 48 patients (75%) and 30 (51%), respectively, received pexidartinib in Part 2 of the ENLIVEN trial; at data cut off, 39 of 48 patients, and 26 of 30 patients (a total of 65 patients) were still receiving pexidartinib in Part 2. A total of 5 patients (6%) discontinued pexidartinib due to adverse events and 6 (8%) patients withdrew consent to remain on study in Part 2.

Table 60. Patient Disposition for Part 2 of ENLIVEN

	Pexidartinib N=61 n (%)	Placebo N=59 n (%)
Patients receiving treatment in Part 2	48 (79)	30 (51)
Completed Part 1; no pexidartinib in Part 2	4 (7)	18 (31)
Ongoing treatment	39 (64)	26 (87)
≥6 months of treatment	48 (79)	26 (87)
≥12 months of treatment	24 (39)	7 (23)
≥18 months of treatment	4 (7)	1 (3.3)
Discontinued treatment	18 (30)	4 (13)
Adverse event	11 (18)	2 (7)
Progressive disease	0	0
Death	0	1 (3.3)
Withdrawal of consent	6 (10)	1 (3.3)
Investigator decision	1 (1.6)	0
Subject noncompliance	0	1 (3.3)
Protocol deviation	0	0

Source: Reviewer generated table – summarizing subject level analysis and exposure datasets (ADSL and ADEX, March 27, 2017 data cut-off date, submitted by Applicant)

Protocol Violations/Deviations

The Applicant defined major protocol violations as protocol ineligibility and substantial treatment compliance errors. The Applicant identified 11 major protocol violations, 4 in the placebo arm and 7 in the pexidartinib arm, in a total of 10 patients. One patient in the pexidartinib arm had 2 major protocol violations (Table 61).

Table 61. Protocol Deviations, ENLIVEN

	Pexidartinib N=61	Placebo N=59
Patients with major protocol violation (%)	6 (10)	4 (7)
Total number of major protocol violations	7	4
Inclusion/exclusion criteria not met-	1	0
Inclusion criteria #6 not met-	2	0
Study drug dosing error	1[a]	1[b]
Patient non-compliance-	0	2
Improper completion of consent-	0	1
Missing data entry in LogPad-	1	0
SAE reporting follow-up incorrect/incomplete-	1	0
Study procedure not completed-	1[c]	0

Source: Reviewer generated table – summarizing protocol deviations dataset (DV, March 27, 2017 data cut-off date, submitted by Applicant)
[a.] Stopped study drug for 3 weeks due to misunderstanding site personnel instruction
[b.] Incorrect kit was dispensed. Patient (b) (6) was not dispensed the kit assigned by the IVRS; took one dose when the site realized the error
[c.] Range of motion, surgical questionnaire, ECGT, coagulation, and urinalysis not completed

Reviewer Comment: *A similar proportion of patients had protocol violations in both the pexidartinib and placebo arms. It is unlikely that the protocol violations had a major impact on the efficacy analyses.*

Table of Demographic Characteristics

Table 62 provides an overview of the demographics for patients enrolled in the ENLIVEN trial. At total of 120 patients were randomized in a 1:1 fashion (Pexidartinib 61; placebo 59). Baseline patient demographics were similar between study arms.

Table 62. Patient Demographic Factors in the ENLIVEN Trial

Characteristic	Pexidartinib N=61 n (%)	Placebo N=59 n (%)
Sex		
Female	35 (57)	36 (61)
Male	26 (43)	23 (39)
Age		
Mean years (SD)	44.6 (13.2)	44.3 (13.6)
Median years (Range)	44.0 (22, 75)	45.0 (18, 79)
18 to 41 years	24 (39)	19 (32)
41 to 65 years	33 (54)	37 (63)
≥65 years	4 (7)	3 (5)
Race		
White	52 (85)	54 (92)
Black or African American	3 (4.9)	1 (1.7)
Asian	1 (1.6)	2 (3.4)
American Indian or Alaska Native	2 (3.2)	0
Native Hawaiian or Other Pacific Islander	2 (3.2)	2 (3.4)
Other	1 (1.6)[1]	0
Ethnicity		
Not Hispanic or Latino	49 (80)	50 (86)
Hispanic/Latino	9 (15)	8 (14)
Unknown	3 (4.9)	1 (1.7)
Region		
United States	23 (38)	22 (37)
Rest of the World	38 (62)	37 (63)

Source: Reviewer generated table – summarizing subject level analysis datasets (ADSL, March 27, 2017 data cutoff date, submitted by Applicant)

[1] Multi-racial

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 63 provides an overview of the baseline disease characteristics for patients enrolled in the ENLIVEN trial. Baseline disease characteristics were similar between study arms.

Table 63. Baseline Disease Characteristics in ENLIVEN Trial

Characteristic	Pexidartinib N=61 n (%)	Placebo N=59 n (%)
PVNS/GCT-TS		
PVNS	52 (85)	53 (90)
GCT-TS	9 (15)	6 (10)
Extremity Involvement		
Upper	5 (8)	5 (9)
Wrist	2 (3.3)	2 (3.4)
Shoulder	1 (1.6)	1 (1.7)
Elbow	1 (1.6)	0
Spine	1 (1.6)	1 (1.7)
Finger	0	1 (1.7)
Lower	56 (92)	54 (92)
Knee	34 (56)	39 (66)
Ankle	14 (23)	7 (12)
Hip	6 (10)	7 (12)
Foot	2 (3.3)	1 (1.7)
Number of Prior Surgeries		
0	29 (48)	28 (48)
1	12 (20)	12 (20)
2	7 (12)	12 (20)
≥3	12 (20)	7 (12)
Prior Systemic Therapy		
None	53 (87)	56 (95)
Imatinib	7 (12)	3 (5)
Nilotinib	1 (1.6)	0
Predicted Probability of Complete Resection[a]		
None	37 (61)	37 (63)
Low	18 (30)	13 (22)
Medium	2 (3.2)	3 (5)
High	1 (1.6)	3 (5)
Not Reported	3 (5)	3 (5)

Characteristic	Pexidartinib N=61 n (%)	Placebo N=59 n (%)
Predicted Post Operative Morbidity[a]		
Mild	2 (3.2)	1 (1.7)
Moderate	24 (39)	25 (42)
Severe	32 (52)	30 (51)
Not Reported	3 (5)	3 (5)

Source: Reviewer generated table – summarizing subject level analysis datasets (ADSL, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Determined by two local surgeons or a multidisciplinary tumor board

Reviewer Comment: *Baseline demographics and disease characteristics were similar between study arms. Additionally, the demographics and baseline characteristics are representative of the wider TGCT population with symptomatic disease that is not amenable to surgery.*

Efficacy Results – Primary Endpoint

The analysis of the primary efficacy endpoint in the ENLIVEN trial (based in a data cutoff date of January 31, 2018) demonstrated a statistically significant difference in ORR between pexidartinib and placebo arms (Table 64).

The ORR was 38% (95% CI 26%, 50%) in the pexidartinib arm compared to no responses (95% CI 0, 6%) in the placebo arm (p<0.0001). The median DOR was not reached; DOR ranged from 6.9+ to 24.9+ months. One responder had progressive disease in follow-up. Among the 23 patients who responded, 22 (96%) had ongoing DOR ≥6 months. Among the 13 patients on follow-up for at least 12 months, 13 had ongoing DOR (data cutoff date of January 31, 2018).

Table 64. Analysis of ORR Per BICR Using RECIST V1.1, ITT Population, ENLIVEN

Response Statistic	Pexidartinib N=61	Placebo N=59
Overall response rate		
ORR, n (%)	23 (38%)	0
(95% CI)	(26%, 50%)	(0, 6%)
Complete responses	15%	0
Partial responses	23%	0
P-value	<0.0001	
Duration of response		
Range	(6.9+, 24.9+)	NA
DOR ≥6 months[1]	22/23	NA
DOR ≥12 months[1]	13/13	NA

Source: Reviewer generated table – summarizing ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant), and time to event analysis dataset (ADTTE, January 31, 2018 data cutoff date, submitted by Applicant)
[1] Number of patients with ongoing DOR/Number of patients on follow-up at specified time (have not yet been censored)

Reviewer Comment: *The primary analysis based on the data cutoff date of March 27, 2017 resulted in an ORR of 39% (95% CI 28%, 52%) in the pexidartinib arm and no responses (95% CI 0, 6%) in the placebo arm (p<0.0001). The median DOR was not reached and ranged from 4.6+ to 24.9+ months in the pexidartinib arm.*

As shown in Table 64, after re-assessment of scans based on the data cutoff date of January 31, 2018, two patients who were considered responders (PR) at the time of the NDA submission, were determined to be non-responders (SD). Similarly, one patient who was considered a non-responder (SD) at the time of the NDA submission, was deemed a responder (CR) at Week 25 based upon the January 31, 2018 data cutoff date.

Efficacy Results – Secondary and Other Relevant Endpoints

Range of Motion

The analysis of the secondary endpoint demonstrated a statistically significant improvement in mean change from baseline ROM at Week 25 for the pexidartinib arm compared to the placebo arm, with an observed difference from placebo of 8.9% (95% CI 2.9, 14.9; p=0.0043) (Table 65). The least square (LS) mean change from baseline in ROM at Week 25 was 15.1% (95% CI 10.9, 19.2) in the pexidartinib arm and 6.2% (95% CI 1.5, 0.9) in the placebo arm.

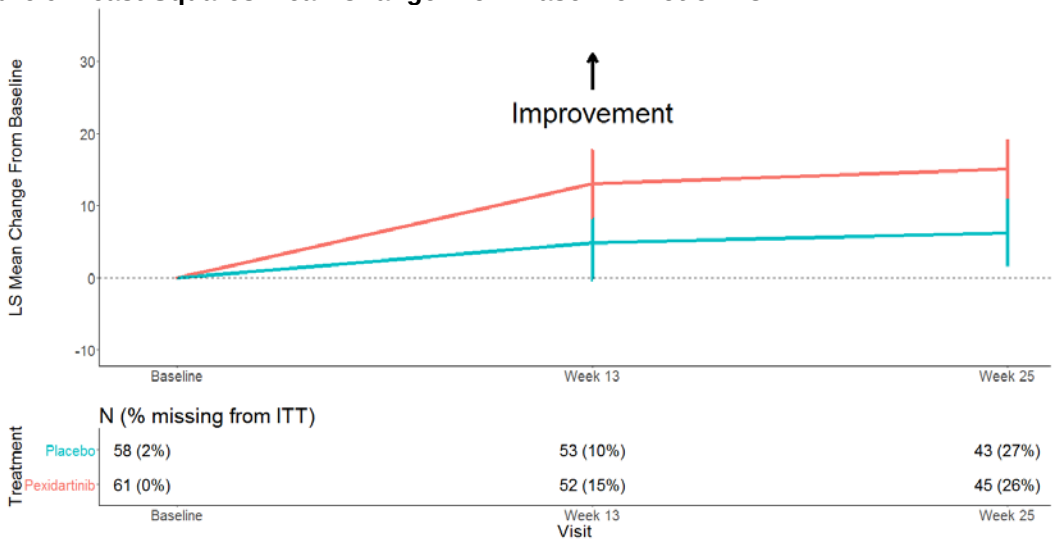
Table 65. Analysis of ROM, ITT Population

	Parameter	Pexidartinib N=61	Placebo N=59
ROM at Baseline	N	61	58
	Mean (SD)	62.5 (24.8)	62.9 (21.8)
	Range	13.3, 115.0	18.0, 115.0
ROM at Week 25	N	50	43
	Mean (SD)	76.5 (18.3)	68.1 (22.3)
	Range	44.4, 133.3	16.7, 136.7
Change From Baseline in ROM at Week 25[1,2]	LS Mean	15.1%	6.2%
	(95% CI)	(10.9, 19.2)	(1.5, 10.9)
	Difference from placebo	8.9%	
	(95% CI)	(2.9, 14.9)	
	P-value	0.0043	

Source: Reviewer generated table – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)
[1] Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, joint type, treatment by visit interaction, baseline by visit interaction, treatment by joint type interaction, baseline by joint type interaction
[2] 32 (27%) patients missing at Week 25

Reviewer Comment: *While this analysis demonstrated a statistically significant improvement in mean change from baseline in ROM for the pexidartinib arm compared to the placebo arm, 27% of assessments were missing as shown in Table 73. There is uncertainty in the magnitude of the treatment due to missing data.*

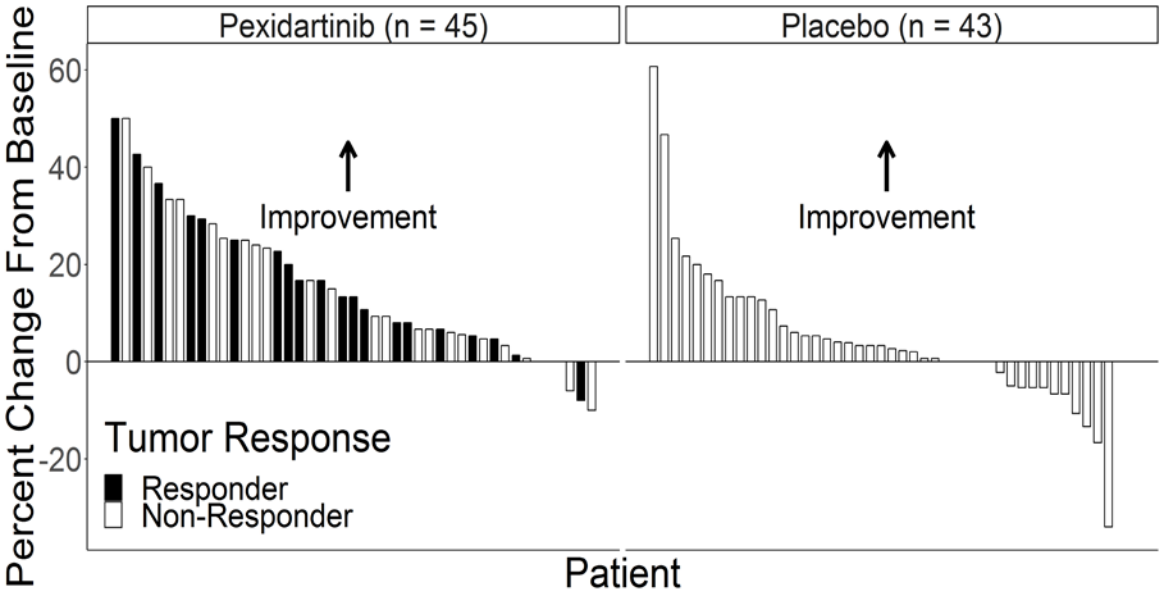
Figure 9. Least Squares Mean Change From Baseline Plot of ROM in ENLIVEN



Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

Figure 10 shows the waterfall plot of change from baseline in ROM at Week 25 by tumor response.

Figure 10. Waterfall Plot of Change From Baseline at Week 25 in ROM by Tumor Response



Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment: *An improvement of ROM was observed for more patients on the pexidartinib arm compared to placebo. Some patients on placebo and pexidartinib who did not have a tumor response per RECIST v1.1 had an improvement in ROM.*

ORR by TVS

The analysis of the secondary efficacy endpoint demonstrated a statistically significant difference in ORR per TVS between pexidartinib and placebo arms (Table 66). The ORR was 56% (95% CI 43%, 67%) in the pexidartinib arm compared to no responses (95% CI 0, 6%) in the placebo arm (p<0.0001). There were 3 complete responses (5%) and 31 partial responses (51%) per TVS.

Table 66. Analysis of Overall Response Rate Per TVS, ITT Population

	Pexidartinib N=61	Placebo N=59
Overall Response Rate, n (%)	34 (56%)	0
(95% CI)	(43%, 67%)	(0, 6%)
P-value	<0.0001	

Source: Reviewer generated table – summarizing response analysis and time to event analysis datasets (ADRS and ADTTE, March 27, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment*. The Applicant proposed that measurement of tumor size by RECIST v 1.1 in patients with TGCT may not fully capture the anti-tumor effects of pexidartinib, due to the tumor's infiltrative growth pattern. To address this concern, the ENLIVEN trial evaluated the ORR by TVS as a key secondary endpoint in ENLIVEN, including it in the hierarchy of testing. The analysis of ORR per TVS demonstrated a statistically significant difference in ORR per TVS between pexidartinib and placebo arms. FDA considered the results of the analysis of ORR by TVS as supportive of pexidartinib's effect on tumor burden, though in the absence of clinical validation, FDA would not consider this endpoint sufficient to stand alone as a primary endpoint for an approval decision.*

Physical Function

ENLIVEN demonstrated a statistically significant improvement in mean change from baseline physical function at Week 25 for the pexidartinib arm compared to the placebo arm, with an observed difference from placebo of 4.7 (95% CI 2.5, 6.9; p<0.0001) (Table 67). The LS mean change from baseline in physical function at Week 25 was 3.6 (95% CI 2.1, 5.1) in the pexidartinib arm and -1.1 (95% CI -2.6, 0.5) in the placebo arm.

Table 67. Analysis of Physical Function, ITT Population

	Parameter	Pexidartinib N=61	Placebo N=59
Physical function at baseline	N	60	57
	Mean (SD)	37.5 (4.9)	38.9 (6.1)
	Range	27.4, 47.7	24.4, 58.0
Physical function at Week 25	N	38	31
	Mean (SD)	40.7 (7.2)	38.1 (6.6)
	Range	23.2, 59.0	22.9, 47.6
Change from baseline in physical function at Week 25[1,2]	LS Mean (95% CI)	3.6 (2.1, 5.1)	-1.1 (-2.6, 0.5)
	Difference from placebo (95% CI)	4.7 (2.5, 6.9)	
	P-value	<0.0001	

Source: Reviewer generated table – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant)
[1] Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, treatment by visit interaction, baseline by visit interaction based on pre-specified model in SAP
[2] 51 (43%) patients missing at Week 25

Reviewer Comment: *While the analysis presented in Table 67 demonstrated a statistically significant improvement in mean change from baseline in Physical Function for the pexidartinib arm compared to the placebo arm, 43% of patient assessments were missing at Week 25 as shown in Table 73. Given the proportion of missing data, the results of this analysis may not reliably estimate treatment effects, and thus, valid inference cannot be made.*

The physical function results presented in Table 67 are based on the pre-specified model in the SAP. The physical function results in the Applicant CSR included additional fixed effects of tumor location, treatment by tumor location interaction, and baseline by tumor location interaction. The Applicant stated that the final SAP inadvertently left out the additional fixed effects.

The results in the CSR were similar to the results based on the model in the SAP. The analysis of the secondary endpoint demonstrated a statistically significant improvement in mean change from baseline physical function at Week 25 for the pexidartinib arm compared to the placebo arm, with a difference from placebo of 5.0 (95% CI 1.9, 8.0); p=0.0019). The LS mean change from baseline in physical function at Week 25 was 4.1 (95% CI 1.8, 6.3) in the pexidartinib arm and -0.9 (95% CI -3.0, -1.4) in the placebo arm.

Worst Stiffness

ENLIVEN demonstrated a statistically significant improvement in mean change from baseline worst stiffness at Week 25 for the pexidartinib arm compared to the placebo arm, with an observed difference from placebo -2.2 (95% CI -3.0, -1.4; p<0.0001) (Table 68). The LS mean change from baseline in worst stiffness at Week 25 was -2.4 (95% CI -3.0, -1.9) in the pexidartinib arm and -0.3 (95% CI -0.9, 0.3) in the placebo arm.

Table 68. Analysis of Worst Stiffness, ITT Population

	Parameter	Pexidartinib N=61	Placebo N=59
Worst stiffness at baseline	N	59	58
	Mean (SD)	5.6 (1.7)	5.9 (1.9)
	Range	1.2, 8.4	1, 9.4
Worst stiffness at Week 25	N	33	35
	Mean (SD)	3.4 (2.3)	5.4 (2.5)
	Range	0, 7.7	1.0, 9.5
Change from baseline in worst stiffness at Week 25[1,2]	LS Mean (95% CI)	-2.4 (-3.0, -1.9)	-0.3 (-0.9, 0.3)
	Difference from placebo (95% CI)	-2.2 (-3.0, -1.4)	
	P-value	<0.0001	

Source: Reviewer generated table – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant)
[1] Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, treatment by visit interaction, baseline by visit interaction based on pre-specified model in SAP
[2] 51 (43%) patients missing at Week 25

Reviewer Comment: *While this analysis demonstrated a statistically significant improvement in mean change from baseline in Worst Stiffness for the pexidartinib arm compared to the placebo arm, 43% of patient assessments were missing at Week 25 as shown in Table 73. Given the proportion of missing data, the results of this analysis may not reliably estimate treatment effects, and thus, valid inference cannot be made.*

BPI-30

The analysis of the secondary efficacy endpoint did not demonstrate a statistically significant difference in worst pain between pexidartinib and placebo arms (Table 69). The worst pain response rate was 31% in the pexidartinib arm and 15% in the placebo arm (p=0.0521, Fisher's Exact test).

Table 69. Analysis of BPI-30 Response Rate, ITT Population

	Pexidartinib N=61	Placebo N=59
BPI-30 Response Rate[1,2], n (%)	19 (31%)	9 (15%)
(95% CI)	(21%, 44%)	(8%, 27%)
P-value[3]	0.0521	

Source: Reviewer generated table – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant)
[1] BPI-30 responder defined as patient who experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and did not experience a ≥30% increase in narcotic analgesic use
[2] 50 (42%) patients missing and assumed non-responders at Week 25
[3] Fisher's Exact Test

Reviewer Comment: *Data were missing 43% of patient assessments were missing at Week 25 as shown in Table 73. Patients with missing assessments were considered non-responders for the BPI-30 endpoint. Given the proportion of missing data, the results of this analysis may not reliably estimate treatment effects, and thus, valid inference cannot be made.*

Durability of Response

Table 64 shows the median DOR for the pexidartinib arm was not reached with a range of 6.9+ to 24.9+ months (based in a data cutoff date of January 31, 2018).

Reviewer Comment*: In a slow-growing tumor, such as TGCT, it is difficult to interpret duration of response without long-term follow-up post response. However, it is reassuring that all but one responder has had persistence of response through the data cutoff date for the application.*

Persistence of Effect

Table 70 shows the exploratory subgroup analyses of ORR based on gender, age, region, tumor extremity location, and type of disease. The subgroup analyses showed no outliers in subpopulations of adequate size compared to the primary analysis of ORR.

Table 70. Subgroup Analysis of Overall Tumor Response Rate in ENLIVEN

		Pexidartinib N=61	
Demographic and Disease Factors		**#Responses/N**	**ORR (95% CI)**
Gender	Female	13/35	47% (23, 54)
	Male	10/26	38% (22, 57)
Age (years)	<65	23/57	40% (29, 53)
	≥65	0/4	0% (0, 5)
Region	U.S.	9/23	39% (22, 59)
	Non-U.S.	14/38	37% (23, 53)
Tumor extremity location	Lower extremity	20/56	36% (24, 49)
	Upper extremity	3/5	60% (23, 88)
Tumor location	Ankle	5/14	36% (16, 61)
	Knee	14/34	41% (26, 58)
	Other lower	1/8	13% (1, 47)
	Upper	3/5	60% (23, 88)
Type of disease	GCT-TS (localized TGCT)	4/9	44% (19, 73)
	PVNS (diffuse TGCT)	19/52	37% (25, 50)

Source: Reviewer generated table – summarizing ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

Reviewer Comment: *These subgroup analyses were exploratory only. Overall, there were no outliers in these subgroups of interest compared to the primary analysis of ORR.*

Table 71 shows the exploratory subgroup analyses of ROM based on tumor location (ankle, knee, other).

Table 71. Subgroup Analysis of Range of Motion by Tumor Location

	LS Mean (95% CI) Pexidartinib, N=61	LS Mean (95% CI) Placebo, N=59	Difference From Placebo (95% CI)
Overall	15.1 (10.9, 19.2)	6.2 (1.5, 0.9)	8.9 (2.9, 14.9)
Ankle (n=23)	17.1 (10.1, 24.0)	12.1 (2.4, 21.9)	5.0 (-6.8, 16.7)
Knee (n=72)	14.5 (9.7, 19.3)	5.5 (1.0, 10.0)	9.0 (2.5, 15.4)
Other (n=24)	13.3 (5.0, 21.6)	0.6 (-7.8, 9.0)	12.7 (1.9, 23.5)

Source: Reviewer generated table – summarizing range of motion (ADFA, March 27, 2017 data cutoff date, submitted by Applicant) and adverse event datasets (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment: *These subgroup analyses were exploratory only. Overall, there were no outliers in tumor location compared to the secondary analysis of ROM.*

Table 72 shows the exploratory subgroup analyses of ROM based on change in hair color for the pexidartinib arm.

Table 72. Subgroup Analysis of Range of Motion by Change in Hair Color in Pexidartinib

	With Hair Color Change	No Hair Color Change
N	35	15
LS Mean Change (95% CI)	14.4 (8.1, 20.7)	16.1 (9.0, 23.2)

Source: Reviewer generated table – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment: *Hair color changed to white in 67% of the patients who received pexidartinib. Although ROM was evaluated by a blinded third-party assessor, the review team considered the risk of unblinding of the clinical assessors given this known adverse reaction associated with pexidartinib, and thus acknowledges the potential for bias in reporting of ROM. However, the exploratory subgroup analysis of ROM by change in hair color change did not show any differences in ROM between patients whose hair color changed to white compared to those whose hair color did not change.*

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

The 'Clinical Outcome Assessments (COA)' and 'Efficacy Results – Secondary and Other Relevant Endpoints' sections of the review provide details of the COA endpoints of ROM, physical function, worst stiffness, and BPI-30.

Extent of Missing COA Data

Table 73 shows the proportion of patients in the ITT population with missing COA data by treatment arm and visit.

Table 73. Proportion of Patients With Missing Data for COA Secondary Endpoints

	Pexidartinib (N=61)				Placebo (N=59)			
ROM								
Visit	Baseline		Week 13	Week 25	Baseline		Week 13	Week 25
% missing	0		15%	26%	2%		10%	27%
Physical function								
Visit	Baseline	Week 9	Week 17	Week 25	Baseline	Week 9	Week 17	Week 25
% missing	2%	38%	36%	38%	3%	31%	32%	47%
Worst stiffness								
Visit	Baseline	Week 9	Week 17	Week 25	Baseline	Week 9	Week 17	Week 25
% missing	3%	51%	39%	46%	2%	36%	49%	41%
BPI worst pain								
Visit	Baseline	Week 9	Week 17	Week 25	Baseline	Week 9	Week 17	Week 25
% missing	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)

Reviewer Comment: *The percent of missing data observed in the secondary COA endpoints of physical function, worst stiffness, and BPI-30 are much higher than acceptable for reliable*

estimation of clinical benefit. Therefore, interpretation of COA secondary endpoints was focused on ROM.

The reasons for missing ROM assessments at Week 25 are shown in Table 74.

Table 74. 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%)
Patient non-compliance		1 (2%)
Withdrawal by Patient	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)

Reviewer Comment: *Although the proportion of patients with missing ROM assessments at Week 25 was similar across the two treatment arms, the reasons for missing data were different for each arm. For half of the patients in the pexidartinib arm, ROM assessments were missing due to adverse event, while ROM assessments for patients in the placebo arm were missing due to reasons such as withdrawal by patient or investigator decision. The differential reasons for missing assessments across arms could indicate informative missingness, which can lead to biased estimation of ROM.*

The most common reasons for missing data (in descending order) 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.

Sensitivity analyses for missing data: Range of Motion (ROM)

At FDA's request, Daiichi Sankyo performed post hoc sensitivity analyses for missing data to address the concern of informative missingness in the COA endpoints.

Daiichi Sankyo performed control-based pattern mixture models (PMM), including Unconditional Jump to Reference model (UR model) and Copy Reference model (CR model) to evaluate how results change if the treatment benefit of patients who discontinued treatment in the pexidartinib arm is assumed to be similar to the observed treatment benefit of patients in the placebo arm. Thus, compared to the secondary analysis of ROM, the treatment benefit is attenuated for the 9 patients who discontinued treatment in the pexidartinib arm. The CR model takes the patient's previous observed ROM assessments into account while the UR model is based on baseline attributes only, hence the term "unconditional."

Tipping point analyses using a delta-adjusting PMM method were performed to determine the percentage of ROM worsening that was needed in the pexidartinib arm to "tip" the results against the pexidartinib arm. The Applicant's analysis started by assuming an average ROM worsening of 1% for the 9 patients who discontinued pexidartinib treatment and 0.5% for the 7 patients with missing data who were still on pexidartinib treatment. The FDA analysis assumed an average ROM worsening of 1% for all patients with missing data on the pexidartinib arm. The penalties (delta) worsened until statistical significance was lost in the treatment effect (p>0.05).

The results of the sensitivity analyses are shown in Table 75. Daiichi Sankyo's delta-adjusting PMM analyses showed that the required penalty for loss of statistical significance was a worsening of an average of 16% for patients who discontinued and 8% for patients with missing data who completed Part 1. FDA's delta-adjusting PMM analyses showed that the required penalty for loss of statistical significance was an average worsening of 12% for patients with missing data in the pexidartinib arm. Additional FDA sensitivity analyses assuming varying levels of ROM worsening for missing data in both the pexidartinib and placebo arms provided results consistent with those presented in Table 75.

Table 75. Sensitivity Analysis for Missing Data of ROM

	Pexidartinib N=61 LS Mean (95% CI)	Placebo N=59 LS Mean (95% CI)	Difference from Placebo LS Mean (95% CI)
Primary results (MMRM)[*1,2]	15.1 (10.9, 19.2)	6.2 (1.5, 10.9)	8.9 (2.9, 14.9)
Unconditional reference[**]	14.0 (9.7, 18.2)	5.0 (0.1, 10.0)	8.9 (2.8, 15.1)
Copy reference[**]	14.0 (9.8, 18.2)	5.1 (0.2, 10.1)	8.9 (2.7, 15.0)
Tipping point analysis: Delta-adjusting PMM Pexidartinib penalty = -16% (-8%)[**]	11.6 (7.0, 16.1)	5.1 (-0.1, 10.3)	6.4 (-0.1, 13.0)
FDA tipping point analysis: Delta-adjusting PMM Pexidartinib penalty = -12%	12.1 (7.7, 16.5)	6.2 (1.3, 11.1)	5.9 (-0.3, 12.2)

Sources: [*]Reviewer generated table – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant),[**]Applicant analyses
[1] Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, joint type, treatment by visit interaction, baseline by visit interaction, treatment by joint type interaction, baseline by joint type interaction
[2] 32 (27%) patients missing at Week 25

Reviewer Comment: *In general, sensitivity analyses based on the missing not at random (MNAR) assumption rely on strong untestable assumptions and are considered exploratory. Based on the pre-specified and sensitivity analyses (Table 75), the estimated within-patient ROM improvement from baseline in the pexidartinib arm ranged from 7% to 19%.*

Establishing Clinically Meaningful Within-Patient Change: ROM

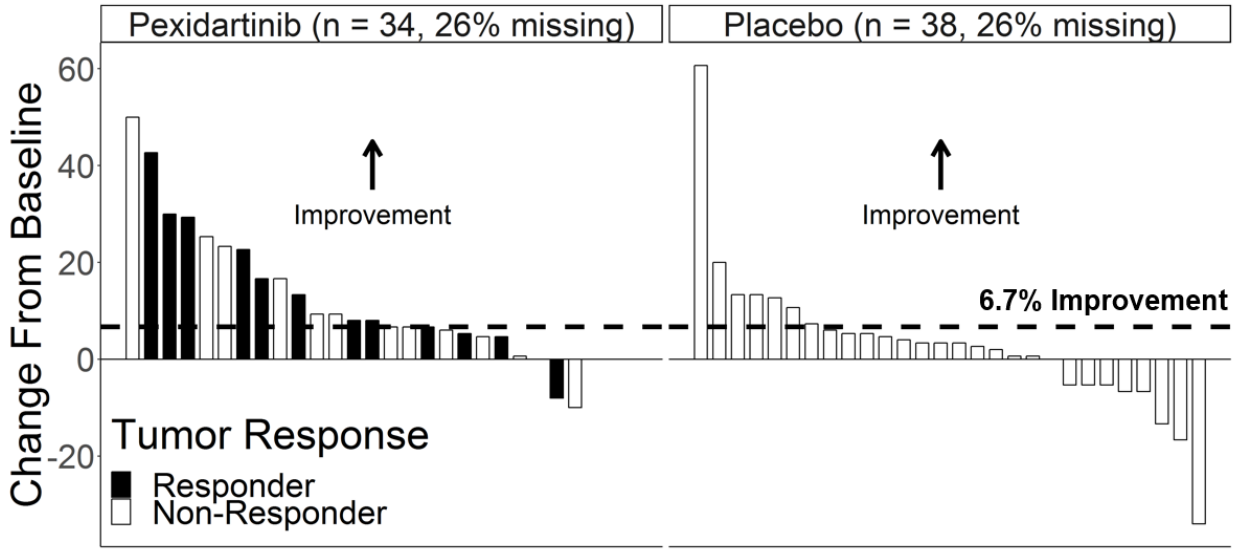
Daiichi Sankyo proposed that a +6.7% threshold for what constitutes a clinically meaningful within-patient change in ROM for the knee only. The normal range of motion for the knee is 150 degrees, so a 6.7% improvement corresponds to a 10-degree improvement for the knee.

The American Medical Association (AMA) Guide to Evaluation of Permanent Impairment Sixth Edition defines knee ROM impairment by the amount of knee flexion (i.e., mild impairment is 80-109 degrees, moderate impairment is 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.

Figure 11 shows the waterfall plot of change from baseline in ROM at Week 25 for patients whose tumor location was at the knee. Assuming a 6.7% threshold represents clinically meaningful functional improvement, 41% of patients in the pexidartinib arm and 18% of patients in the placebo arm had a clinically meaningful improvement in ROM at the knee.

Figure 11. Waterfall Plot of Change From Baseline at Week 25 in ROM of the Knee



Reviewer Comment: *The Applicant stated that a threshold was proposed for the knee only because there is no widely used standard of improvement in ROM for other joints as it depends on the specific joint as well as the degree of impairment at baseline. Due to limited justification, it remains unclear whether a 6.7% improvement represents a clinical benefit to patients whose tumor is located at the knee. However, Figure 11 shows that more patients achieved clinically meaningful functional improvement from pexidartinib compared to placebo using the 6.7% threshold. This trend was observed for a range of thresholds for clinical meaningfulness.*

An anchor-based approach to establish a threshold(s) of clinical meaningfulness was not feasible due to the substantial amount of missing data in other COA endpoints and global scales.

Based on the pre-specified and sensitivity analyses (Table 134), the estimated within-patient ROM improvement for the knee in the pexidartinib arm ranged from 6% to 19%.

8.2. PLX108-01

8.2.1. Study Design

Trial Design

PLX108-01 was a single arm, open-label, multicenter dose-escalation, dose expansion trial of pexidartinib designed to evaluate safety, tolerability, PK and pharmacodynamic (PD) activity of ascending doses of pexidartinib in patients with solid tumor. PLX108-01 included a dose escalation phase in which a recommended Phase 2 dose was selected, and an Extension cohort phase with additional patients who received pexidartinib at the RP2D. The Extension cohort phase included the following 6 cohorts:

- Mucoepidermal carcinoma (MEC) of the salivary gland
- Pigmented villonodular synovitis (PVNS)
- Gastrointestinal stromal tumor (GIST)
- Anaplastic thyroid carcinoma (ATC)
- Solid tumors with document malignant pleural of peritoneal effusions
- Miscellaneous tumor tumors for which a scientific rationale exists for treatment with pexidartinib

Patients in the Extension cohorts were treated at 1000 mg/day divided twice daily. Patients were followed every 8 weeks for safety and tumor response as assessed by CT scan. Approximately 10 patients were to be enrolled in each of the Extension cohorts and up to 20 patients in the miscellaneous Extension cohort, for a total of approximately 70 patients with the possibility of 30 additional patients in a specific cohort if necessary. Participants were to remain on treatment until tumor progression, as long as there were no unacceptable toxicities.

The TGCT cohort included patients who had a histologically confirmed diagnosis of inoperable progressive or relapsing TGCT or resectable tumor requiring mutilating surgery as well as demonstrated progressive disease in the last 12 months. Patients were enrolled and followed for safety and tumor response. The TGCT cohort was enlarged to include a total of 39 patients.

Eligibility Criteria

Inclusion criteria:

1. Male or female patients ≥18 years old
2. For the dose escalation cohorts, patients with advanced, incurable, solid malignancies in which the target kinases are thought to be linked to disease pathophysiology and whose cancers are confirmed histologically. The tumors must fulfill both of the following criteria:
    a. refractory to standard therapy, or standard or curative therapy does not exist or is not considered appropriate by the investigator, and
    b. tumor proliferation or metastasis could be driven or promoted in part by Flt3, Kit, or Fms/CSF-1 activity.

3. For the Extension cohorts, patients must have measurable disease by RECIST criteria and meet the following disease-specific criteria:
    a. For PVNS (including tenosynovial giant cell tumor), patients must have a histologically confirmed diagnosis of inoperable progressive or relapsing PVNS, or resectable tumor requiring mutilating surgery, as well as demonstrated progressive disease in the last 12 months
4. All associated toxicity from previous or concurrent cancer therapy must be resolved (to ≤ Grade 1 or Baseline) prior to administration of PLX3397.
5. ECOG performance status 0 or 1.
6. Life expectancy ≥3 months.
7. Adequate hematologic, hepatic, and renal function (absolute neutrophil count ≥1.5 x 10^9/L, Hgb >9 g/dL, platelet count ≥100 x 10^9/L, AST/ALT ≤2.5x ULN or <5x ULN in the presence of liver metastases, albumin ≥3 g/dL, creatinine ≤1.5x ULN or calculated CrCl >60 mL/min using Cockcroft-Gault formula).

Exclusion Criteria

1. Specific anti-cancer therapy within 3 weeks prior to study drug administration.
2. Investigational drug use within 28 days of the first dose of PLX3397.
3. Uncontrolled intercurrent illness.
4. Refractory nausea and vomiting, malabsorption, external biliary shunt, or significant small bowel resection that would preclude adequate absorption.
5. QTcF ≥450 msec (for males) or ≥470 msec (for females) at screening.
6. The presence of a medical or psychiatric condition that, in the opinion of the Principal Investigator, makes the patient inappropriate for inclusion in this study.

Reviewer Comment: *The eligibility criteria for Study PLX108-01 are similar to those of the ENLIVEN trial. The most notable difference is that patients with TGCT did not have to be symptomatic and must have progressed in the last 12 months to be enrolled in Study PLX108-01, while in the ENLIVEN trial, patients must have been symptomatic and there was no requirement for recent progression. Both of these trials required that patients have disease that was inoperable or disease wherein surgery would result in worsening physical function; this reviewer concludes that these differences in the eligibility criteria will not likely render a pooled efficacy analysis uninterpretable.*

Dose Modification and Management Guidelines

Reducing or interrupting the dose for toxicity could take place at time during the dose extension cohorts according to the following guidelines (Table 76).

Table 76. Dose Modifications, Excluding Hepatic Toxicities, PLX-108-01: Neutropenia

Toxicity Grade (CTCAE v4)	PLX3397 Dose Changes During Current Treatment Period	Dose Adjustments for Resumption of Treatment
HEMATOLOGIC TOXICITY		
Grade 3 or Grade 4 neutropenia		
1st Appearance	Interrupt until ANC recovers	Once recovered to ANC $\geq 1\times10^9$/L, resume at same dose. If ANC does not recover to $\geq 1\times10^9$/L after 7 days, reduce dose by 200 mg.
2nd Appearance	Interrupt until ANC recovers	Once resolved to ANC $\geq 1\times10^9$/L, reduce dose by 200 mg. If ANC does not recover to $\geq 1\times10^9$/L after 7 days, reduce dose by an additional 200 mg.
3rd Appearance	Interrupt until ANC recovers	If ANC does not recover to $\geq 1\times10^9$/L after 14 days, discontinue permanently.
Grade 3 or Grade 4 febrile neutropenia		
1st Appearance	Interrupt until ANC and fever recover; provide growth factor support if clinically appropriate	Once resolved to ANC $\geq 1\times10^9$/L and T $\leq$38˚C, reduce dose by 200 mg.
2nd Appearance	Interrupt until ANC and fever recover; provide growth factor support if clinically appropriate	Once resolved to ANC $\geq 1\times10^9$/L and T $\leq$38˚C, reduce dose by an additional 200 mg.
3rd Appearance	Discontinue permanently	N/A

ANC = absolute neutrophil count;
CTCAE = Common Toxicity Criteria for Adverse Events;
T = temperature

Source: PLX108-01 Protocol Version 11 dated October 22, 2018

Table 77. Dose Modifications, Excluding Hepatic Toxicities, PLX-108-01: Thrombocytopenia and Non-Hematologic Toxicity

Toxicity Grade (CTCAE v4)	PLX3397 Dose Changes During Current Treatment Period	Dose Adjustments for Resumption of Treatment
Grade 4 thrombocytopenia		
1st Appearance	Interrupt until PLT $\geq 75\times10^9$/L	Reintroduce at same dose
2nd Appearance	Interrupt until PLT $\geq 75\times10^9$/L	Reduce dose by 200 mg
3rd Appearance	Interrupt until PLT $\geq 75\times10^9$/L	Reduce dose by an additional 200 mg
4th Appearance	Discontinue permanently	N/A
NON-HEMATOLOGIC TOXICITY		
Related Grade 3 (excluding transaminase increases [see below]): start symptomatic treatment when possible		
1st Appearance	Interrupt until resolved (grade 0–1)	Reduce by 200 mg if symptoms persist for ≥5 days despite supportive management
2nd Appearance	Interrupt until resolved (grade 0–1)	Reduce by an additional 200 mg
3rd Appearance	Discontinue permanently	N/A
Related Grade 4 (excluding transaminase increases [see below]): start symptomatic treatment when possible		
1st Appearance	Interrupt until resolved (grade 0–1)	Reduce by 200 mg
2nd Appearance	Discontinue permanently	N/A
Transaminase Increases (See Table 3 and Table 4)		
Prolonged QTcF		
QTcF >500 msec on at least 2 separate ECGs (i.e., Grade 3).	Hold PLX3397 until recovery to QTcF ≤500 msec	Upon recovery to QTcF ≤500 msec (Grade ≤2), restart at a reduced dose (minimum reduction decrement of 200 mg). Monitor ECG and electrolytes, including potassium, magnesium, and calcium, after dose modification of PLX3397 for QTcF prolongation
QTcF interval remains >500 msec and increased >60 msec from pretreatment values after controlling cardiac risk factors for QT prolongation (e.g., electrolyte abnormalities, congestive heart failure, and bradyarrhythmias).	Permanently discontinue PLX3397	N/A.

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CTCAE = Common Toxicity Criteria for Adverse Events; INR = international normalized ratio; N/A = not applicable; PLT = platelets; QTcF = QT invertval corrected using Fridericia's formula; T = temperature; ULN = upper limit of normal.

Source: PLX108-01 Protocol Version 11 dated October 22,2018

Table 78 displays the specific dose modification guidelines for liver function abnormalities from the last version of the protocol dated October 22, 2018.

Table 78. Dose Modification Guidelines for Liver Function Abnormalities

Toxicity Grade CTCAE v4	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[b] 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); no increase in bilirubin[a]	Re-check ALT and AST immediately. Hold study drug. Monitor 2×/wk.[2] Check for changes to medications and for symptoms.	Resolution to Grade 0-1 or baseline (no bilirubin increase) within 14 d. ALT and AST not decreasing within 14 d of holding study drug.	Restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule). *Proceed to liver evaluation*.[3] Restart only on resolution to Grade 0-1/baseline at 1 dose lower (reduce by one 200 mg capsule). For max AST or ALT >8x ULN, consult with Medical Monitor prior to re-start.
Grade 4 ALT or AST (>20x ULN)	Discontinue treatment. Monitor 2×/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. *Proceed to liver evaluation*.[3] 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[1] with any bilirubin increase or signs of hypersensitivity	Discontinue treatment. Monitor 2×/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. *Proceed to liver evaluation*.[3] If clear confirmed alternate cause, restart on resolution to Grade 0-1 or baseline at 1 dose lower (reduce by one 200 mg capsule).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.
[1] Increase in bilirubin is defined as all of the following: total bilirubin > ULN, total bilirubin >20% above baseline, & direct bilirubin is > ULN. If all these conditions are met, bilirubin should be immediately re-checked. Pexidartinib treatment should be immediately discontinued for increased bilirubin unless and until there is a clear, confirmed alternate cause.
[2] If ALT, AST, or bilirubin worsens during the monitoring period, follow the applicable guidance for the worst toxicity grade.
[3] See protocol specified Liver Evaluation Guidelines below.
Source: PLX108-01 Protocol Version 11 dated October 22,2018

Study Endpoints

The primary objective for the dose escalation phase was to evaluate the safety and PK of pexidartinib. The primary efficacy endpoint of the extension phase was ORR per RECIST v1.1 as assessed by investigator every eight weeks.

Statistical Analysis Plan

Since the primary objective was safety, the study was not powered for ORR. The maximum sample size for each cohort was 40 patients. The analysis of ORR was descriptive based on

patients who received at least one dose of pexidartinib. The exact method was used to estimate the two-sided 95% CI for ORR.

8.2.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated in the NDA clinical study report for the ENLIVEN trial that the study was conducted in accordance with:

1. Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2. The International Conference on Harmonisation (ICH) Good Clinical Practices (GCP) Guidelines [E6]
3. Applicable laws and regulations
4. The protocol
5. Food and Drug Administration (FDA) GCP guidelines, FDA Financial Disclosure regulations

Financial Disclosure

The Applicant submitted a list of investigators (Refer to NDA Module 1.3.4, Attachment 1) and FDA form 3454 certifying that all of the investigators listed in Attachment 1 had no financial arrangements as defined in 21 CFR 54.2 (a, b, and f) that could affect the outcome of the trial. No financial disclosures were submitted for any investigator in this NDA. See Section 19.2 Financial Disclosure.

Patient Disposition

The data cut-off date for analysis of Study PLX108-01 was March 3, 2017. The first patient was enrolled on November 16, 2011, and the last patient was enrolled on June 5, 2015.

Disposition for patients in Study PLX108-01 was generally similar to that observed in the ENLIVEN trial. Table 79 displays the disposition for patient enrolled in Study PLXC108-01.

Table 79. Patient Disposition in Study PLX108-01

Disposition	TGCT N=39 n (%)
Discontinued	24 (62)
Adverse Event	12 (31)
Progressive Disease	4 (10)
Patient noncompliance	4 (10)
Patient decision	2 (5)
Lost to follow-up	1 (2.6)
Other	1 (2.6)

Source: Reviewer generated table – summarizing subject level analysis and exposure datasets (ADSL and ADEX, March 3, 2017 data cut-off date, submitted by Applicant)

Table of Demographic Characteristics

Table 80 displays the baseline demographics for patients with TGCT enrolled in Study PLX108-01.

Table 80. Patient Demographic Factors in Study PLX108-01

Characteristic	TGCT Patients Treated with Pexidartinib N=39 n (%)
Sex	
Female	22 (56)
Male	17 (44)
Age	
Mean years (SD)	45.1 (14.0)
Median years (Range)	42.0 (22, 80)
18 to 41 years	15 (38)
42 to 65 years	22 (56)
≥65 years	2 (5)
Race	
White	33 (85)
Black or African American	3 (8)
Asian	3 (8)
Ethnicity	
Not Hispanic or Latino	35 (90)
Hispanic/Latino	4 (10)
Region	
United States	39 (100)

Source: Reviewer generated table – summarizing subject level analysis datasets (ADSL, March 3, 2017 data cutoff date submitted by Applicant)

Reviewer Comment: *The baseline demographics for patients with TGCT enrolled in Study PLX108-01 were generally similar to the ENLIVEN trial.*

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 81 displays the baseline disease characteristics for the patients with TGCT enrolled in Study PLX108-01.

Table 81. Patient Baseline Disease Characteristics Study PLX108-01

	TGCT Patients Treated with Pexidartinib N=39 n (%)
Extremity Involvement	
Upper	3 (8)
Forearm	1 (2.5)
Wrist	1 (2.5)
Elbow	1 (2.5)
Lower	36 (92)
Knee	21 (54)
Hip	7 (18)
Ankle/Foot	7 (18)
Gastrocnemius muscle	1 (2.5)
Prior Surgery	31 (79)
Priory Systemic Therapy	
Kinase Inhibitor	4 (10)
Other	2 (5)

Source: Reviewer generated table – summarizing subject level analysis datasets (ADSL, March 3,2017 data cutoff date submitted by Applicant)

Reviewer comment: *The baseline disease characteristics for patients with TGCT enrolled in Study PLX108-01 were generally similar to the ENLIVEN trial. There were a similar proportion of patients with lower extremity versus upper extremity involvement as well as a similar proportion of patients who had received prior systemic therapy. Similar to patients enrolled in the ENLIVEN trial, the TGCT cohort in Study PLX108-01 was more likely to have had at least one prior surgery prior to receiving pexidartinib.*

Efficacy Results - Primary Endpoint

Table 82 displays the efficacy results for Study PLX108-01.

Table 82. Analysis of ORR Per Investigator Assessment, ITT Population, PLX108-01

	TGCT Cohort N=39
Overall Response Rate	
ORR, n (%)	23 (59%)
(95% CI)	(42%, 74%)
Duration of Response	
Median (months)	NR
Range	(1.8+, 53.2+)

Source: Reviewer Generated table summarizing response analysis (ADRS, March 2, 2017 data cut-off date, submitted by Applicant) and time to event analysis datasets (ADTTE, January 31, 2018 data cut-off date, submitted by Applicant)

Reviewer comment: *The effect observed from the primary analysis of ORR in the TGCT Cohort was comparable to the effect observed in ENLIVEN.*

8.2.3. Integrated Assessment of Effectiveness

The primary efficacy outcome measure in ENLIVEN was overall response rate (ORR) at Week 25 as assessed by blinded independent central review (BICR) according to the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. ENLIVEN was designed to enroll a total of 126 patients to provide 90% power to detect a difference in ORR at a two-sided alpha level of 0.05, assuming an ORR of 10% in the placebo arm and an ORR of 35% in the pexidartinib arm.

ENLIVEN enrolled a total of 120 patients (pexidartinib arm n=61; placebo arm n=59). The study population was 59% female, and 88% White. The median age was 45 years (range: 18-79) and 63% of patients were enrolled ex-US. Tumor distribution was as follows: 8% of patients had upper extremity involvement, and 92% of patients had lower extremity involvement.

Table 83 summarizes the primary efficacy results of ORR at Week 25 of the ENLIVEN trial and PLX108-01.

Table 83. Major Efficacy Analysis Results

	Pexidartinib[a] N=61	PLX108-01[b] N=39
Overall Response Rate (ORR) at Week 25 per RECIST v1.1		
ORR (%)	38%	49%
(95% CI)	(26%, 50%)	(34%, 64%)
P-value[c]	<0.0001	NA
Duration of Response (DOR)[d]		
Range	(6.9+, 24.9+)	(1.8+, 53.2+)
DOR ≥6 months	22/23	12/15
DOR ≥12 months	13/13	12/14

Source: Reviewer generated table – summarizing ENLIVEN response analysis dataset (ADRS, January 31, 2018 data cutoff date), and time to event analysis dataset (ADTTE, January 31, 2018 data cutoff date) and PLX108-01 response analysis dataset (ADRS, March 2, 2017 data cut-off date), and time to event analysis dataset (ADTTE, March 2, 2017 data cutoff date).
[a] Response evaluated by BICR
[b] Response evaluated by investigator
[c] Compared to placebo arm in which no responses were observed 0% (95% CI: 0, 6),
[d] Number of patients with ongoing DOR/Number of patients on follow-up for specified time (have not yet been censored

The primary efficacy analysis for ENLIVEN was pre-specified at a landmark of 25 weeks. As seen Table 84 in with follow-up until January 31, 2018 for ENLIVEN and March 2, 2017 for PLX-108-01, increased tumor response rates were seen in all cohorts, including patients who crossed-over from placebo to pexidartinib in ENLIVEN. Pooled data are not presented in Table 84 due to the differences in how the primary endpoint was evaluated between ENLIVEN and PLX108-01 (BICR versus investigator assessment).

Table 84. Overall Response Rate With Longer Follow up

	ENLIVEN Pexidartinib Part 1 and 2[a] N=61	ENLIVEN Crossover Part 2[a] N=30	PLX108-01 TGCT Cohort[b] N=29
Confirmed ORR (95% CI)	52% (40, 64)	53% (36, 70)	62% (45, 77)

Source: Reviewer generated table – summarizing ENLIVEN response analysis dataset (ADRS, January 31, 2018 data cutoff date), and time to event analysis dataset (ADTTE, January 31, 2018 data cutoff date) and PLX108-01 response analysis dataset (ADRS, March 2, 2017 data cut-off date), and time to event analysis dataset (ADTTE, March 2, 2017 data cutoff date).
[a] Response evaluated by BICR
[b] Response evaluated by investigator

Due to the slow-growing nature of TGCT, ENLIVEN was designed with clinical outcome assessments as secondary endpoints to assess TGCT-specific symptoms and functional impacts. ENLIVEN demonstrated a statistically significant improvement in mean change from baseline to Week 25 for those patients who were randomized to pexidartinib compared to those who were randomized to placebo for the COA secondary endpoints of ROM, physical function, and worst stiffness. However, the proportion of patients with missing data for ROM, physical function, and worst stiffness was significant at 27%, 43%, and 43%, respectively; the proportion of patients missing data for these endpoints was similar across study arms, with differences in the reasons for missing data. Only clinician-reported ROM was included in the evaluation of efficacy for pexidartinib. Overall, the analyses show that there appears to be a treatment benefit of pexidartinib on ROM, but that the magnitude is not clear and the estimated within-patients ROM improvement in the pexidartinib arm ranged from 7 to 19%.

TVS was defined in ENLIVEN as the estimated volume of the maximally distended synovial cavity or tendon sheath involved, measured in 10% increments. ORR by TVS was 56% (95% CI: 43%, 67%) in patients randomized to the TURALIO arm and 0% in patients randomized to the placebo arm; p<0.0001.

Reviewer Comment*: Although TVS is an endpoint which has not been validated as a surrogate for any of the established endpoints for clinical benefit claims in oncology, and has not yet been used as an endpoint reasonably likely to predict clinical benefit in oncology patients, , there is emerging evidence suggesting that it may be a reasonable way to assess anti-tumor activity in certain tumor types (e.g. tumors that track along compartment walls such as the pleural or intra-articular space which may be less amenable to response criteria that rely on the sum of the diameters of target lesions). The analysis of ORR by TVS demonstrated a statistically significant difference between the pexidartinib and placebo arms. FDA considered the results of the ORR by TVS score to be supportive of the anti-tumor activity of pexidartinib in patients with TGCT.*

8.3. Review of Safety

8.3.1. Safety Review Approach

The clinical review of safety of pexidartinib in patients with TGCT which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery was primarily based on the ENLIVEN trial. The majority of the safety evaluation is based on the first 25 weeks of treatment to allow for comparison between the 61 patients randomized to pexidartinib and the 59 patients randomized to placebo. A detailed description of the aspects of the ENLIVEN trial that are relevant to safety assessment (i.e., eligibility criteria, toxicity monitoring and management guidelines, and relevant modifications of the protocol) are provided in section 8.1.1 PLX108-10 (ENLIVEN). In order to better understand the safety of pexidartinib in the indicated population, a review of adverse events, laboratory assessments, and patient narratives was completed for all patients with TGCT treated with pexidartinib. This included an additional 30 patients from the ENLIVEN trial who crossed over from placebo in Part 1 of ENLIVEN, to receive pexidartinib in Part 2, and 39 patients from Study PLX108-01, a dose escalation and dose extension study.

To support the safety evaluation, the Applicant also submitted a safety database comprised of 630 pexidartinib-treated patients enrolled in commercial- sponsored trials, and 138 pexidartinib-treated patients enrolled in investigator- initiated trials for whom summary safety data were provided. In the studies comprising this pooled database, patients received pexidartinib as a single agent or in combination with other therapies. Table 85 lists all studies included in the pooled safety analysis population; this pooled population includes 174 patients with malignant solid tumors, and 90 patients with acute myeloid leukemia (AML) who received pexidartinib as monotherapy at a variety of doses and 236 patients with malignant solid tumors who received pexidartinib in combination with other anti-neoplastic therapies. In addition, the Applicant provided summary information on 138 patients with both solid and hematologic malignancies who received pexidartinib in investigator-initiated studies.

Table 85. Studies to Support Safety

Study	Pexidartinib N=768	Disease Type
Studies in patients with TGCT		
PLX108-10 (ENLIVEN)	91	TGCT
PLX108-01 (TGCT Cohort)	39	TGCT
Studies of pexidartinib monotherapy in patients with solid tumors and AML		
PLX108-01 (non-TGCT cohort)	93	Non-TGCT solid tumors
PLX108-03	20	Hodgkin's lymphoma
PLX108-04	38	Glioblastoma multiforme (GBM)
PLX108-05	90	AML
PLX108-06	6	Prostate Cancer
PLX108-13	6	KIT-mutant melanoma
PL3397-A-A103	11	Solid Tumors
Studies of pexidartinib in combination with other therapies		
PLX108-07	68	+paclitaxel in solid tumors
PLX108-08	65	+temozolomide, radiation in GBM
PLX108-09	13	+vemurafenib BRAF mutant melanoma
PLX108-14	78	+pembrolizumab in solid tumors
PLX121-01	12	+PLX9486 in solid tumors
Investigator initiated studies		
Investigator initiated studies (8)	138[a]	Solid and hematologic tumors

Source: Reviewer generated table based upon Table 1.1 of Summary of Clinical Safety
[a] The pooled safety population (TGCT and non-TGCT; n=630) only includes patients exposed to pexidartin b in commercial-sponsored trials, and therefore excluded these 138 patients.

8.3.2. Review of the Safety Database

The median duration of exposure to pexidartinib for patients enrolled in ENLIVEN (n=91) and in Study PLX108-01 (n=39) was 43 weeks or 10 months (range: 2 to 211 weeks [49 months]). Refer to Table 86 for exposure by small time interval across both studies, and in the total TGCT population. A majority of patients in ENLIVEN (68%) were exposed to pexidartinib for 6 or more months; no patients received pexidartinib for up to 2 years.

Table 86. Duration of Exposure to Pexidartinib for All TGCT Patients

Study Drug Exposure	ENLIVEN Trial N=91 n (%)	Study PLX108-01 N=39 n (%)	All TGCT Patients N=130 n (%)
2 days to 1 month	4 (4.4)	3 (8)	7 (5)
>1 month to 3 months	6 (7)	1 (2.6)	7 (5)
>3 months to 6 months	19 (21)	3 (8)	22 (17)
>6 months to 9 months	21 (23)	5 (13)	26 (20)
>9 months to 12 months	27 (30)	5 (13)	32 (25)
>12 months to 18 months	13 (14)	4 (10)	17 (13)
>18 months to 24 months	1 (0.8)	2 (5)	3 (2.3)
>24 months	0	16 (41)	16 (12)

Source: Reviewer generated table summarizing ENLIVEN and PLX108-01 subject level analysis exposure analysis datasets (ADSL and ADEX, March 27, 2017 data cutoff date, submitted by Applicant) and PLX108-01 subject level analysis and exposure analysis datasets (ADSL and ADEX, March 3, 2017 data cutoff date, submitted by Applicant)

The duration of exposure in the patients who received pexidartinib as monotherapy in the supportive safety database was shorter than that observed in the TGCT population in ENLIVEN and in Study PLX108-01. Among the 274 non-TGCT patients treated with pexidartinib as a single agent, the median duration of exposure was 7.9 weeks (1.8 months) with a range of ≤1 day to 82 weeks (19 months).

Reviewer Comment: *At the time of data cut off of March 27, 2017, only 19 patients had been treated for more than 18 months and only 16 patients had been treated for more than two years. The 120-day safety updated provided some information about longer exposure, please see Table 108. Patients with TGCT will likely be exposed to pexidartinib as a chronic medication and the exposure in TGCT patients in this application does not provide a comprehensive evaluation for what will happen with long term exposure to pexidartinib.*

Relevant characteristics of the safety population:

Table 87 summarizes the demographics for the TCGT population. Baseline demographics were similar between patients randomized to pexidartinib in Part 1 of ENLIVEN and pooled TGCT population. For details of the demographic data for the randomized portion of ENLIVEN see Table 62.

Table 87. Demographics of Patients With TGCT Treated With Pexidartinib

Characteristic	Randomized to Pexidartinib in ENLIVEN N=61 n (%)	Pooled Pexidartinib TGCT Patients N=130 n (%)
Sex		
Female	35 (57)	73 (56)
Male	26 (43)	57 (44)
Age		
Mean years (SD)	44.6 (13.2)	45.5 (13.4)
Median years (range)	44.0 (22, 75)	45 (36, 55)
<50 years	39 (64)	84 (65)
≥50 years to <65 years	18 (30)	38 (29)
≥65 years	4 (7)	8 (6)
Race		
White	52 (85)	115 (89)
Black or African American	3 (4.9)	6 (4.6)
Asian	1 (1.6)	4 (3.1)
American Indian or Alaska Native	2 (3.2)	2 (1.5)
Native Hawaiian or other Pacific Islander	2 (3.2)	2 (1.5)
Other	1 (1.6)[a]	1 (0.8)

Source: Reviewer generated table – summarizing ENLIVEN subject level analysis dataset (ADSL, March 27, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment: *Based on review of the literature, the key demographic features of age, race, and gender from ENLIVEN are similar to the general TGCT population.*

Adequacy of the safety database:

The data submitted in support of the safety evaluation of pexidartinib in the indicated population from ENLIVEN and Study PLX108-01 was accurate in representation of investigator-submitted information including CRFs and narratives, complete with limited missing data and information, generally accessible in organization, internally consistent, and thorough in scope of assessments and collected information.

For the broader safety database, the commercially sponsored trials submitted as supportive safety information include Legacy Clinical Study Reports and datasets, biopsy reports and narrative when available, as well as pooled safety analysis. For the investigator-initiated trials, the Applicant provided study reports and narratives and liver biopsy reports when applicable. These submissions were also accurate, internally consistent, and provided supportive

information about the safety of pexidartinib. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

For ENLIVEN and PLX108-01, the Applicant submitted SDTM and ADAM data sets. ADAM datasets were primarily used for analysis and the key derived variable were checked. This reviewer found that the derived flags and variables were correct and consistent with the define file definitions.

For the commercially sponsored trials, the Applicant provided legacy data sets and summary data in the integrated summary and for the investigator-initiated trials legacy study reports were provided.

Categorization of Adverse Event

The Applicant used the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1 to map the AETERM term reported by an Investigator on a CRF to the MedDRA AEDECOD term. The reviewer evaluated the accuracy of the coding performed by the Applicant by direct comparison of the AETERM term to the AEDECOD term for the 1636 adverse events (AEs) from ENLIVEN submitted with the application and 712 of the AETERMS matched the AEDECOD exactly. This reviewer manually analyzed the remaining 924 terms and found that, with few exceptions, the coding was consistent and appropriate. The reviewer identified 2 AEs (<0.1% of all AEs) in which the coding appeared incorrect. One was in the placebo arm and one was in the pexidartinib arm and neither was considered related to study drug by the investigator nor resulted in an action with the study drug. These differences in coding are unlikely to affect the overall risk assessment of pexidartinib.

The protocol for ENLIVEN defined a treatment emergent adverse event (TEAE) as an AE that occurred on or after the date of the first exposure to study drug or placebo, before the data cutoff, and within 28 days (inclusive) of the date of last exposure to study drug or placebo.

Routine Clinical Tests

Refer to Section 8.3.3 (laboratory assessment) and (ECG) for discussion on the adequacy of hematology monitoring, chemistry monitoring, vital signs, and ECG monitoring during ENLIVEN. Refer to Section 19.5 for full schedule of events for ENLIVEN.

Reviewer Comment: *The clinical monitoring specified in the ENLIVEN trial (laboratory parameters, clinical examinations, vital signs) appears appropriate to monitor the safety of pexidartinib.*

8.3.3. Safety Results

Deaths

There was one death on ENLIVEN (Part 1 and Part 2). The death occurred in a patient who was initially randomized to receive placebo in Part 1 or ENLIVEN and who also continued to receive pexidartinib in Part 2; the death was due to cardiac arrest and was assessed as being unrelated to the study drug. A summary of the narrative provided by the Applicant is below.

Patient Narrative

- 79-year-old white male randomized to placebo in Part 1 of ENLIVEN. The patient's past medical history included atrial fibrillation, first degree heart block, thoracic aortic aneurysm, ascending aortic aneurysm, carotid artery atherosclerotic disease, hypertension, pericardial effusion, venous insufficiency, and sleep apnea. His concomitant medications included losartan, sotalol, paracetamol, oxycodone, and apixaban. The patient completed Part 1 of ENLIVEN with no adverse events. Upon completion of Part 1 of ENLIVEN, the patient crossed over and received pexidartinib 800 mg daily. Eight days after initiating pexidartinib, the patient was noted to have an AST 1.4× ULN (an increase from his baseline prior to initiating pexidartinib) with normal ALT and total bilirubin. Peak laboratory values were ALT 4.7× ULN, AST 2.7× ULN, ALP 1.8× ULN, and total bilirubin within normal limits. Pexidartinib was interrupted on Day 57 of treatment and restarted on Day 64 at a reduced dose. ALT and ALP normalized, and AST improved to 1.3× ULN. On day 297 of pexidartinib the patient was still taking 600 mg daily of pexidartinib and presented to the emergency room due to chest pain. Upon arrival the patient lost consciousness and experienced a cardiac arrest. Resuscitative measures were undertaken (norepinephrine and chest compressions) resulting in a palpable pulse. An ultrasound of the heart showed pericardial effusion in the setting of a Type A aortic dissection. The patient underwent pericardiocentesis however, the patient's pulse was lost. Prolonged and intensive cardiopulmonary resuscitation was performed on the patient, however, after 30 minutes without a pulse, care was withdrawn. The patient died of cardiac arrest. The cause of death was considered to be aortic dissection.

Reviewer Comment*: Based upon the review of the narrative, this reviewer agrees that the death described above was not likely related to treatment with pexidartinib.*

Serious Adverse Events

A total of 8 (13%) of patients in the pexidartinib arm and 1 (1.7%) patient in the placebo arm experienced non-fatal serious adverse events (SAEs) during the first 25 weeks of ENLIVEN. As displayed in Table 88, the majority of the SAEs experienced by patients in the pexidartinib arm were related to hepatotoxicity.

Table 88. SAEs in the First 25 Weeks of Treatment, ENLIVEN

	Randomized to Pexidartinib N=61		Randomized to Placebo N=59	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	8 (13.1)	7 (11.5)	1 (1.7)	1 (1.7)
Investigations				
Liver function test abnormality	2 (3.3)	2 (3.3)	0	0
Increased transaminases	1 (1.6)	1 (1.6)	0	0
Hepatic enzymes abnormal	1 (1.6)	1 (1.6)	0	0
Hepatobiliary disorders				
Hepatotoxicity[a]	2 (3.3)	2 (3.3)	0	0
Infections and infestations				
Hepatitis A	1 (1.6)	0	0	0
Hepatitis E	1 (1.6)	0	0	0
Skin and subcutaneous disorders				
Rash	1 (1.6)	1 (1.6)	0	0
Nervous system disorders				
Migraine	1 (1.6)	1 (1.6)	0	0
Neoplasms, benign and malignant				
Endometrial cancer	0	0	1 (1.7)	1 (1.7)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Includes PT terms of liver disorder and hepatotoxicity

Reviewer Comment: *This analysis of SAEs for both Part 1 of ENLIVEN and for all TGCT patients treated with pexidartinib reveals that the most common SAE are related to hepatotoxicity (refer to Section 8.3.4 Analysis of Submission-Specific Safety Issues for further evaluation of hepatotoxicity).*

Table 89 summarizes the SAEs for patients in the pooled TGCT population (n=130).

Table 89. SAEs for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61			ENLIVEN Crossover Part 2 N=30			Pooled Pexidartinib TGCT Patients N=130		
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**Grade 5 n (%)**
All patients with adverse event	9 (15)	9 (9.9)	0	3 (10)	1 (3.3)	1 (3.3)	16 (12)		
Investigations									
Liver function test abnormality	2 (3.3)	2 (3.3)	0	0	0	0	2 (1.5)	2 (1.5)	0
Increased transaminases	1 (1.6)	1 (1.6)	0	0	0	0	1 (0.8)	1 (0.8)	0
Hepatic enzymes abnormal	1 (1.6)	1 (1.6)	0	0	0	0	1 (0.8)	1 (0.8)	0
Skin and subcutaneous disorders									
Rash[a]	2 (3.3)	1 (1.6)	0	0	0	0	2 (1.5)	1 (0.8)	0
Cardiac disorders									
Cardiac arrest	0	0	0	1 (3.3)	0	1 (3.3)	1 (0.8)	0	1 (0.8)
Hepatobiliary disorders									
Hepatotoxicity[b]	2 (3.3)	2 (3.3)	0	0	0	0	2 (1.5)	2 (1.5)	0
Cholecystitis	0	0	0	0	0	0	1 (0.8)	1 (0.8)	0
Infections and infestations									
Hepatitis A	1 (1.6)	0	0	0	0	0	1 (0.8)	0	0
Hepatitis E	1 (1.6)	0	0	0	0	0	1 (0.8)	0	0
Nervous system disorders									
Migraine	1 (1.6)	1 (1.6)	0	0	0	0	1 (0.8)	1 (0.8)	0
Neoplasms, benign and malignant									
Adenosquamous carcinoma of the cervix	0	0	0	1 (3.3)	1 (3.3)	0	1 (0.8)	1 (0.8)	0
Rectal adenocarcinoma	0	0	0	1 (3.3)	0	0	1 (0.8)	0	0
Renal cell carcinoma	0	0	0	0	0	0	1 (0.8)	0	0
Metabolism and nutrition disorder									
Hyponatremia	0	0	0	0	0	0	1 (0.8)	1 (0.8)	0
Musculoskeletal and connective tissue disorders									
Neck pain	0	0	0	0	0	0	1 (0.8)	1 (0.8)	0
Renal and urinary disorders									
Acute renal failure	0	0	0	0	0	0	1 (0.8)	1 (0.8)	0

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Includes PT terms of Rash and popular rash

[b] Includes PT terms hepatotoxicity and liver disorder

Overall, the evaluation of SAEs in the broader TGCT population shows a similar proportion of patients that experienced SAEs compared to those observed during the randomized portion of ENLIVEN. There was one patient in the ENLIVEN trial initially randomized to placebo who crossed over to pexidartinib who developed adenosquamous carcinoma of the cervix and one patient treated with pexidartinib in Study PLX108-01 who developed renal cell carcinoma three years after initiating pexidartinib therapy. Brief narrative summaries of these patients' course are below:

- The patient with adenosquamous carcinoma of the cervix had a history of cervical dysplasia and vaginal bleeding prior to enrolling on the trial. During ENLIVEN, the patient had multiple pap tests due to ongoing dysplasia and vaginal bleeding. She was initially randomized to placebo and crossed over to pexidartinib. On Day 113 she was diagnosed with adenocarcinoma of the cervix. She underwent a hysterectomy and bilateral salpingectomy on Day 147. She received chemotherapy and radiotherapy from Day 177 to 267. She was off of pexidartinib from Day 125 to 267. She restarted pexidartinib at 800 mg daily on Day 267 and the event of adenocarcinoma was thought to be resolved on Day 267. She continued on pexidartinib until data cut off which occurred on Day 433. Given her pre-existing cervical dysplasia and vaginal bleeding, this reviewer agreed with the Applicant's conclusion that the event adenocarcinoma of the cervix was unlikely to be related to pexidartinib.

- The patient with renal cell carcinoma received pexidartinib on Study PLX108-01. He was a 63-year-old smoker who initiated pexidartinib in (b) (6) He experienced hematuria in (b) (6) as was diagnosed with renal cell carcinoma on (b) (6) (b) (6) The patient underwent nephrectomy on (b) (6) Pexidartinib was interrupted for surgery but restarted on (b) (6) The event was considered resolved on (b) (6) The patient discontinued from the trial in (b) (6) (b) (6) due to noncompliance.

Both patients resumed pexidartinib after the malignancies were treated.

Reviewer Comment: *Both cases were associated with confounding factors that preclude a definitive conclusive determination of causality. However, based on the available information, this reviewer determined that the first case above was unlikely related to pexidartinib therapy due to the history of cervical dysplasia prior to the initiation of pexidartinib. In the second case, it is unclear whether the renal cell carcinoma is related to treatment with pexidartinib. The patient has a history of smoking, but no other risk factors for the development for renal cell carcinoma. Although the role of pexidartinib cannot be excluded in the case of renal cell carcinoma, the overall rate of 2nd malignancies in ENLIVEN is not higher than what would be expected as background in the population of patients treated with pexidartinib. Additionally, as described in Section 5.5 of this review, pexidartinib is not genotoxic and a risk of 2nd malignancies was not predicted by nonclinical toxicology studies. Therefore, this reviewer concludes that there is no evidence to suggest that pexidartinib is associated with the development of 2nd malignancies.*

Dropouts and/or Discontinuations Due to Adverse Effects

The majority of patients in both treatment arms remained on therapy for the first 25 weeks of ENLIVEN. As shown in Table 90, only 8 patients discontinued treatment with pexidartinib due to an adverse event Seven of the eight patients who discontinued pexidartinib did so due to an adverse event related to hepatotoxicity. The seventh patient discontinued due to hypertension. Table 90 outlines the adverse events leading to discontinuation of therapy in the first 25 weeks of ENLIVEN.

Table 90. AEs Leading to Discontinuation During the First 25 Weeks of Treatment, ENLIVEN

	Randomized to Pexidartinib N=61		Randomized to Placebo N=59	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	8 (13)	6 (10)	0	0
Investigations				
Increased ALT	3 (4.9)	2 (3.3)	0	0
Increased AST	3 (4.9)	1 (1.6)	0	0
Increased LDH	1 (1.6)	1 (1.6)	0	0
Abnormal hepatic enzymes	1 (1.6)	1 (1.6)	0	0
Increased LDH	1 (1.6)	1 (1.6)		
Hepatobiliary disorders				
Hepatotoxicity[a]	2 (3.3)	2 (3.3)	0	0
Vascular disorders				
Hypertension	1 (1.6)	0	0	0

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Includes the PT terms hepatotoxicity and liver disorder

Table 91 displays the patients with TGCT treated with pexidartinib who experienced an adverse event leading to permanent discontinuation of pexidartinib.

Table 91. AEs[a] Leading to Discontinuation of Pexidartinib for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled Pexidartinib TGCT Patients N=130	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	11 (18)	7 (11)	3 (10)	1 (3.3)	26 (20)	17 (13)
Investigations						
Increased ALT	3 (4.9)	2 (3.3)	1 (3.3)	0	7 (5)	3 (2.3)
Increased AST	3 (4.9)	1 (1.6)	0	0	4 (3)	1 (0.8)
Hepatobiliary disorders						
Hepatotoxicity[b]	2 (3.3)	2 (3.3)	0	0	2 (1.6)	2 (1.5)
Nervous system disorders						
Cognitive disorders	0	0	0	0	3 (2.3)	3 (2.3)
Musculoskeletal and connective tissue disorders						
Arthralgia/Myalgia	0	0	1 (3.3)	0	2 (1.6)	0
General disorders and administration site conditions						
Fatigue	0	0	0	0	3 (2.3)	3 (2.3)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Occurring in ≥2 patients

[b] Includes PT terms hepatotoxicity and liver disorder

Dose Interruptions and Reductions

The results of an analysis of adverse events leading to delay in therapy not resulting in treatment discontinuation during the first 25 weeks of treatment in ENLIVEN and in the proposed TGCT population is shown in Table 92 and Table 93. Overall, 33% of patients in the pexidartinib arm experienced treatment interruption due to AEs during the first 25 weeks of ENLIVEN compared to 10% in the placebo arm. The most common adverse events (occurring in >5% of patients) leading to dose interruption in the pexidartinib treated patients were increased AST (13% in pexidartinib arm versus 0% in the placebo arm), increased ALT (10% in pexidartinib arm versus 0% in the placebo arm), nausea (5% in pexidartinib arm versus 0% in the placebo arm), and increased alkaline phosphatase (7% in pexidartinib arm versus 0% in the placebo arm).

Table 92. AEs[a] Leading to Interruptions During the First 25 Weeks of Treatment, ENLIVEN

System Organ Class Preferred Term	Randomized to Pexidartinib N=61		Randomized to Placebo N=59	
	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
All patients with adverse event	20 (33)	14 (23)	6 (10)	3 (5)
Investigations				
Increased AST	8 (13)	5 (8)	0	0
Increased ALT	6 (10)	6 (10)	0	0
Increased alkaline phosphatase	4 (7)	3 (4.9)	0	0
Increased bilirubin	2 (3.3)	0	0	0
Increased GGT	2 (3.3)	2 (3.3)	0	0
Gastrointestinal disorders				
Nausea	5 (8)	0	0	0
Vomiting	3 (4.9)	0	0	0
Abdominal pain	2 (3.3)	0	1 (1.7)	0
Nervous system disorders				
Dizziness	3 (4.9)	1 (1.6)	0	0
Headache[b]	2 (3.3)	1 (1.6	1 (1.7)	0
Metabolism and nutritional disorders				
Hypertriglyceridemia	0	0	2 (3.4)	2 (3.4)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)

[a] Occurring in ≥2 patients

[b] Includes PT terms for migraine and headache

Table 93. AEs[a] Leading to Interruptions of Pexidartinib for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled Pexidartinib TGCT Patients N=130	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	26 (43)	17 (28)	10 (33)	7 (23)	63 (48)	33 (25)
Investigations						
Increased AST	8 (13)	5 (8)	2 (7)	1 (3.3)	13 (10)	7 (5)
Increased ALT	6 (10)	6 (10)	2 (7)	2 (7)	11 (8)	6 (4.6)
Increased alkaline phosphatase	4 (7)	3 (4.9)	0	0	6 (4.6)	3 (2.3)
Increased bilirubin	3 (4.9)	0	0	0	3 (2.3)	0
Increased GGT	2 (3.3)	2 (3.3)	0	0	2 (1.6)	2 (1.5)
Gastrointestinal disorders						
Nausea	5 (8)	0	0	0	9 (7)	0
Vomiting	3 (4.9)	0	0	0	8 (6)	0
Abdominal pain	2 (3.3)	0	0	0	3 (2.3)	0
Diarrhea	0	0	0	0	3 (2.3)	1 (0.8)
General disorders and administrative site conditions						
Facial edema[b]	2 (3.3)	0	2 (7)	1 (3.3)	5 (3.8)	1 (0.8)
Nervous system disorder						
Dizziness	3 (4.9)	1 (1.6)	0	0	3 (2.3)	1 (0.8)
Headache[c]	2 (3.3)	1 (1.6)	1 (3.3)	0	4 (3.1)	2 (1.5)
Cognitive disorders	0	0	0	0	2 (1.6)	0
Hepatobiliary disorders						
Hepatotoxicity[d]	2 (3.3)	2 (3.3)	0	0	2 (1.6)	2 (1.5)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Occurring in ≥2 patients

[b] Includes the PT terms eye edema, eyelid edema, periorbital edema, and facial edema

[c] Includes PT terms migraine and headache

[d] Includes the PT terms hepatotoxicity and liver disorder

Adverse events leading to dose reductions only occurred in patients in the pexidartinib arm (7%) in Part 1 of ENLIVEN. Table 94 shows the adverse events resulting in dose reductions during the first 25 weeks of ENLIVEN. All of these events were related to hepatotoxicity.

Table 94. AEs Leading to Reductions During the First 25 Weeks of Treatment, ENLIVEN

	Randomized to Pexidartinib N=61		Randomized to Placebo N=59	
System Organ Class Preferred Term	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
All patients with adverse event	4 (7)	1 (1.6)	0	0
Investigations				
Increased ALT	3 (4.9)	1 (1.6)	0	0
Increased AST	1 (1.6)	0	0	0
Increased alkaline phosphatase	1 (1.6)	0	0	0
Increased hepatic enzymes	1 (1.6)	0	0	0
Increased transaminases	1 (1.6)	0	0	0

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment*: Adverse events leading to dose reductions of pexidartinib in ENLIVEN were based upon adverse event evaluation by the investigator and may underestimate the proportion of patients who experienced hepatotoxicity. Refer to Table 105 for an evaluation of laboratory abnormalities associated with hepatoxicity that occurred during ENLIVEN.*

Table 95 summarizes adverse events leading to dose reductions of pexidartinib for the entire TGCT population. While the majority of these adverse events were related to hepatotoxicity, there were also events of fatigue in 12 (9%) patients and memory impairment in 3 (2.3%) which led to dose reductions.

Table 95. AEs[a] Leading to Reductions of Pexidartinib for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled Pexidartinib TGCT Patients N=130	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	6 (10)	2 (3.3)	4 (13)	1 (3.3)	34 (30)	8 (6)
Investigations						
Increased ALT	3 (4.9)	1 (1.6)	0	0	6 (4.6)	3 (2.3)
Increased AST	2 (3.3)	0	0	0	5 (3.8)	2 (1.5)
Increased Alkaline Phosphatase	1 (1.6)	0	1 (3.3)	0	3 (2.3)	0
General Disorders and administrative site conditions						
Fatigue	0	0	1 (3.3)	0	12 (9)	1 (0.8)
Nervous system disorders						
Headache	0	0	1 (3.3)	0	2 (1.6)	0
Memory impairment	0	0	1 (3.3)	0	3 (2.3)	0
Hepatobiliary disorders						
Hepatotoxicity	1 (1.6)	0	0	0	1 (0.8)	0
Musculoskeletal and connective tissue disorders						
Myalgia	0	0	1 (3.3)	0	1 (0.8)	0

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Occurring in ≥2 patients

Reviewer Comment: *Three patients with TGCT experienced memory impairment that resulted in a dose reduction; one patient who crossed over to pexidartinib from placebo in ENLIVEN and two patients who were enrolled in Study PLX108-01. For a full discussion of memory impairment and other cognitive disorders please see section 8.3.7.*

Treatment Emergent Adverse Events and Adverse Reactions

This review analyzed common treatment emergent adverse events (TEAEs) in ENLIVEN based upon the system organ class and the preferred term of the MedDRA hierarchy. Table 96 shows the most common adverse events by System Organ Class (with >10% incidence in the safety analysis population).

Table 96. TEAEs[a] by System Organ Class During the First 25 Weeks of Treatment, ENLIVEN

System Organ Class	Randomized to Pexidartinib N=61 n (%)	Randomized to Placebo N=59 N (%)
Skin and subcutaneous tissue disorders	52 (85)	10 (17)
General disorders and administration site conditions	41 (67)	26 (44)
Gastrointestinal disorders	40 (66)	38 (64)
Nervous system disorders	28 (46)	21 (36)
Musculoskeletal and connective tissue disorders	25 (41)	24 (41)
Investigations	35 (57)	7 (12)
Eye Disorders	22 (36)	4 (7)
Infections and infestations	13 (21)	13 (22)
Vascular Disorders	12 (20)	6 (10)
Respiratory, thoracic and mediastinal disorders	11 (18)	5 (9)
Blood and lymphatic system disorders	9 (15)	1 (1.7)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Occurring in ≥15% of patients

Table 97 lists the most common TEAEs (≥10%) in patients treated with pexidartinib in Part 1 of ENLIVEN by MedDRA preferred terms and grouped by MedDRA system organ class. The most common TEAEs by preferred term (occurring in ≥20% of patients) in the pexidartinib arm group were skin and subcutaneous tissue disorders (changes in hair color, rash), general disorders and administration site conditions (asthenia/fatigue, facial edema), investigations (increased AST, increased ALT), gastrointestinal disorders (nausea, diarrhea, vomiting), dysgeusia, and arthralgia/myalgia. The most common adverse event experienced in patients randomized to pexidartinib in ENLIVEN was hair color changes, occurring in 67% of patients. The majority of these hair color changes (47 of the 60 patients) were described as a hypopigmentation, whitening or loss of hair color.

Reviewer Comment: *Hair pigmentation is regulated by several factors including the receptor tyrosine kinase, c-kit. Pexidartinib inhibits both CSF1R as well as c-KIT. The c-KIT inhibition is likely responsible for the high rate of hair color changes observed in ENLVIEN. In ENLIVEN, 68 patients treated with pexidartinib experienced hair color changes and 60 (88%) of these did not*

resolve prior to the data cut off. It is unclear whether these did not resolve because the hair color change is permanent or because the patients remained on pexidartinib until the data cut off and the hair color change only resolved upon discontinuation of pexidartinib. With other c-kit inhibitors, such as sunitinib, the hair color change resolved upon discontinuation of the medication.

Table 97. TEAEs[a] During the First 25 Weeks of Treatment, ENLIVEN

	Randomized to Pexidartinib N=61		Randomized to Placebo N=59	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	60 (98)	27 (44)	55 (93)	7 (11)
Skin and subcutaneous tissue disorders				
Changes in hair color	41 (67)	0	2 (3.4)	0
Rash[b]	16 (26)	1 (1.6)	4 (7)	0
Pruritus	10 (16)	0	2 (3.4)	0
General disorders and administration site conditions				
Asthenia/fatigue	39 (64)	0	24 (41)	0
Facial edema[c]	21 (34)	1 (1.6)	4 (7)	0
Peripheral edema	8 (13)	0	2 (3)	0
Investigations				
Increased AST	24 (39)	6 (10)	0	0
Increased ALT	17 (28)	6 (10)	1 (1.7)	0
Increased alkaline phosphatase	9 (15)	4 (7)	0	0
Increased LDH	7 (12)	1 (1.6)	0	0
Gastrointestinal disorders				
Nausea	23 (38)	0	24 (41)	0
Diarrhea	12 (20)	0	15 (25)	0
Vomiting	12 (20)	1 (1.6)	3 (5)	0
Abdominal pain[d]	10 (16)	0	10 (17)	0
Constipation	7 (12)	0	3 (5)	0
Dry mouth	6 (10)	0	2 (3.4)	0
Nervous system disorders				
Dysgeusia	15 (25)	0	1 (1.7)	0
Headache	11 (18)	0	11 (19)	0
Dizziness	6 (10)	1 (1.6)	9 (15)	0
Musculoskeletal and connective tissue disorders				
Arthralgia/myalgia	15 (25)	3 (4.9)	15 (25)	1 (1.7)
Metabolism and nutritional disorders				
Decreased appetite	10 (16)	0	6 (10)	0
Vascular disorders				
Hypertension	9 (15)	3 (4.9)	6 (10)	0

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Occurring in >10% of patients
[b] Includes the PT terms Rash, Maculo-papular rash, follicular rash, dermatitis acneiform, pruritic rash and urticaria
[c] Includes the PT terms eye edema, eyelid edema, periorbital edema, and facial edema
[d] Includes the PT terms abdominal pain, Upper abdominal pain, abdominal rigidity

The most common treatment emergent adverse events (TEAEs) in the overall TGCT population are displayed in Table 98. The most common TEAEs by SOC and by preferred term (occurring in ≥20% of patients) were skin and subcutaneous tissue disorders (changes in hair color, rash), general disorders and administration site conditions (asthenia/fatigue, facial edema),

investigations (increased AST, increased ALT), gastrointestinal disorders (nausea, diarrhea, vomiting), dysgeusia, and arthralgia/myalgia.

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Table 98. TEAEs[a] for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled Pexidartinib TGCT Patients N=130	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
All patients with adverse event	60 (98)	32 (53)	30 (100)	7 (23)	129 (99)	56 (43)
Skin and subcutaneous tissue disorders						
Changes in hair color	41 (67)	0	25 (83)	0	72 (55)	0
Rash[b]	16 (26)	1 (1.6)	4 (7)	0	43 (33)	1 (0.8)
Pruritus	10 (16)	0	2 (3.4)	0	27 (21)	0
Erythema	2 (3.3)	0	5 (17)	0	15 (12)	0
General disorders and administration site conditions						
Asthenia/Fatigue	41 (67)	0	10 (33)	0	51 (66)	1 (0.8)
Facial Edema[c]	25 (41)	1 (1.6)	9 (30)	1 (3.3)	55 (42)	2 (1.5)
Peripheral edema	8 (13)	0	5 (17)	0	27 (21)	0
Investigations						
Increased AST	27 (44)	7 (12)	5 (17)	1 (3.3)	39 (30)	11 (8)
Increased ALT	19 (31)	7 (12)	7 (23)	2 (7)	33 (25)	13 (10)
Increased alkaline phosphatase	9 (15)	4 (7)	1 (3.3)	1 (3.3)	14 (11)	5 (3.8)
Increased LDH	7 (12)	0	3 (10)	0	10 (8)	0
Gastrointestinal disorders						
Nausea	24 (40)	0	6 (20)	0	56 (43)	0
Diarrhea	16 (26)	0	8 (27)	0	38 (29)	0
Vomiting	13 (21)	1 (1.6)	2 (7)	0	27 (21)	2 (1.5)
Abdominal pain[d]	13 (21)	0	2 (7)	0	21 (16)	0
Constipation	7 (12)	0	3 (10)	0	21 (16)	0
Dry mouth	7 (12)	0	4 (13)	0	15 (12)	0
Stomatitis	4 (7)	0	3 (10)	0	10 (8)	0
Nervous system disorders						
Dysgeusia	16 (26)	0	7 (23)	0	37 (28)	0
Headache	13 (21)	0	5 (17)	0	31 (24)	0
Dizziness	8 (13)	1 (1.6)	4 (13)	0	23 (18)	1 (0.8)
Memory impairment	0	0	3 (10)	0	8 (6)	0
Musculoskeletal and connective tissue disorders						
Arthralgia/myalgia	17 (28)	3 (4.9)	15 (25)	1 (1.7)	57 (44)	5 (3.8)
Pain in extremity	6 (10)	0	3 (10)	0	19 (15)	0

	ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled Pexidartinib TGCT Patients N=130	
System Organ Class Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Metabolism and nutritional disorders						
Decreased appetite	10 (16)	0	3 (10)	0	22 (17)	0
Vascular disorders						
Hypertension	12 (20)	3 (4.9)	6 (20)	2 (7)	27 (21)	5 (3.8)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Occurring in >10% of patients

[b] Skin includes the following PT terms dermatitis, dermatitis acneiform, dermatitis exfoliative, eczema, rash, maculo-papular rash popular rash, pruritic rash

[c] Includes the PT terms of eye, edema, eyelid edema, periorbital edema, and facial edema

[d] Includes the PT terms abdominal pain and upper abdominal pain

Reviewer Comment: *Approximately 20% of patients with TGCT treated with pexidartinib across the development program experienced hypertension; the majority of these were Grade 1 or 2 and did not lead to dose modifications (reductions or interruptions) or discontinuations of pexidartinib. FDA conducted a detailed analysis of to describe the scope and severity of hypertension to characterize this potential risk of pexidartinib in the ENLIVEN trial, given that TGCT is a nonfatal disease and that patients may receive long term treatment with pexidartinib. Refer to Section 8.3.4 of this review for a full evaluation of hypertension related to pexidartinib therapy. Ultimately, as described later in the review, the events of hypertension in ENLIVEN were manageable and did not result in serious adverse outcomes.*

Laboratory Findings

ENLIVEN required laboratory testing at baseline and at regularly scheduled intervals. The incidence of laboratory abnormalities is based on a denominator consisting of patients with a baseline and at least one on-study test for each of the laboratory tests. Table 99 summarizes the incidence of laboratory abnormalities. Only patients with treatment-emergent laboratory abnormalities are included in the numerator in the calculation of incidence.

Table 99. Laboratory Abnormalities[a,b] During the First 25 Weeks of Treatment, ENLIVEN

	Randomized to Pexidartinib N=61			Randomized to Placebo N=59		
	n	All Grades n (%)	Grade 3-4 n (%)	n	All Grades n (%)	Grade 3-4 n (%)
Hematologic						
Decreased neutrophil count	61	27 (44)	2 (3.3)	59	5 (9)	0
Decreased lymphocytes	61	23 (38)	1 (1.6)	58	2 (3.4)	0
Decreased hemoglobin	61	18 (29)	0	59	8 (14)	1 (1.7)
Decreased platelets	61	9 (15)	0	59	3 (5)	0
Chemistry						
Increased LDH[c]	61	56 (92)	0	59	3 (5)	0
Increased AST	61	55 (90)	7 (12)	59	9 (15)	0
Increased ALT	61	41 (67)	12 (20)	59	13 (22)	0
Increased cholesterol	61	31 (50)	3 (4.9)	59	16 (27)	0
Increased alkaline phosphatase	61	24 (39)	3 (4.9)	59	1 (1.7)	0
Decreased phosphate	61	15 (25)	2 (3.3)	59	3 (5)	0
Increased total bilirubin	61	7 (12)	2 (3.3)	59	0	0

Source: Reviewer generated table – summarizing ENLIVEN laboratory analysis dataset (ADLB, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Occurring in >10% of patients
[b] Laboratory incidence is based on a denominator consisting of patients with a baseline and at least one on-study test for each of the test.
[c] LDH: Grade 1: >ULN to ≤2.5x ULN; Grade 2: >2.5 to ≤5x ULN; Grade 3: >5 to ≤20x ULN; Grade 4: >20x ULN

Table 100 displays the incidence of laboratory abnormalities in all patients treated with pexidartinib in ENLIVEN. Only patients with treatment-emergent laboratory abnormalities are included in the numerator in the calculation of incidence.

Reviewer Comment: *The incidence of adverse events of increased ALT, AST, or increased transaminases (a composite term including the following PT terms: increased transaminases, abnormal liver function test, hepatic enzyme abnormal, hepatic enzyme increased) was 28%, 39%, and 11% respectively in Part 1 of ENLIVEN. Since adverse events are based upon*

investigator assessment and reporting, there may not be total overlap in the incidence rates with laboratory-based assessments. As shown in Table 99, the incidence of patients with elevated liver transaminases based upon laboratory values is higher than per AE reporting. Therefore, this reviewer used laboratory evaluations as the primary basis for evaluation of hepatotoxicity. Please see section 8.3.4 Analysis of Submission-Specific Safety Issues for further evaluation of hepatotoxicity.

Table 100. Laboratory Abnormalities[a,b] for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61			ENLIVEN Crossover Part 2 N=30			Pooled Pexidartinib TGCT Patients N=130		
	n	All Grades n (%)	Grade 3-4 n (%)	n	All Grades n (%)	Grade 3-4 n (%)	n	All Grades n (%)	Grade 3-4 n (%)
Hematologic									
Decreased neutrophil count	61	35 (57)	2 (3.3)	30	14 (46)	0	130	61 (47)	3 (2.3)
Decreased lymphocytes	61	26 (43)	1 (1.6)	30	11 (37)	1 (3.3)	130	54 (42)	5 (3.8)
Decreased hemoglobin	61	21 (34)	0	30	9 (30)	0	130	52 (40)	1 (0.8)
Decreased platelets	61	10 (16)	0	30	2 (7)	0	130	21 (16)	0
Chemistry									
Increased LDH[c]	61	56 (92)	0	30	29 (97)	0	129	121 (94)	0
Increased AST	61	55 (90)	7 (12)	30	27 (90)	1 (3.3)	130	130 (88)	12 (9)
Increased ALT	61	41 (67)	12 (20)	30	19 (63)	2 (7)	130	79 (61)	17 (13)
Increased cholesterol	61	31 (50)	3 (4.9)	30	17 (57)	0	129	66 (51)	3 (2.3)
Increased alkaline phosphatase	61	24 (39)	3 (4.9)	30	8 (27)	0	130	42 (32)	4 (3.1)
Decreased phosphate	61	24 (39)	4 (7)	30	9 (30)	1 (3.3)	129	53 (41)	11 (9)
Increased total bilirubin	61	7 (12)	2 (3.3)	30	0	0	130	11 (8)	4 (3.1)

Source: Reviewer generated table – summarizing ENLIVEN laboratory analysis dataset (ADLB, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 laboratory analysis dataset (ADLB, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Occurring in >10% of patients

[b] Laboratory incidence is based on a denominator consisting of patients with a baseline and at least one on-study test for each of the test.

[c] LDH: Grade 1: >ULN to ≤2.5x ULN; Grade 2: >2.5 to ≤5x ULN; Grade 3: >5 to ≤20x ULN; Grade 4: >20x ULN

Vital Signs

In ENLIVEN, temperature, blood pressure and heart rate were measured at screening, Day 1 and 15 of cycle 1 and on day 1 of each cycle thereafter, at study termination, and when deemed necessary. Table 101 displays the abnormal vital signs that occurred during the first 25 weeks of therapy in ENLIVEN. The majority of vital sign measurements of temperature, heart rate and weight were within normal range and there were not any notable differences between patients treated with pexidartinib and those treated with placebo.

In the Applicant's analyses, 'elevated' systolic blood pressure was defined as ≥180 mmHg regardless of change from baseline. FDA's approach was to identify patients with a systolic blood pressure of ≥120 mmHg with an increase in baseline of ≥20 mg, as this criterion is more conservative and is consistent with Grade 1 hypertension according to CTCAE version 4.1.

Elevated systolic blood pressure defined as ≥120 mmHg with increase from a baseline of ≥20 mmHg occurred in 13% of patients treated with pexidartinib compared with 1.7% of patients treated with placebo. Elevated diastolic blood pressure defined as ≥80 mmHg with increase from baseline ≥20 mmHg occurred in 8% of pexidartinib treated patients versus no elevations in the placebo treated patients. Hypertension was reported as an adverse event in 15% of patients treated with pexidartinib, which reflects the measured vital signs.

Table 101. Abnormal Vital Signs During the First 25 Weeks of Treatment, ENLIVEN

Vital Sign	Randomized to Pexidartinib N=61 n (%)	Randomized to Placebo N=59 N (%)
Systolic blood pressure (mmHg)[a]		
High	10 (16)	3 (5)
Low	0	1 (1.7)
Diastolic blood pressure (mmHg)[b]		
High	5 (8)	0
Low	0	1 (1.7)
Pulse (beats per minute)[c]		
High	0	0
Low	0	1 (1.7)
Weight (kg)[d]		
High	0	0
Low	0	1 (1.7)
Body temperature (^{0}C)[e]		
High	6 (10)	3 (5)
Low	3 (4.9)	2 (3.3)

Source: Reviewer generated table – summarizing ENLIVEN vital signs analysis dataset (ADVS, March 27, 2017 data cutoff date, submitted by Applicant)

[a] High/Low systolic blood pressure: ≥120 mmHg with increase from baseline ≥20 mm Hg/≤ 90 mmHg with decrease from baseline of ≥20 mmHg

[b] High/Low diastolic blood pressure: ≥80 mmHg with increase from baseline ≥20 mmHg/≤ 50 mmHg with decrease from baseline of ≥20 mmHg

[c] High/Low pulse rate: ≥120 beats per minute with increase from baseline of ≥15 beats per minute/≤50 bpm with decrease from baseline of ≥15 bpm

[d] High/Low weight (kilograms): ≥10% increase from baseline/ ≥10% decrease from baseline

[e] High/Low body temperature: ≥37.5^{0}C/≤35^{0}C

Reviewer Comment: *The incidence of hypertension according to adverse event reports was 15% in the pexidartinib arm and 10% in the placebo. For patients in the pexidartinib arm, the incidence is similar to the proportion of patients who are identified as having a high systolic blood pressure upon vital sign review. However, there were more adverse events of hypertension reported in the placebo arm than were observed upon vital sign review. For a full evaluation of hypertension please see section 8.3.4 Analysis of Submission-Specific Safety Issues.*

Table 102 summarizes the abnormal vital signs that occurred in all pexidartinib treated patients with TGCT.

Table 102. Abnormal Vital Signs for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 & 2 N=61	ENLIVEN Crossover Part 2 N=30	Pooled Pexidartinib TGCT Patients N=130
Systolic blood pressure (mmHg)[a]			
High	17 (28)	8 (27)	31 (24)
Low	0	1 (3.3)	3 (2.3)
Diastolic blood pressure (mmHg)[b]			
High	7 (11)	2 (7)	17 (13)
Low	1 (1.6)	0	1 (0.8)
Pulse (beats per minute)[c]			
High	0	0	1 (0.8)
Low	3 (4.9)	0	6 (4.6)
Weight (kg)[d]			
High	4 (7)	0	10 (8)
Low	1 (1.6)	0	1 (0.8)
Body temperature (^{0}C)[e]			
High	7 (11)	1 (3.3)	11 (8)
Low	4 (7)	1 (3.3)	5 (3.8)

Source: Reviewer generated table – summarizing ENLIVEN vital signs analysis dataset (ADVS, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 vital signs analysis dataset (ADVS, March 3, 2017 data cutoff date, submitted by Applicant)

[a] High/Low systolic blood pressure ≥120 mmHg with increase from baseline ≥20 mm Hg/≤ 90 mmHg with decrease from baseline of ≥20 mmHg

[b] High/Low diastolic blood pressure: ≥80 mmHg with increase from baseline ≥20 mmHg/≤ 50 mmHg with decrease from baseline of ≥15 mmHg

[c] High/Low pulse rate: ≥120 beats per minute with increase from baseline of ≥15 beats per minute/≤ 50 bpm with decrease from baseline of ≥15 bpm

[d] High/Low weight (kilograms): ≥10% increase from baseline/ ≥10% decrease from baseline

[e] High/Low body temperature: ≥37.5^{0}C/≤ 35^{0}C

Electrocardiograms (ECGs)

ENLIVEN required 12-lead ECGs at baseline, week 1, 3, and at the end of therapy. QTc was evaluated using Fridericia's correction formula. All patients had a baseline and at least 1 postbaseline QT interval measurement. In Part 1 of ENLIVEN, 9 (15%) of the pexidartinib treated patients and 3 (5%) of the placebo treated patients had a QTcF >450 ms and <500 ms. One patient in each group (1.7% in pexidartinib treated patients and 1.6% in placebo treated patients) had A QTcF >500 ms. QRS was increased by >30 ms compared to baseline in 3 (4.9%) pexidartinib treated patients and 7 (11%) of patients who received placebo. Of these patients 2 (3.3%) of the pexidartinib treated patients had an increase in QRS of >60ms compared to 1 (1.7%) of patients randomized to placebo. Additionally, 1 (3.3%) crossover patient in Part 2 had

a QTcF >450 ms and ≤500 ms. Four (6.6%) patients in Part 1 and/or Part 2 of the study had a >30 ms change in QRS from baseline as did 1 (3.3%) crossover patient in Part 2.

QT The effect of pexidartinib was evaluated in a double-blind, placebo- and active-controlled, 3-treatment, single-dose, crossover study in 36 healthy volunteers (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. Exposure-response analysis suggests that pexidartinib is associated with a modest QTc shortening effect as shown in Table 103.

Table 103. Point Estimates and the 90% CI By Exposure-Response Analysis

ECG Parameter	Treatment	Concentration	ΔQTcF (ms)	90% CI
QTc	Pexidartinib	1.9 µg/mL	-5.1	(-7.0, -3.3)
QTc	Moxifloxacin	1.8 µg/mL	15.9	(13.5, 18.3)

In ENLIVEN, a baseline and at least 1 maximum postbaseline QT interval measurement was available for all pexidartinib- and placebo-treated patients. Using the QTcF correction for maximum postbaseline value, 8 (13.1%) pexidartinib-treated patients and 3 (5.1%) placebo patients had a QTcF >450 ms and ≤480 ms postbaseline; 1 (1.6%) patient in the pexidartinib group and no patients in the placebo group had a QTcF >480 ms and ≤500 ms; and 1 patient in each group (1.7% and 1.6% for the pexidartinib and placebo groups, respectively).

A greater proportion of patients in the placebo group (7 patients, 11.9%) had a >30 ms change from baseline in QTcF than those in the pexidartinib group (3 patients, 4.9%). Two (3.3%) patients in the pexidartinib group had a >60 ms change in QTcF from baseline compared with 1 (1.7%) patient in the placebo group.

For the pexidartinib-treated patients in Part 1 and/or Part 2 of Study PLX108-10, the QTcF analyses using imputed heart rate and RR only were similar to these analyses described for the pexidartinib-treated patients in Part 1. Additionally, 1 (3.3%) crossover patient in Part 2 had a QTcF >450 ms and ≤480 ms. Four (6.6%) patients in Part 1 and/or Part 2 of the study had a >30 ms change in QTcF from baseline as did 1 (3.3%) crossover patient in Part 2.

Reviewer Comment: *Based on the results of the thorough QT study, at two times the mean maximum exposure of 400 mg twice daily, pexidartinib does not prolong the QTC interval and therefore is unlikely to have arrhythmogenic potential. This conclusion is supported by the lack of QT prolongation in pexidartinib-treated patients on ENLIVEN compared to placebo.*

8.3.4. Analysis of Submission-Specific Safety Issues

The risk of hepatotoxicity or liver injury was identified as serious risk during the development of pexidartinib. The Applicant provided the results of a detailed analysis of this toxicity in the ENLIVEN trial and for the pooled safety population. FDA also conducted detailed analyses for the following additional safety concerns: hypertension and cognitive impairment; the results of these analyses are described below.

Liver Injury

FDA's evaluation of hepatotoxicity relied primarily on the reporting of adverse events and laboratory assessments, but also included patient narratives, case report forms, and liver biopsy images and pathology reports when available. The overall evaluation of liver injury for pexidartinib was primarily based on the ENLIVEN trial. This review includes a detailed evaluation across the entire TGCT population (n=130) and data from the pooled data from commercially-sponsor clinical studies (n=630), and of summary data from investigator-initiated clinical studies (n=138), as shown in Table 85. The primary review team consulted experts in hepatotoxicity within the FDA (i.e., consulted with a review team in the Division of Gastroenterology and Inborn Errors Products [DGIEP]), as well as with an external pathologist during the course of the evaluation of liver injury. The information that follows is a high-level summary of all input received by the primary reviewer.

Adverse Events of Liver Injury

Table 104 displays the adverse events associated with liver injury observed in all patient with TGCT treated with pexidartinib, based upon MedDRA preferred term.

Table 104. AEs Associated With Liver Injury for All Patients With TGCT

	ENLIVEN Placebo Part 1 N=59		ENLIVEN Pexidartinib Part 1 N=61		ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled TGCT Patients N=130	
MedDRA Preferred Term	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)	All Grades n (%)	Grade 3-4 n (%)
Any patient with an adverse event associated with liver injury	3 (5)	1 (1.7)	28 (46)	13 (21)	28 (46)	13 (21)	9 (30)	4 (13)	40 (31)	17 (13)
Increased AST	0	0	24 (39)	6 (10)	24 (39)	6 (10)	5 (17)	1 (3.3)	30 (23)	10 (8)
Increased ALT	1 (1.7)	0	17 (28)	6 (10)	17 (28)	6 (10)	7 (23)	2 (7)	26 (20)	12 (9)
Increased alkaline phosphatase	0	0	9 (15)	4 (7)	9 (15)	4 (7)	1 (3.3)	1 (3.3)	10 (8)	4 (3.1)
Increased Transaminases[a]	0	0	7 (11)	4 (7)	7 (11)	4 (7)	1 (3.3)	0	9 (7)	5 (3.8)
Increase gamma-glutamyl transferase	1 (1.7)	0	3 (4.9)	2 (3.3)	3 (4.9)	2 (3.3)	0	0	3 (2.3)	2 (1.5)
Increased bilirubin[b]	1 (1.7)	1 (1.7)	3 (4.9)	1 (1.6)	3 (4.9)	1 (1.6)	0	0	5 (3.8)	2 (1.5)
Hepatotoxicity[c]		0	2 (3.2)	1 (1.6)	2 (3.2)	1 (1.6)	1 (3.3)	1 (3.3)	3 (2.3)	2 (1.5)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Includes the PT terms of increased transaminases, abnormal liver function test, hepatic enzyme abnormal, hepatic enzyme increased

[b] Includes PT terms of increased bilirubin and hyperbilirubinemia

[c] Includes the PT terms hepatotoxicity, hepatocellular injury, liver disorder

Reviewer Comment: *Adverse event reporting for the increased lab values of AST, ALT, alkaline phosphatase, gamma-glutamyl transferase, and bilirubin may be limited by the CTCAE grading definitions which include a wide range of values. For example, Grade 1 ALT increase includes > ULN -3x ULN, Grade 2 includes >3x ULN -5x ULN, Grade 3 includes >5x ULN to 20x ULN, and Grade 4 includes >20x ULN. The analysis of liver injury based upon clinical laboratory supported a more precise assessment of this toxicity in patients with TGCT who experienced liver injury.*

Laboratory Evaluation for Liver Injury

Elevated transaminases were observed in the majority of patients with TGCT treated with pexidartinib in the ENLIVEN trial as well as in Study PLX108-01.

Table 105 shows that 10-12% of patients experienced elevated total bilirubin when compared to baseline. Approximately 3% of patients with TGCT experienced both an increase in total bilirubin 2× ULN and an increase in ALT or AST 3× ULN, which is considered indicative of drug induced hepatotoxicity; similar rates (2.7%) were observed among the 264 patients with solid tumors and AML treated with pexidartinib as a single agent in commercial-sponsored trials (Table 106).

Reviewer Comment: *The imbalance in the incidence of liver injury between arms on the ENLIVEN trial, characterized by elevations in serum aminotransferase levels accompanied by increases in serum bilirubin, is highly suggestive of a causal association between pexidartinib treatment and the risk of liver injury. According to the FDA Guidance on Drug Induced Liver Injury, Hy's law can be used to identify a drug causing hepatocellular injury sufficient to impair bilirubin excretion. In order to meet the criteria for Hy's laws all of the following must be met:*

- *An AST or ALT greater than 3x ULN*
- *A total bilirubin >2x ULN*
- *No initial findings of cholestasis evidenced by an increased alkaline phosphatase,*
- *No other reason for the combination of increased transaminases and total bilirubin*

The presence of Hy's law cases may predict that serious idiosyncratic drug induced liver injury (DILI) cases may be more likely in post-marketing treatment population. In ENLIVEN, no cases meetings strict Hy's Law criteria were identified because all the patients with an increase in ALT or AST and total bilirubin had a concomitant elevation in alkaline phosphatase. However, given that bile duct injury has been observed with pexidartinib use, the presence of cholestasis characterized by an increase in alkaline phosphatase may not represent a separate process. Therefore, for the purposes of this review, this reviewer defined severe liver injury as an AST or ALT ≥3x ULN with a total bilirubin of ≥2x ULN regardless of alkaline phosphatase; approximately 3% of patients who received pexidartinib met this definition of severe liver injury.

Table 105. Elevated ALT, AST and Total Bilirubin for All Patients With TGCT

	ENLIVEN Placebo Part 1 N=59	ENLIVEN Pexidartinib Part 1 N=61	ENLIVEN Pexidartinib Part 1 & 2 N=61	ENLIVEN Crossover Part 2 N=30	Pooled Pexidartinib TGCT Patients N=130
ALT > ULN	13 (22)	41 (67)	41 (67)	22 (73)	83 (64)
≥3× ULN	0	21 (34)	21 (34)	4 (13)	29 (22)
≥5× ULN	0	14 (23)	14 (23)	2 (7)	19 (15)
≥10× ULN	0	4 (7)	4 (7)	0	6 (4.9)
AST > ULN	9 (15)	55 (90)	55 (90)	27 (90)	116 (89)
≥3× ULN	0	18 (30)	18 (30)	3 (10)	28 (22)
≥5× ULN	0	7 (12)	7 (12)	1 (3.3)	12 (9)
≥10× ULN	0	2 (3.3)	2 (3.3)	0	2 (1.5)
Bilirubin > ULN	1 (1.7)	7 (12)	7 (12)	0	13 (10)
≥2× ULN	0	3 (4.9)	3 (4.9)	0	5 (3.8)
≥2× baseline	17 (29)	21 (34)	21 (34)	3 (10)	35 (27)
TBIL ≥2× ULN and AST or ALT ≥3× ULN	0	3 (4.9)	3 (4.9)	0	4 (3.1)

Source: Reviewer generated table – summarizing ENLIVEN laboratory analysis dataset (ADLB, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 laboratory analysis dataset (ADLB, March 3, 2017 data cutoff date, submitted by Applicant)

Reviewer Comment: *A potential challenge in interpreting analyses based upon laboratory values of AST and ALT is that institutions have different cut offs for what represents the upper limit of normal for AST or ALT. In ENLIVEN, the upper limit of normal for AST and ALT ranged from 30-35 U/L and the data safety monitoring committee for ENLIVEN used an upper limit of normal of 40 U/L. In order to take into account these institutional differences, and consistent with the usual approach to identifying cases of severe liver injury, this reviewer reported all values for AST, ALT and total bilirubin as a multiple of the local upper limit of normal rather.*

At baseline, 6 of the 61 patients (10%) randomized to pexidartinib in Part 1 of ENLIVEN had pre-existing elevations in transaminases. Five of these 6 patients had values that were <5x ULN and the sixth patient had an ALT 6x ULN. None of the patients with elevated AST or ALT at baseline experienced severe liver injury, characterized as a total bilirubin ≥2x ULN with concurrent AST or ALT ≥3x ULN.

Table 106. Liver Injury in Non-TGCT Patients Treated With Pexidartinib as a Single Agent

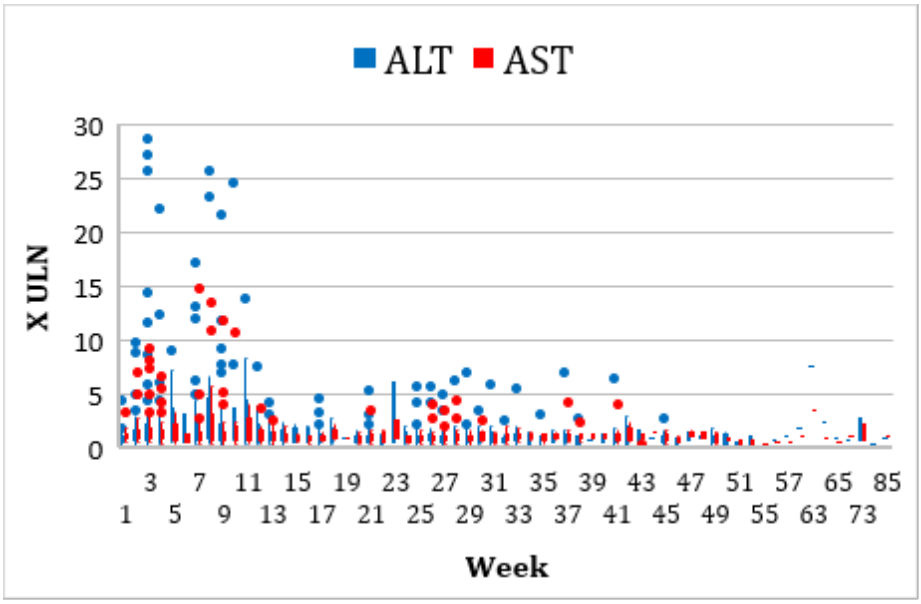
	Non-TGCT Solid Tumors			AML
	200-600 mg/day N=24	900-1200 mg/day N=150	Total N=174	800-5000 mg/day N=90
Laboratory Test	n (%)	n (%)	n (%)	n (%)
ALT	21%	33%	31%	28%
≥3x ULN	8%	11%	10%	4.4%
≥5x ULN	0	8%	7%	3.3%
AST	63%	79%	77%	72%
≥3x ULN	8%	12%	11%	22%
≥5x ULN	4%	8%	8%	4.4%
Bilirubin	4.2%	17%	16%	20%
≥2x ULN	4.2%	4.0%	4.0%	9%
≥2x baseline	8.3%	15%	14%	17%
TBIL ≥2x ULN and AST or ALT ≥3x ULN	4.2%	1.3%	1.7%	4.4%

Source: Reviewer generated table – reproduced from the Clinical Summary of Safety and from the Clinical Study Report for Trial PLX108-13

Reviewer Comment: *Across the entire development program there was a similar rate of patients who experienced serious liver injury regardless of whether patients had TGCT, non-TGCT solid tumors, or AML. Additionally, based on the testing of doses ranging from 200-5000 mg/day, the aminotransferase elevation associated with an elevated total bilirubin did not appear to be dose-dependent and was observed at similar rates across all clinical trials evaluating pexidartinib.*

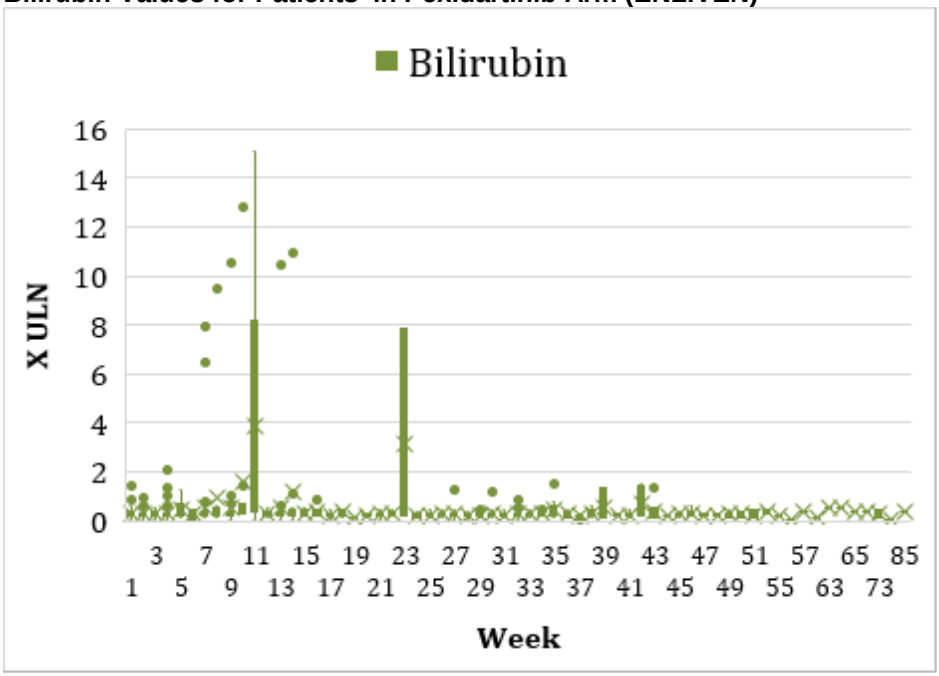
ALT, AST and total bilirubin were monitored throughout the ENLIVEN trial and the majority of first instances of elevations (97%) in AST, ALT and total bilirubin in patients randomized to pexidartinib occurred during the first two months of treatment. Figure 12 and Figure 13 show an analysis of the timing of transaminase and total bilirubin elevations based on laboratory data.

Figure 12. ALT/AST Values for Patients* in Pexidartinib Arm ENLIVEN



Source: Reviewer generated graph – summarizing ENLIVEN laboratory analysis dataset (ADLB, March 27, 2017 data cutoff date, submitted by Applicant)
* Each patient randomized to pexidartin b has all of their ALT or AST results represented in this graph.

Figure 13. Total Bilirubin Values for Patients* in Pexidartinib Arm (ENLIVEN)



Source: Reviewer generated graph -- summarizing laboratory analysis dataset (ADLB, March 27, 2017 data cutoff date, submitted by Applicant)
* Each patient randomized to pexidartin b has all of their total bilirubin results represented in this graph.

Action Taken in Response to Liver Toxicity

Table 107 displays the action taken with pexidartinib in response to elevations in transaminases. Fifty-five of the 61 patients in Part 1 of ENLIVEN experienced elevated liver transaminases, 7 of them with concurrent elevations in bilirubin. Eight patients had dose

interruption and were re-challenged with pexidartinib after improvement in transaminases. Of these 8 patients, 4 successfully resumed pexidartinib either at the same or a reduced dose and 4 had recurrence of transaminase elevation following re-challenge ultimately leading to permanent discontinuation

Table 107. Action Taken in Response to Liver Injury[a], Part 1 ENLIVEN

Action Taken with Pexidartinib	AST or ALT <5x ULN N=41 n (%)	AST or ALT ≥5x ULN N=11 n (%)	Total Bilirubin ≥2x ULN & ALT/ AST ≥3x ULN N=3 n (%)
None	38 (93)	2 (18)	0
Dose interrupted	0	8 (73)	0
Patient re-challenged	0	8 (73)	0
Discontinued after re-challenge	0	4 (36)	0
Dose reduced	2 (4.8)	7 (64)	0
Drug withdrawn	1 (2.4)	4 (36)	3 (100)

Source: Reviewer generated table – summarizing laboratory analysis, adverse event analysis, and exposure analysis datasets (ADLB, ADAE, and ADEX, March 27, 2017 data cutoff date, submitted by Applicant)
[a] Patients may be counted more than once as they may have had multiple action taken with pexidartinib in response to liver injury

All of the 55 patients in Part 1 of ENLIVEN who experienced elevated transaminases with or without bilirubin elevations, improved with no intervention, dose modification (dose interruption or reduction) or withdrawal of drug. Although, the majority of patients had laboratory values that returned to within normal limits or their baseline, 18 patients did not recover to within normal limits. Fifteen of these patients improved to 1.1 to 2x ULN and 3 of these patients improved to 2 to 2.7x ULN.

Reviewer Comment: *Patients who experienced an AST or ALT elevation of >10x ULN of required dose withdrawal in order for AST or ALT to improve. Therefore, the label for pexidartinib states that pexidartinib should be discontinued at an AST or ALT >10x ULN.*

120-day Safety Update

On February 28, 2019, the Applicant submitted updated safety data based on a data cutoff date of August 31,2018, which provided an additional 17 months of follow up to the data cutoff date at the time of the NDA submission for the ENLIVEN trial. This increased follow provided a longer duration of exposure as seen in Table 108. The safety update submission also included the interim results of Study PL3397-A-U126 (based on a data cutoff date of October 24, 2018) which enrolled 30 patients with solid tumors, including 9 patients with TGCT. Overall, the review of the Safety Update submission did not reveal any notable changes in the incidence or severity of hepatotoxicity in the ENLIVEN trial, or in the overall development program. However, two new cases of liver injury (i.e., ALT or AST ≥3x ULN and total bilirubin ≥2x ULN) were reported from Study PL3397-A-U126. One of these cases occurred in a patient with TGCT.

Table 108. Duration of Exospore All TGCT Patients, 120-Day Safety Update

Study Drug Exposure	ENLIVEN Trial N=91 n (%)	Study PLX108-01 N=39 n (%)	Study PL3397-1-U126 N=9 n (%)	All TGCT Patients N=139 n (%)
2 days to 1 month	4 (4.4)	3 (8)	1 (11)	8 (6)
>1 month to 6 months	9 (10)	4 (10)	7 (77)	20 (14)
>6 months to 12 months	15 (16)	9 (23)	1 (11)	25 (18)
>12 months to 18 months	12 (13)	5 (13)	0	17 (12)
>18 months to 24 months	13 (14)	2 (5)	0	15 (11)
>24 months to 36 months	34 (37)	2 (5)	0	36 (26)
>36 months to 48 months	4 (4.4)	6 (15)	0	10 (7)
>48 months	0	8 (21)	0	8 (6)

Reviewer Comment: *The 120-day safety update provides a longer duration of exposure to pexidartinib for patients with TGCT; importantly, no new cases of livery injury were observed on patients on the ENLIVEN study with longer follow-up, consistent with the observation that the majority of the cases of severe liver injury occur within the first few months of pexidartinib treatment. However, the long-term effects of pexidartinib on the liver are still uncertain.*

Table 109. Elevated ALT, AST and Total Bilirubin for All Patients With TGCT

	ENLIVEN Pexidartinib Part 1 and 2 N=61	ENLIVEN Crossover Part 2 N=30	Pooled Pexidartinib TGCT Patients N=139
ALT > ULN	41 (67)	22 (73)	85 (61)
≥3× ULN	21 (34)	5 (17)	31 (22)
≥5× ULN	14 (23)	3 (10)	19 (14)
≥10× ULN	4 (7)	0	6 (4.3)
AST > ULN	55 (90)	27 (90)	122 (88)
≥3× ULN	18 (30)	6 (20)	31 (22)
≥5× ULN	8 (13)	2 (7)	12 (9)
≥10× ULN	2 (3.3)	0	3 (2.1)
Bilirubin > ULN	7 (12)	0	14 (10)
≥2× ULN	3 (4.9)	0	4 (3.5)
≥2× baseline	21 (34)	3 (10)	38 (27)
TBIL ≥2× ULN and AST or ALT ≥3× ULN	3 (4.9)	0	4 (3.5)

Source: Reviewer generated table – summarizing ENLIVEN laboratory analysis dataset (ADLB, August 30, 2018 data cutoff date, submitted by Applicant), PLX1108-01 laboratory analysis dataset (ADLB, August 30, 2018 data cutoff date, submitted by Applicant) and PL3397-A-U126 clinical study report (CSR, October 24, 2018 data cutoff date)

Patient Narratives

The Applicant submitted narrative for the following events:

- Deaths during treatment or within 30 days of treatment discontinuation
- Deaths after 30 days of treatment discontinuation reported as related to pexidartinib
- SAEs
- Discontinuations due to AEs, excluding disease progression
- AEs judged to be of special interest
- Events meeting liver function test signature criteria of transaminases increase with hyperbilirubinemia

Below are narratives for the 3 patients (4.9%) in the ENLIVEN trial who developed signs of drug-induced liver injury as characterized by a total bilirubin ≥2× ULN and an AST or ALT ≥3× ULN, and, for the 2 patients receiving pexidartinib across the entire safety database (i.e., commercially-sponsored and investigator-initiated; n=768) who experienced irreversible hepatotoxicity.

TGCT Population

Severe Liver Injury

- 75-year-old female randomized to pexidartinib with transaminases and total bilirubin (TBIL) within normal limits at the time of enrollment in the ENLIVEN trial. Patient was started on pexidartinib 1000 mg/day and reduced to 800 mg/day on Day 15 per protocol. During screening and upon enrollment of the trial the patient was not taking any medications; however, on Day 1 of the trial the patient was started on atorvastatin. On Day 29 of the trial, the patient was noted to have an ALT 6× ULN, AST 5× ULN, ALP 2× ULN, TBIL 2× ULN, and direct bilirubin (DBIL) 6× ULN. Peak laboratory values were ALT 6× ULN, AST 6× ULN, ALP 2× ULN, TBIL 15× ULN and DBIL 84× ULN. Pexidartinib was interrupted and then permanently discontinued due to hepatoxicity. The atorvastatin was also discontinued. The patient underwent a liver biopsy that showed fatty liver and cholestasis with ductopenia. Additionally, the patient required hospitalization and treatment with 2 courses of bilirubin dialysis. The event of hepatotoxicity was consider resolved on Day 217 (7.1 months) when the TBIL was 1.1 mg/dL.

- 52-year-old male randomized to pexidartinib with transaminases and TBIL within normal limits at the time of enrollment in the ENLIVEN trial. Patient was started on pexidartinib 1000 mg/day and reduced to 800 mg/day on Day 15 per protocol. On Day 29 of the trial the patient was noted to have an ALT 3× ULN and AST 4× ULN, and ALP, TBIL and DBIL that were within normal limits. Peak laboratory values were ALT 9× ULN, AST 5× ULN, ALP 2× ULN, TBIL 7× ULN and DBIL 18× ULN. Pexidartinib was first interrupted when patient presented with jaundice and TBIL was also elevated and then permanently discontinued. A computed tomography (CT) scan of the abdomen was performed and showed a contracted gallbladder with mild enhancement of the gallbladder wall without definite intra- or extrahepatic ductal dilation. The patient did not require any additional

treatment for hepatotoxicity. On Day 58 (1.9 months), the event of hepatotoxicity was consider resolved with the following lab values ALT 2× ULN, AST 3× ULN, and ALP 2× ULN; and TBIL and DBIL were within normal limits.

- 67-year-old female randomized to pexidartinib with transaminases and TBIL within normal limits at the time of enrollment in the ENLIVEN trial. Patient was started on pexidartinib 1000 mg/day and reduced to 800 mg/day on Day 15 per protocol. On Day 43 of the trial the patient was noted to have ALT 3× ULN, AST 4× ULN, and ALP 1× ULN; TBIL and DBIL were within normal limits. Peak laboratory values were ALT 8× ULN, AST 5× ULN, ALP 3× ULN, TBIL 7× ULN and DBIL 4× ULN. Pexidartinib was permanently discontinued on Day 43 of the trial. An abdominal ultrasound and echography showed increased signal intensity meaning hepatic steatosis without pathological images; no dilatation of the bile duct; gallbladder was of normal size and liquid content without stones or other findings. The patient required hospitalization as well as antimicrobial treatment for cholangitis. Day 118 (3.9 months) the event of hepatotoxicity was considered resolved when the transaminases and total bilirubin were within normal limits.

Overall Safety Database

Irreversible Hepatotoxicity

- A 60-year-old female with breast cancer initiated on Trial IST3397-006 with liver enzymes and TBIL within normal limits at enrollment. The patient received pexidartinib at 600 mg BID and paclitaxel 155 mg IV weekly. On Day 19, the patient presented with fever, chills, sore throat, and right upper quadrant pain. The patient was noted to have ALT 1× ULN and AST 2× ULN; ALP, TBIL and DBIL were within normal limits. Peak laboratory abnormalities were ALT 12× ULN, AST 8× ULN, ALP 4× ULN, TBIL 25× ULN, and DBIL 5× ULN. Pexidartinib and paclitaxel were permanently discontinued due to the initial hepatic abnormalities. Liver biopsy revealed cholestasis and severe steatosis. Hepatologist consultation suspected drug-induced vanishing bile duct syndrome. Other medical complications associated with hepatoxicity and elevated bilirubin were a diagnosis of cholecystitis resulting in cholecystectomy; pathology was noted to be consistent with cholecystitis. Approximately 20 months after the first dose of study medications, the patient underwent a liver transplantation. On Day 103, post-transplant hepatic parameters were within normal range.

- A 66-year-old female with Stage IIIC mucosal melanoma was initiated on trial PLX108-13 with hepatic enzymes ALT 2× ULN, AST 2× ULN and TBIL within normal limits at screening. The patient was started on pexidartinib 1000 mg/day, cisplatin, temozolomide, and recombinant human endostatin. On Day 21, ALT 8× ULN, AST 11× ULN, TBIL was reported to be Grade 2 (laboratory value not reported) and DBIL was elevated to Grade 3 (laboratory value not reported). Peak laboratory abnormalities were ALT 10× ULN, AST 11× ULN, ALP 5× ULN, TBIL 18× ULN, and DBIL 60× ULN. Pexidartinib was permanently discontinued on Day 26. A CT scan demonstrated residual tumors in

the vaginal mucosa with no liver or lung metastasis. An abdominal ultrasound noted multiple hepatic cysts and possible chronic cholecystitis. The gallbladder showed poor filling with rough wall thickening but no dilation, and liver was normal in size and morphology. Medical treatments for hepatic failure included *silybum marianum*, UDCA, and unspecified Chinese herbal medication as well as two rounds of bilirubin absorption. The patient continued to receive 'liver-protecting' therapy including Chinese herbs but refused food and water for 2 weeks prior to coma. On Day 123 the patient died due to disease progression and cachexia. Hepatic enzymes and total bilirubin had continued to worsen until the time of death.

Reviewer Comment: *Pexidartinib use is clearly associated with liver injury. Across the development program 0.3% of patients experienced irreversible liver injury. Although none of the cases of irreversible liver injury occurred in a patient with TGCT; 3.1% of patients with TGCT and 4.9% of patients in Part 1 of ENLIVEN who received pexidartinib had laboratory values consistent with severe liver injury.*

The mechanism of action causing bile duct injury is unknown. There are two patterns of liver injury suggested by the laboratory evaluations. The first is an isolated aminotransferase elevation (i.e., hepatocellular injury) that occurs in the absence of bilirubin elevations. This is the most common liver injury observed, and, in general, improves with no intervention or dose modification (see Table 107). The second pattern is an aminotransferase elevation that occurs with a concurrent increase in bilirubin, which may be life-threatening. In these cases a high-grade aminotransferase elevation is usually observed. As seen in Table 107 and the patient narratives, these patients require discontinuation of pexidartinib and may require prolonged hospitalization and other supportive care. Liver biopsies from patients with this second pattern of livery injury reveal bile duct damage and ductopenia. Because serial biopsies were not performed in any patients, it is unknown whether the injury to bile ducts is progressive, and whether it occurs even in the setting of an (at least temporary) improvement or normalization of the biochemical laboratory parameters. Furthermore, it is unclear whether pexidartinib causes subacute and/or chronic/indolent injury that may not be detectable at first but could eventually result in clinically significant sequalae. Therefore, it is unclear whether measures taken to achieve normalization of transaminases address any subclinical effects of the drug on the liver, if they occur. An additional area of uncertainty is the potential long-term effect of pexidartinib on the liver. While it is reassuring that clinically significant liver injury appeared only in the first few months of pexidartinib exposure based on the available clinical trial data, only 69 patients have been exposed to pexidartinib for more than 18 months and 8 for more than four years. Since in the TGCT population, pexidartinib will be indicated for long-term use, it will be important to study the effects of long-term exposure in the post-market setting.

Based on the uncertainties of liver toxicity the proposed labeling incudes a black box warning with the following information:

- *Pexidartinib can cause serious and potentially fatal liver injury*
- *Monitor liver tests prior to initiation of TURALIO and at specified intervals during treatment. Withhold and dose reduce or permanently discontinue TURALIO based on severity of hepatotoxicity*
- *Pexidartinib is available only through a restricted program called the TURALIO Risk Evaluation and Mitigation Strategy (REMS) Program*

Section 5.1 of the proposed label also includes a warning and precaution that describes the risk of liver toxicity and provides information about monitoring and action that should be taken if liver toxicity occurs.

Hypertension

Hypertension was identified as a safety concern in patients who received pexidartinib. Below is comprehensive review of hypertension in ENLIVEN and the pooled TGCT population that received pexidartinib.

Hypertension was reported in 15% of patients treated with pexidartinib in Part 1 of ENLIVEN and in 18% of patients with TGCT who received pexidartinib (Table 110). Additionally, as seen in Table 102 of abnormal vital signs in all patients with TGCT treated with pexidartinib, 19% of patients experienced a blood pressure ≥120 mmHg with increase from baseline ≥20 mm Hg**.**

Table 110. Summary of Hypertension for All Patients With TGCT

	Placebo N=59	Pexidartinib Part 1 N=61	Pexidartinib Part 1 and 2 N=61	Cross Over to Pexidartinib N=30	Pooled Pexidartinib TGCT Patients N=130
All Grade[a] AEs	6 (10)	9 (15)	12 (20)	6 (20)	24 (18)
Grade 3-4 AEs	0	3 (4.9)	3 (4.9)	2 (7)	10 (8)
Serious AEs	0	0	0	0	0
Grade 3-4 Serious AEs	0	0	0	0	0
AEs Leading to discontinuation	0	1 (1.6)	1 (1.6)	0	1 (0.8)
AEs leading to dose reductions	0	0	0	0	0
AEs leading to dose interruptions	0	1 (1.6)	1 (1.6)	1 (3.3)	2 (1.5)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)
[a] Grade 1: SBP 120-139 mmHg or DBP 80-89 mmHg; Grade 2: SBP 140-159 mmHg or DBP 90-99mmHg; Grade 3 SBP≥160 mmHg or DBP≥100 mmHg; Grade 4: Life-threatening consequences (e.g., malignant hypertension, transient or permanent neurological deficit, hypertensive crisis)

Reviewer Comment: *TGCT is a nonfatal disease and patients have the potential to receive pexidartinib for long term therapy. Therefore, patients who experience hypertension due to pexidartinib therapy may require additional medications or may experience complications. Understanding the incidence, severity, and outcome is important to the risk: benefit assessment of pexidartinib.*

Concomitant Medications for Hypertension

As seen in Table 111, in Part 1 of ENLIVEN 15% of patients who received pexidartinib required medication to treat hypertension that occurred after the start of pexidartinib therapy. A similar proportion of the pooled pexidartinib TGCT patients required medication for adverse events of hypertension that occurred after pexidartinib therapy was initiated.

Reviewer Comment: *Among the 61 patients enrolled in Part 1 of ENLIVEN who received pexidartinib, a total of 6 patients were receiving anti-hypertension medication prior to starting pexidartinib. Of these six patients two patients required a change in their anti-hypertension regimen (i.e., to add a second medication), after the start of pexidartinib therapy.*

Table 111. Concomitant Medications[a] for Hypertension for All Patients With TGCT

	Pexidartinib Part 1 N=61	Pexidartinib Part 1 and 2 N=61	Cross Over to Pexidartinib N=30	Pooled Pexidartinib TGCT Patients N=130
Concomitant Medication Needed	9 (15)	13 (21)	7 (23)	22 (17)
ACE inhibitors	1 (1.6)	2 (3.3)	4 (13)	7 (5)
Aldosterone antagonists	0	0	1 (3.3)	1 (0.8)
Angiotensin II antagonists	3 (4.9)	4 (7)	2 (7)	6 (4.6)
Beta blocking agents	1 (1.6)	3 (4.9)	0	3 (2.3)
Dihydropyridine derivatives	4 (7)	5 (8)	2 (7)	8 (6)
Diuretics	1 (1.7)	2 (3.3)	0	2 (1.5)
Sulfonamides	0	1 (1.6)	0	1 (0.8)
Thiazides	1 (1.7)	2 (3.3)	3 (10)	7 (5)
Angiotensin II antagonists and diuretics	1 (1.7)	1 (1.6)	0	1 (0.8)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset and concomitant medication analysis dataset (ADAE and ADCM March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset and concomitant medication analysis dataset (ADAE and ADCM, March 3, 2017 data cutoff date, submitted by Applicant)
[a] Patients who initiated medications for treatment of hypertension after the initiation of pexidartinib treatment

Patient Narratives

The following narratives were included for patients who had action taken with pexidartinib related to hypertension.

- 54-year-old female who was randomized to pexidartinib in the ENLIVEN trial. No history of hypertension was reported prior to enrolling in ENLIVEN and blood pressure (BP) was 108/68 at baseline. The patient was started on pexidartinib 1000 mg/day and reduced to 800 mg/day on Day 15 per protocol. On Day 40 the patient was reported as having Grade 2 hypertension (no vital signs were reported). No action was taken with pexidartinib and no treatment was reported for hypertension. On Day 41, pexidartinib was interrupted for other adverse events and hypertension resolved on Day 43. On Day 45 pexidartinib was restarted at the same dose of 800 mg/day. On Day 64, the patients BP was reported as 139/77 mmHg and the patient was reported with hypertension Grade 2 no action was taken with pexidartinib or medication started in reaction to adverse event of hypertension. On Day 65 the dose of pexidartinib was reduced to 400 mg/day secondary to patient request. On Day 85 the patient's BP increased to 148/84 mmHg and furosemide was started as needed. On Day 89 pexidartinib was interrupted due to hypertension and was restarted on the same day. On Day 94, pexidartinib was permanently discontinued due to Grade 2 hypertension. On Day 96 the patient was treated with amlodipine (a calcium channel blocker) 5 mg orally once daily for hypertension. On Day 106, hypertension worsened to Grade 2 (no vital signs reported) and the dose of amlodipine was increased. On Day 113, the patients BP improved to 126/79 mmHg and on Day 124 the hypertension resolved.

- 56-year-old female randomized to the pexidartinib arm in the ENLIVEN trial. No history of hypertension was reported at the time of enrollment. Baseline BP was 140/85 mmHg. The patient was started on pexidartinib 1000 mg/day. On an unspecified day, Grade 3 hypertension was reported and pexidartinib was interrupted and amlodipine was started. The patient resumed pexidartinib on Day 13 and dose was reduced on Day 15 to 800 mg per protocol. The patient remained on amlodipine and continued on pexidartinib therapy until the time of data cut off. At the time of data cut off, the patient's BP was 140/80 mmHg which is Grade 2 hypertension per CTCAE guidelines.

Reviewer Comment: *Hypertension occurred in a greater proportion of patients randomized to pexidartinib in Part 1 of ENLIVEN than in patients randomized to placebo. The higher proportion of patients experiencing hypertension was confirmed by an analysis of vital signs. Additionally, across all TGCT patients treated with pexidartinib, 18-23% experienced an adverse event of hypertension. The majority of these events were Grade 1 or 2 and did not lead to any action being taken with pexidartinib. In ENLIVEN, one patient experienced a dose interruption and one patient discontinued pexidartinib permanently secondary to hypertension. Most of the patients did require medication for their hypertension. However, with concomitant medication use most patients were able to stay on pexidartinib with improvement in the blood pressure parameters. Hypertension is thus considered a manageable adverse reaction. Hypertension will be included*

in the package insert in section 6 as a frequent adverse reaction in order to inform prescribers of the risk of increased blood pressure while on pexidartinib.

Cognitive Impairment

Cognitive impairment was identified as a potential safety concern in patients who received pexidartinib. As seen in Table 112, among the 130 patients with TGCT who received pexidartinib, 21 (16%) experienced adverse events associated with cognitive impairment. However, the incidence of cognitive impairment was the same (5%) in patients who received pexidartinib and in those who received placebo in Part 1 of ENLIVEN.

Table 112. Summary of Cognitive Impairment[a] for All Patients With TGCT

	Placebo N=59	Pexidartinib Part 1 N=61	Pexidartinib Part 1 &2 N=61	Cross Over to Pexidartinib N=30	Pooled Pexidartinib TGCT Patients N=130
All Grade AEs	3 (5)	3 (5)	3 (5)	3 (10)	21 (16)
Grade 3-4 AEs	0	0	0	0	0
Serious AEs	0	0	0	0	0
AEs Leading to discontinuation	0	0	0	0	4 (3.1)
AEs leading to dose reductions	0	0	0	1 (3.3)	6 (4.6)
AEs leading to dose interruptions	0	0	0	1 (3.3)	5 (3.8)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

[a] Adverse events included in the evaluation of cognitive impairment included the following PT terms: cognitive disorder, memory impairment, amnesia, confusional state, disturbance in attention, and attention deficit/hyperactivity

Table 113 displays the specific adverse events associated with cognitive impairment in all patients with TGCT treated with pexidartinib, by MedDRA preferred term.

Table 113. AEs Associated With Cognitive Impairment for All Patients With TGCT

	ENLIVEN Placebo Part 1 N=59		ENLIVEN Pexidartinib Part 1 N=61		ENLIVEN Pexidartinib Part 1 & 2 N=61		ENLIVEN Crossover Part 2 N=30		Pooled Pexidartinib TGCT Patients N=130	
MedDRA Preferred Term	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**	**All Grades n (%)**	**Grade 3-4 n (%)**
Any patient with an adverse event associated with cognitive impairment	3 (5)	0	3 (5)	0	3 (5)	0	3 (10)	0	21 (16)	0
Cognitive disorder	0	0	2 (3.3)	2 (3.3)	0	0	0	0	9 (7)	0
Memory impairment	1 (1.7)	0	0	0	0	0	3 (10)	0	7 (5)	0
Amnesia	1 (1.7)	0	0	0	1 (1.6)	0	0	0	5 (3.8)	0
Confusional state	0	0	0	0	0	0	0	0	3 (2.3)	0
Disturbance in attention	1 (1.7)	0	0	0	0	0	0	0	2 (1.5)	0
Attention deficit/hyperactivity	0	0	1 (1.6)	0	1 (1.6)	0	0	0	1 (0.8)	0

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset (ADAE, March 27, 2017 data cutoff date, submitted by Applicant) and PLX1108-01 adverse event analysis dataset (ADAE, March 3, 2017 data cutoff date, submitted by Applicant)

Patient Narratives

Below are the patient narratives for patients with TGCT who experienced cognitive impairment while receiving pexidartinib.

- 20-year-old female who was randomized to placebo in Part 1 of ENLIVEN. No past medical history was reported. The patient had a normal hepatic laboratory evaluation at the time of enrollment. After completing Part 1, the patient crossed over to pexidartinib 800 mg/day. On Day 8 of pexidartinib the patient's AST was 1.8× ULN, ALT, TBIL, ALP, and DBIL remained normal throughout treatment while AST fluctuated between the ULN and 2x ULN. No action was taken with pexidartinib due to elevated AST. On Day 156 of pexidartinib 800 mg/day, the patient developed Grade 1 memory impairment. No action was taken with pexidartinib. The patient was continuing pexidartinib at the time of data cut off and the memory impairment was ongoing at the time of the last available report.

- 75-year-old female initially randomized to placebo in Part 1 of ENLVIEN. Past medical history included high cholesterol. Concomitant medications included atorvastatin. The patient had a normal hepatic laboratory evaluation at the time of enrollment. After completing Part 1, the patient crossed over to pexidartinib 800 mg/day. On Day 8 of pexidartinib therapy, the patient's was AST 1.3× ULN and remained elevated for the remainder of pexidartinib treatment with a peak value of 2.7× ULN. On Day 29 of pexidartinib, ALT also became elevated at 1.1× ULN and remained elevated for 3 weeks with a peak value of 2.3× ULN. After this time, the ALT returned to normal. The TBIL, ALP and DBIL remained within normal limits throughout pexidartinib treatment. On Day 34, pexidartinib was reduced to 600 mg/day secondary to fatigue. On Day 168, while receiving 600 mg/day of pexidartinib, the patient developed Grade 2 memory impairment and pexidartinib was interrupted. On Day 188 pexidartinib was restarted at a reduced of 400 mg/day. The memory impairment improved to Grade 1 after dose interruption and reduction. The patient was continuing pexidartinib at the time of data cut off and the memory impairment was ongoing at the time of the last available report.

- 55-year-old male initially randomized to placebo in Part 1 of in ENLIVEN. Past medical history included hypercholesterolemia and hypertension. Concomitant medications included amlodipine, omeprazole, and atorvastatin. The patient had a normal hepatic laboratory evaluation at the time of enrollment. After completing Part 1 the patient crossed over to pexidartinib 800 mg/day. On Day 43 of pexidartinib therapy, the patient had an ALT of 1.1x ULN and AST of 1.2x ULN. On Day 64, both ALT and AST were within normal limits and remained so for the remainder of pexidartinib therapy. TBIL, ALP, and DBIL remained within normal limits throughout treatment. On Day 338 of 800 mg/day of pexidartinib the patient developed Grade 1 memory impairment. The pexidartinib dose was reduced (reduced dose not provided) due memory impairment. The patient was continuing pexidartinib at the time of data cut off and the memory impairment was ongoing at the time of the last available report.

- 31-year-old male randomized to pexidartinib in Part 1 of ENLIVEN. No past medical history was reported. Concomitant medication included cetirizine, gabapentin, gabapentin enacarbil, hydrocodone bitartrate/paracetamol, tizanidine hydrochloride, oxycodone hydrochloride, and morphine sulphate. At baseline and throughout the study, the patient's hepatic laboratory evaluations were within normal limits. On Day 1, the patient received pexidartinib 1000 mg/day and per the protocol, the dose of the pexidartinib was reduced to 800 mg/day on Day 15. On Day 146, the patient developed Grade 1 cognitive disorder and Grade 2 restless legs syndrome. No action was taken with pexidartinib and no treatment was reported for the events. On Day 169, the patient entered Part 2 and continued to receive pexidartinib 800 mg/day. On Day 253, the patient experienced Grade 1 irritability and on Day 281, the patient developed Grade 1 amnesia (short term memory loss). No action was taken with pexidartinib and no treatment was reported for the events. The patient withdrew from the study on Day 355. The reason for patient's withdrawal was not provided. The events of cognitive disorder, irritability, and amnesia were ongoing at the time of the last available report.

- 29-year-old male randomized to pexidartinib in Part 1 of ENLIVEN. No relevant medical history or concomitant medications were reported. At baseline and throughout the trial the patient's hepatic laboratories were reported as normal. On Day 1 the patient received pexidartinib 1000 mg/day and reduced to 800 mg/day on Day 15 per protocol. On Day 20, the patient developed Grade 1 cognitive disorder. No action was taken with pexidartinib and no treatment was reported for the event. On Day 25, the event of cognitive disorder resolved. On Day 169, the patient entered Part 2 of the study and continued to receive pexidartinib 800 mg/day. The patient was continuing pexidartinib at the time of data cut off with no further events related to cognitive impairment.

- 41-year-old female enrolled on Study PLX108-01. No past medical history or concomitant medication were reported. On Day 385 the patient experienced Grade 1 disturbance in attention. On Day 448 the disturbance in attention increased to Grade 2 and pexidartinib was interrupted. On Day 386, the patient reported Grade 1 intermittent concentration impairment and on Day 540 the concentration impairment increased to Grade 2 and pexidartinib was permanently discontinued. After permanent discontinuation the events of disturbance in attention and intermittent concentration impairment resolved on Day 561.

- 48-year-old female enrolled on Study PLX108-01. Past medical history includes fatigue, depression, hyperparathyroidism, and iron deficiency anemia. Concomitant medications included diphenhydramine and bupropion. On Day 22, the dose of pexidartinib was reduced to 800 mg/day secondary to Grade 2 nausea. On Day 279, the patient experienced Grade 1 memory impairment. No action was taken. On Day 312 the patient had her dose reduced to 400 mg/day secondary to Grade 2 fatigue. At this time the memory impairment was reported as ongoing. On Day 504, pexidartinib was permanently discontinued due to ongoing fatigue and memory impairment. On Day 697, the fatigue and memory impairment had resolved.

- 33-year-old female enrolled in Study PLX108-01. No past medical history was reported. Concomitant medications included azelaic acid, desloratadine, topical clindamycin, dexlansoprazole, Epiduo ointment, hydrocortisone cream, and lansoprazole. On Day 9 the patient experienced Grade 2 memory impairment which resulted in a dose reduction of pexidartinib to 800 mg/day. The memory impairment improved to Grade 1 on Day 161. On Day 193, the patient experienced Grade 1 cognitive disorder resulting in reduction of pexidartinib to 400 mg/day. On Day 510, pexidartinib was discontinued due to continuing memory impairment. After permanent discontinuation the memory impairment resolved.

- 33-year-old male enrolled on Study PLX108-01. No past medical history was reported, and concomitant medication included cetirizine. On Day 5, the patient experienced Grade 1 cognitive disorder and pexidartinib was permanently discontinued on Day 16. On Day 74 the cognitive disorder was considered resolved.

Reviewer Comment: *Cognitive impairment occurred in 16% of patients with TGCT treated with pexidartinib across the development program, with all but one case classified as mild to moderate (Grade 1-2). However, for unclear reasons, the rate of cognitive impairment was higher in patients enrolled on Study PLX108-01 than in ENLIVEN, and on the randomized portion of ENLIVEN, the rate of cognitive impairment was the same in patients randomized to pexidartinib as it was in those randomized to placebo.*

A review of the narrative summaries of patients with TGCT treated with pexidartinib who experienced cognitive impairment did not reveal any predisposing factors or underlying conditions that increased the likelihood that a patient would develop cognitive impairment. There were no standard protocol-specified guidelines for managing toxicity in the protocols for ENLIVEN or Study PLX108-01 which limits our ability to draw conclusions about causality from de-challenge/re-challenge information. However, the majority of patients who discontinued, interrupted or dose reduced pexidartinib due to cognitive impairment experienced improvement or resolution of the adverse event upon implementation of these measures. In the absence of other causal factors, the temporality of the association, and the resolution of symptoms with dose interruptions, dose reductions, or permanent discontinuation this reviewer concludes that cognitive impairment may be associated with pexidartinib treatment. Given that TGCT occurs in patients between 20 and 60 and that patients will potentially receive long term therapy with pexidartinib, events that could may impair their cognitive functioning (e.g., ability to work, operate heavy machinery, or motor vehicles), are important to understand. This reviewer recommends that cognitive impairment be included in section 6 of the pexidartinib prescribing information. As events of cognitive impairment were overall rare and low-grade across the development program, and a clear causal association with pexidartinib has not been established (rates comparable on both arms of ENLIVEN), the reviewer does not recommend restrictions on activities of daily living in the absence of symptoms.

8.3.5. Safety Analyses by Demographic Subgroups

Sex

In Part 1 of ENLIVEN, female patients represented 57% of the patients randomized to pexidartinib and 61% of patients randomized to placebo. Table 114 shows the incidence of treatment emergent adverse events by treatment and sex. Overall there is does not appear to be any notable differences between females and males and there is no evidence to suggest that sex affects the tolerability of pexidartinib.

Table 114. Comparison of AEs by Sex for the First 25 Weeks of Treatment, ENLIVEN

	ENLIVEN N=61		Placebo N=59	
MedDRA Preferred Term	Female N=35 n (%)	Male N=26 n (%)	Female N=36 n (%)	Male N=23 n (%)
Any TEAE	35 (100)	25 (96)	33 (92)	22 (96)
Any SAE	7 (11)	1 (3.8)	1 (2.8)	0
TEAEs leading to study drug action				
TEAEs leading to discontinuation	6 (17)	2 (8)	0	0
TEAEs leading to interruption/reduction	16 (46)	7 (27)	4 (11)	2 (9)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset and subject listing analysis dataset (ADAE and ADSL March 27, 2017 data cutoff date, submitted by Applicant)

Age

In Part 1 of ENLIVEN, only 4 (7%) patients who received pexidartinib and 3 (5%) of patients who received placebo were ≥65 years of age. The proportion of patients ≥65 years of age is too small to draw any conclusions about the safety of pexidartinib in this patient population.

Race

In the safety population of ENLIVEN, the majority of patients in each arm were White (85% in the patients randomized to pexidartinib and 92% in the patients randomized to placebo). Table 115 summarizes the incidence of TEAEs by race (White v. other) for patients randomized to pexidartinib and placebo. The relative homogeneity of patient population in ENLIVEN with regards to race does not allow for meaningful comparisons to be made across race categories.

Table 115. Comparison of AEs by Race for the First 25 Weeks of Treatment, ENLIVEN

	ENLIVEN N=61		Placebo N=59	
MedDRA Preferred Term	White N=52 n (%)	Other N=9 n (%)	White N=54 n (%)	Other N=5 n (%)
Any TEAE	51 (98)	9 (100)	50 (93)	5 (100)
Any SAE	6 (12)	2 (17)	1 (1.9)	0
TEAEs leading to study drug action				
TEAEs leading to discontinuation	7 (14)	1 (11)	0	0
TEAEs leading to interruption/reduction	20 (38)	3 (33)	4 (7)	2 (40)

Source: Reviewer generated table – summarizing ENLIVEN adverse event analysis dataset and subject listing analysis dataset (ADAE and ADSL March 27, 2017 data cutoff date, submitted by Applicant)

8.3.6. Specific Safety Studies/Clinical Trials

No specific safety studies or clinical trials were submitted with this NDA.

8.3.7. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

A two-year carcinogenicity study with pexidartinib in rats and a 26-week carcinogenicity study in rasH2 transgenic mice were performed by the Applicant. Animals treated with pexidartinib did not show statistically significant increases in neoplastic lesions compared to control treated animals. Please see Section 5.5.3 for details.

Human Reproduction and Pregnancy

Two patients became pregnant during pexidartinib treatment; both were patients with TGCT enrolled in ENLIVEN. One patient was a 36-year-old whose treatment was interrupted after a positive pregnancy test; this patient resumed pexidartinib after electing to terminate the pregnancy. The second patient was a 42-year-old whose treatment was interrupted after a positive pregnancy test and resumed after the patient experienced a spontaneous abortion.

Pediatrics and Assessment of Effects on Growth

No studies have been performed to assess effects on growth and no pediatric trials have been completed. See Section 10 for details.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is no expected drug abuse potential for pexidartinib. There were no cases of overdose across all submitted studies. In the case of overdose, pexidartinib is not expected be dialyzable due to high plasma protein binding.

8.3.8. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Pexidartinib is a new molecular entity in the US and has no marketing approvals globally.

Expectations on Safety in the Postmarket Setting

The safety profile of pexidartinib in the postmarket setting is expected to be similar to what was observed from the safety data from clinical trials submitted to support this NDA. The incidence of all adverse events, including liver injury related events, is expected to be higher in a patient population receiving treatment outside the tightly controlled setting of a clinical trial. With regards to the potentially life-threatening risk of hepatotoxicity, FDA expects that the implementation of a Risk Mitigation and Evaluation Strategy (REMS) to ensure that prescribers are informed of the serious risk of pexidartinib and of the need for rigorous laboratory monitoring, and that pharmacies verify physician certification prior to dispensing the drug, will mitigate this risk. Additionally, consistent with postmarket adverse event monitoring through the FDA Adverse Event Reporting System (FAERS), FDA will continue to assess the safety profile of pexidartinib post-approval and weigh the observed risks against the benefits of the drug in the indicated population. FDA will also require that the Applicant conduct a post marketing study to further assess the long-term risk of pexidartinib in patients who experience serious adverse liver injury. Refer to Section 12 Risk Evaluation and Mitigation Strategies (REMS), and Section 13 Postmarketing Requirements and Commitment, for details.

8.3.9. Integrated Assessment of Safety

The primary assessment of the safety of pexidartinib in the indicated population was based upon the results of the ENLIVEN trial which randomized (1:1) 120 patients with TGCT to receive pexidartinib (n=61) or placebo (n=59) in the 2-part multicenter study. The results of Study PLX108-01 (n=39) provided additional data to support the assessment of safety in patients with TGCT. Overall, a total of 768 patients constituted the pexidartinib safety database included in the NDA submission; the safety database included studies of pexidartinib administered as a single agent and in combination with other agents, in patients with TGCT (n=130) and solid tumor and hematologic malignancies, in commercially-sponsored and investigator-initiated trials.

In ENLIVEN, patients received pexidartinib 400 mg orally in the morning and 600 mg orally in the evening each day for 2 weeks followed by 400 mg orally twice daily until disease progression or unacceptable toxicity. Seventy-nine percent of patients received pexidartinib for 6 months or longer and 66% for greater than one year.

One patient in ENLIVEN experienced a Grade 5 event (cardiac arrest); this patient was initially randomized to receive placebo in Part 1 of ENLIVEN and received pexidartinib in Part 2. The death was deemed unrelated to the study drug.

Overall, the proportion of patients who experienced one or more adverse events during Part 1 of ENLIVEN was similar across study arms (pexidartinib: 98%; placebo 93%); however, the

proportion of patients who experienced Grade 3-4 adverse events was higher on the pexidartinib arm (44%) compared to the placebo arm (11%). The most common (>20%) adverse reactions, including laboratory abnormalities, in patients who received pexidartinib were: increased lactate dehydrogenase (LDH), increased AST, hair color changes, fatigue, increased ALT, decreased neutrophils, increased cholesterol, increased ALP, decreased lymphocytes, eye edema, decreased hemoglobin, rash, dysgeusia and decreased phosphate.

In addition to the common AEs, hypertension and cognitive impairment were also observed in patients who received pexidartinib. Hypertension occurred in a greater proportion of patients randomized to pexidartinib than to placebo in Part 1 in ENLIVEN and was observed in approximately 20% of all TGCT patients treated with pexidartinib. One patient randomized to pexidartinib required discontinuation secondary to hypertension and 2 patients with TGCT treated with pexidartinib required dose interruption due to hypertension. As seen in Table 111, 17% of patients with TGCT treated with pexidartinib required medication to treat hypertension that occurred after the initiation of pexidartinib therapy. Additionally, among the 61 patents enrolled in Part 1 of ENLIVEN, 6 patients who were already receiving anti-hypertensive medication prior to starting pexidartinib required the addition of a second medication after the start of pexidartinib therapy. Cognitive impairment (a composite term that includes cognitive disorders, memory impairment, disturbance in attention and confusional state) occurred in 16% of the 130 patients with TGCT who received pexidartinib across the development program, although it was reported in just 5% of patients enrolled to either pexidartinib or placebo arm of the randomized portion of ENLIVEN, making a causality assessment less certain. All of these adverse events were Grade 1 or 2. Four of these adverse events led to discontinuation of pexidartinib. Additionally, 6 events led to dose reduction and 5 led to dose interruptions of pexidartinib.

Serious adverse reactions were reported in 13% of patients; the most frequent (occurring in more than 1 patient) included abnormal liver tests (3.3%) and hepatotoxicity (3.3%). Permanent discontinuation of pexidartinib due to an adverse reaction occurred in 13% of patients; the most frequent adverse reactions (occurring in more than 1 patient) requiring permanent discontinuation included increased ALT (4.9%), increased AST (4.9%) and hepatotoxicity (3.3%). Dose reductions or interruptions occurred in 38% of patients; the most frequent adverse reactions (occurring in more than 1 patient) requiring a dosage reduction or interruption were increased ALT (13%), increased AST (13%), nausea (8%), increased ALP (7%), vomiting (4.9%), increased bilirubin (3.3%), increased GGT (3.3%), dizziness (3.3%), and abdominal pain (3.3%).

Overall, the risk of liver injury in patients who are exposed to pexidartinib was a major review issue. In the ENLIVEN trial, serum transaminase elevations occurred in a majority of patients; elevations in alanine transaminase (ALT) and aspartate transaminase (AST) occurred in 67% and 90% of patients, respectively; bilirubin increases occurred less frequently in 12% of patients. Approximately 5% of patients in the ENLIVEN trial experienced a pattern of serum transaminase and bilirubin elevation that is indicative of severe liver injury, characterized by AST or ALT greater than 3 times the upper limit of normal (ULN) with concurrent bilirubin increases greater than 2 times the ULN. Across the overall development program in patients with and without

TGCT, a similar frequency and severity in serum transaminase and bilirubin abnormalities was observed.

There were 2 cases of irreversible liver injury among the 768 patients in the overall development program of pexidartinib; one patient subsequently underwent liver transplantation, and another died due to several factors including liver failure. In the few patients with evidence of liver severe injury whose clinical workup included biopsies, including the 2 patients with irreversible liver injury, there was evidence of bile duct injury or ductopenia.

There remain uncertainties about the long-term effects of treatment with pexidartinib. Although the majority of patients who experienced serum transaminase and bilirubin elevations while receiving pexidartinib had improvement to baseline levels with dose reductions, dose interruption, and/or discontinuation of pexidartinib, some patients had a prolonged time to recovery despite the implementation of these measures. Because serial biopsies were not performed in most patients with evidence of liver injury, the scope of the liver injury that may occur in the setting of clinically 'normal' or 'improved' serum transaminase and bilirubin levels is unknown. Furthermore, it is unclear whether exposure to pexidartinib causes subacute and/or chronic/indolent injury which is not detectable at first with laboratory monitoring, but which may eventually result in adverse clinical outcomes.

Ultimately, the risk of hepatotoxicity was manageable in ENLIVEN through dose modifications and/or withdrawal of pexidartinib, including in those who patients who experienced serious events with long recovery periods. In the post-approval setting, the risk of hepatotoxicity can be mitigated with careful selection of patients so that they reflect the indicated population, careful laboratory and clinical monitoring, dosage modifications, and drug withdrawal as outlined in the prescribing information, and with implementation of a restricted distribution program.

The review team recommends a boxed warning for hepatotoxicity and distribution of pexidartinib through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program; this program will include a patient registry to provide additional information to further characterize the risk of hepatotoxicity outside the clinical trial setting and to assess the potential risk of liver injury associated with long-term pexidartinib treatment. The review team also recommends that the applicant, as a postmarketing requirement, conduct a trial to evaluate the long-term risk of hepatic failure in patients with TGCT who experience severe liver injury while on pexidartinib. Such a trial should also evaluate the mechanism of action of liver injury through the collection of liver biopsies and be designed to identify patient populations at highest risk of severe liver injury and to provide evidence-based dose modifications and monitoring recommendations.

SUMMARY AND CONCLUSIONS

8.4. Statistical Issues

The ENLIVEN trial demonstrated a statistically significant improvement in ORR and mean change from baseline to Week 25 in ROM for pexidartinib compared to those who were randomized to placebo. However, there were concerns of estimating the treatment effect of secondary COA endpoints due to substantial missing data and interpreting the clinical benefit of secondary endpoints.

Although the COA secondary endpoints of ROM, physical function, and worst stiffness were statistically significant, the percent of patients with missing data at Week 25 for ROM, physical function, and worst stiffness were 27%, 43%, and 43%, respectively. The percent of missing data is much higher than acceptable for reliable estimation of physical function, worst stiffness, and BPI-30. Therefore, interpretation was focused on ROM, which still had over 25% missing data at the time of the primary analysis.

In addition to the extent of missing data, missingness in the COA endpoint data itself may be indicative of worsening of symptoms while on treatment (i.e., informative missingness). The primary concern regarding missing ROM data is that the assessments may not be missing at random and therefore may lead to a biased interpretation of the benefit of pexidartinib based on COA data. Post hoc sensitivity analyses were performed to evaluate the impact of missing data assumptions for ROM. Based on pre-specified and sensitivity analyses, the estimated within-patient ROM improvement in the pexidartinib arm ranged from 7% to 19%.

Interpretation of the observed ROM results was limited by several factors. First, the Applicant changed the hierarchical order of the secondary endpoints after a substantial amount of missing data was discovered. Although this was done prior to unblinding the outcome data, the decision to change the hierarchy of the secondary endpoints is acknowledged as a weakness of the ENLIVEN results. Since BPI-30 was not statistically significant and was originally the first secondary endpoint to be tested, the remaining COA endpoints, including ROM, would not have been tested for inference had the endpoints not been rearranged.

Second, although ROM was evaluated by a blinded third-party assessor, there was potential for unblinding because hair color changed to white for 67% of the patients on pexidartinib. Since ENLIVEN was a double-blind study, this can cause unblinding of the clinical assessors leading to potential bias in reporting of ROM. However, FDA's exploratory subgroup analysis did not show any differences in ROM between patients whose hair color changed to white compared to those whose hair color did not change.

Finally, while statistical significance is demonstrated for small group level mean differences, the clinical meaningfulness of within-patient change is unclear. Daiichi Sankyo proposed that a +6.7% threshold for what constitutes a clinically meaningful within-patient change for ROM for the knee only, which corresponds to 10 degrees. In the ENLIVEN trial, while the majority of patients' tumor is in the knee joint, close to 40% of patients have disease in other joints. The

Applicant stated that a threshold was proposed for the knee only because there is no widely used standard of improvement in ROM for other joints as it depends on the specific joint as well as the degree of impairment at baseline. There appears to be some clinical benefit of pexidartinib on ROM because more patients in the pexidartinib arm (41%) had a clinically meaningful improvement in ROM at the knee compared to the placebo arm (18%) assuming a 6.7% threshold represents clinically meaningful functional improvement.

The ENLIVEN trial demonstrated a statistically significant improvement in ORR and mean change from baseline to Week 25 in ROM for pexidartinib compared to those who were randomized to placebo. Although a treatment benefit was demonstrated for ROM, there is uncertainty in the magnitude of the treatment effect due to missing data. Additionally, interpretation of the effect is unclear due limited information on clinical meaningfulness for the target patient population in ENLIVEN.

8.5. Conclusions and Recommendations

ENLIVEN met the primary endpoint of BICR-assessed ORR per RECIST v 1.1 with an ORR of 38% (95% CI 26%, 50%) in the pexidartinib arm and no responses (95% CI 0, 6%) in the placebo arm ($p<0.0001$). Additional responses occurred with prolonged exposure to pexidartinib, and a post-hoc analysis conducted with a median follow-up time of 61 weeks showed an ORR of 52% on the pexidartinib arm of ENLIVEN, similar to that observed in TGCT patients across the development program. On ENLIVEN, the median DOR was not reached and ranged from 6.9+ to 24.9+ months. One patient had progressive disease in follow-up. Among the 23 patients who responded, 22 (96%) had ongoing responses at 6 months of follow-up. Among the 13 patients on follow-up for at least one year, 13 had ongoing responses.

Due to the slow-growing nature of TGCT, tumor response by itself may not predict clinical benefit. Thus, ENLIVEN was designed with clinical outcome assessments as secondary endpoints to assess TGCT-specific symptoms and functional impacts. ENLIVEN demonstrated a statistically significant improvement in mean change from baseline to Week 25 for those patients who were randomized to pexidartinib compared to those who were randomized to placebo for the COA secondary endpoints of ROM, physical function, and worst stiffness. However, the proportion of patients with missing data for ROM, physical function, and worst stiffness was significant at 27%, 43%, and 43%, respectively. Sensitivity analyses for physical function and worst stiffness evaluating the impact of missing data assumptions would not mitigate the concern of bias in interpretation of clinical benefit due to the substantial amount of missing data for physical function and worst stiffness. Therefore, only clinician-reported ROM was included in the evaluation of efficacy for pexidartinib. Overall, the analyses show that there appears to be a treatment benefit of pexidartinib on ROM, but that the magnitude is not clear and the estimated within-patients ROM improvement in the pexidartinib arm ranged from 7 to 19%..

Analysis of safety data included in the application confirmed a clear signal for liver injury associated with pexidartinib. The acute risk of liver injury associated with pexidartinib has been well-characterized. Most pexidartinib-associated elevations in transaminases or bilirubin are

mild or moderate and resolve with either no intervention or temporary interruption of pexidartinib. However, across the development program, 3.1% of patients with TGCT had laboratory values consistent with severe liver injury, two of which had a prolonged time to recovery and required additional supportive care, and 0.3% of all pexidartinib-treated patients experienced irreversible liver injury.

The mechanism of action causing bile duct injury is unknown. Liver biopsies were obtained in only 8 of the 768 patients in the pexidartinib safety database and serial biopsies were not performed in any patients. Thus, it is unknown whether pexidartinib-induced injury to bile ducts is progressive, and whether it continues even in the setting of an improvement in or normalization of the biochemical laboratory parameters. Furthermore, it is unclear whether pexidartinib causes subacute and/or chronic/indolent injury that is initially undetectable by routine laboratory monitoring but that may result in clinically relevant sequellae with long term exposure to pexidartinib. Therefore, it is unclear whether measures taken to achieve normalization of transaminases address any potential subclinical effects of the drug on the liver.

Overall, ENLIVEN demonstrated a statistically significant and clinically meaningful increase in ORR at 25 weeks for patients treated with pexidartinib compared to those who received placebo. The improvement in ORR was supported by the observation that ORR increases to 53% with longer follow-up, by the near universal durability of responses at 6 and 12 months, and by a 7 to 19% improvement in ROM at 25 weeks. Pexidartinib causes liver injury that is generally self-limited or manageable with temporary dose interruption, but, in rare cases, may be severe or irreversible. The Risk Evaluation and Mitigation Strategy (REMS) agreed to by the Applicant and the FDA (see Section 11 of this review) will help mitigate this risk by educating providers about the appropriate patient population to receive pexidartinib, as well as about the risk and the importance of monitoring liver tests, and by restricting distribution to patients whose providers are fulfilling the requirements of the REMS. Additionally, the REMS will collect information about the frequency of severe liver toxicity outside of the clinical trial setting which will provide information about the risk of liver toxicity with longer term exposure and whether the REMS is successfully mitigating the risk. Finally, the Applicant has agreed to conduct a postmarketing trial to evaluate the long-term risk of hepatic failure in patients with TGCT who experience severe liver injury while on pexidartinib. This trial will also evaluate the mechanism of action of liver injury through the collection of liver biopsies, help identify patient populations at highest risk of severe liver injury, and generate information that can be used to refine dose modification and monitoring recommendations. Therefore, we are recommending approval for this application for pexidartinib for the treatment 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.

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9. Advisory Committee Meeting and Other External Consultations

The Division referred this application to the Oncologic Drugs Advisory Committee (ODAC); the meeting was held on May 14, 2019. The major issues for discussion were: the assessment of clinical benefit, and the assessment of an identified risk of liver injury in pexidartinib-treated patients. FDA requested that the advisory committee discuss the following topic:

- whether the benefits of pexidartinib, as characterized by a clinically meaningful reduction in tumor burden and an improvement in range of motion, outweigh its risk of hepatoxicity.

A summary of the major issues is provided below.

Assessment of Clinical Benefit: Interpreting the clinical meaningfulness of the observed ORR in the context of a disease setting characterized by an often progressive and debilitating but slow-growing and benign tumor poses some challenges in evaluating the durability of tumor responses in the ENLIVEN trial. Patients with TGCT experience symptoms such as pain, stiffness, swelling, and impairment in ROM, which can cause severe functional impairment. Therefore, the evaluation of the effects of pexidartinib on the symptomatic aspects of the disease requires COAs that are valid, reliable and clinically relevant. A key issue for this application is whether the results of the COA measures provide evidence of benefit for the functional aspects of the disease. While the analysis of the COA secondary endpoints of ROM, physical function, and worst stiffness demonstrated a statistically significant improvement in mean change from baseline to Week 25 for the pexidartinib arm compared to the placebo arm, the interpretability of these results is limited due to several factors, including uncertainty regarding the threshold for what constitutes a clinically meaningful within-patient change in ROM, and a high level of missing data at Week 25. A primary concern regarding missing COA data is that the assessments may not be missing at random, therefore imputation may lead to a biased interpretation of the benefit of pexidartinib based on COA data.

Characterization of Liver Injury: A key issue for this application has been to define the risk of liver injury in patients who receive pexidartinib. A majority of patients who received this drug experienced elevations in transaminase values. In the ENLIVEN trial, ALT, AST, and total bilirubin elevations occurred in 67%, 90%, and 12% of patients, respectively, with Grade ≥3 severity in one third of patients. In the ENLIVEN trial, 4.9% (upper bound of the 95% CI: 13.7%) of patients had laboratory abnormalities indicative of drug induced liver injury (i.e., a total bilirubin of greater than or equal to 2x the upper limit of normal [ULN] and an AST or ALT greater than or equal to 3x the ULN. This pattern was consistent with that observed in a pooled analysis of all TGCT patients in the pexidartinib development program (N=130). The majority of patients in the TGCT population who experienced transaminase elevations and total bilirubin increase had improvement to baseline levels with dose reductions, dose interruption, and/or discontinuation of pexidartinib.

In the pooled safety population of 630 pexidartinib-treated patients with solid tumors or hematologic malignancies who received pexidartinib as a single agent or in combination with

other therapies in commercial-sponsored trials, 2.5% (upper bound of the 95% CI: 4.1%) of patients had a total bilirubin of greater than or equal to 2x the ULN and an AST or ALT greater than or equal to 3x the ULN.

Across the overall development program (commercial-sponsored and investigator-initiated trials), two of 768 pexidartinib-treated patients (observed rate 0.3%; upper bound of the 95% CI: 0.9%) experienced irreversible liver injury, resulting in liver transplantation in one patient and death in another.

There were eight patients across the development program (n=768) in whom liver biopsies were obtained to evaluate significant transaminase and/or total bilirubin abnormalities while receiving pexidartinib; the findings reveal a pattern of hepatocellular injury as well as injury to bile ducts/ ductopenia. Because serial liver biopsies were not performed in these patients, determining whether the injury to bile ducts, when present, is progressive even in the setting of an improvement or normalization of the biochemical laboratory parameters, is an area of uncertainty. Furthermore, it is unclear in what proportion of patients pexidartinib causes subacute or chronic injury and if any ongoing subacute or chronic injury may result in clinically important sequalae such as liver failure resulting in the need for liver transplantation or death.

An additional area of uncertainty is the lack of understanding of the potential long-term effects of pexidartinib given that patients with TGCT will likely be exposed to pexidartinib as a chronic medication. In the ENLIVEN trial, a small number of patients had long-term exposure to pexidartinib: 22 patients had been treated for more than 18 months, 17 patients had been treated for more than 24 months, and one patient had been treated for more than 48 months at the time of data cut off.

Summary of Discussion:

During the discussion, many committee members concluded that pexidartinib demonstrated clinical benefit based on the observed response rate; however, many felt that although the patient-reported outcome data also suggested clinical benefit, there was less certainty in this conclusion due to the amount of missing data. The committee members agreed that hepatotoxicity represented an important concern, and generally agreed that a Risk Evaluation and Mitigation Strategy (REMS) is needed to educate prescribers and further evaluate this risk outside of the clinical trial setting, although one committee member argued that laboratory monitoring is a standard part of clinical practice and felt that any REMS instituted should attempt to minimize burden to the prescriber.

FDA requested that the advisory committee vote on the following questions:

- Does the demonstrated benefit of pexidartinib outweigh the risks of the drug in the proposed indication?

  Vote Result: Yes: 12 No: 3 Abstain: 0

The majority of the committee agreed that the demonstrated benefit of pexidartinib outweighs the risks of the drug in the proposed indication. Several committee members who voted “Yes” emphasized the lack of treatment options for patients with TGCT as a factor in their vote. Those

voting “No” stated concerns over liver toxicity, and whether pexidartinib might get inappropriately used in patients with a good surgical option in clinical practice. Please see the transcript for details of the Committee discussion.

10. Pediatrics

Trials with safety or efficacy data pertaining to pediatric patients were not included in this NDA. Pexidartinib is exempt from the requirement to assess the safety and effectiveness of the product for the claimed indication in all pediatric age categories under 21 CFR 314.55(d), Exemption for Orphan Drugs. PLX3397-HCl (pexidartinib) was granted orphan drug status (#13-4199) for the "Treatment of pigmented villonodular synovitis/giant cell tumor of tendon sheath".

11. Labeling Recommendations

11.1. Prescription Drug Labeling

The table below summarizes changes to the proposed prescribing information made by FDA. See the final approved prescribing information for TURALIO (pexidartinib) accompanying the approval letter for more information.

Table 116. Highlights of Significant Labeling Changes (High-Level Changes and Not Direct Quotations)

Section	Proposed Labeling	Approved Labeling
General	Format was not consistent with Selected Requirement of Prescribing Information (SRPI).	Revised format in accordance with SRPI.
Boxed Warning	…	Revised based on changes made to Boxed Warning (FPI) and Warnings and Precautions (5.1).
Dosage and Administration	Included recommendations for dosage modifications for adverse reactions and drug interactions.	Revised to emphasize instructions to take TURALIO without food and moved information about dosage modifications for specific populations and drug interactions to the relevant headings (Boxed Warning and Drug Interactions).
Contraindications	(b) (4)	(b) (4) See summary of labeling changes made to the Full Prescribing Information.
Adverse Reactions	…	Revised the most common list to incorporate adverse reactions that occurred above the specified rate based on the changes made to the tables in Clinical Trials Experience (6.1).
Drug Interactions	…	Revised based on changes made to Drug Interactions (7.2).
Specific Populations	…	Add recommended dosage modifications for renal impairment based on changes made to Renal Impairment (8.6)

Table 117. Significant Labeling Changes: Full Prescribing Information

Section	Proposed Labeling	Approved Labeling
Boxed Warning	…	Revised to be consistent with changes made to Warnings and Precautions (5.1, 5.2) and recommended language to describe REMS program.
Dosage and Administration, Important Administration Information	…	Added this subsection to emphasize that TURALIO should be administered without food, because taking TURALIO with food can increase exposure and increased exposure may increase the risk for hepatotoxicity.
Dosage and Administration, Administration	(b) (4)	Omitted this subsection and included the administration information in the subsection for the recommended dosage.
Dosage and Administration, (b) (4) Dose Modifications for Adverse Reactions	(b) (4)	Consolidated this information into a single subsection based on current labeling practices. Revised the table describing dosage modifications for adverse reactions to clarify monitoring and dosage modifications for hepatotoxicity based on specific hepatic laboratory values.
Dosage and Administration, Dose Modifications for Strong CYP3A Inhibitors and UGT Inhibitors	Included a single subsection to describe the recommended dosage modifications when certain drugs are coadministered with TURALIO.	Added a second subsection to describe an interaction with gastric acid reducing agents.
Dosage and Administration, Dosage Modification for Renal Impairment	…	Added a subsection to provide the recommended dosage modifications for renal impairment.
Contraindication	(b) (4)	(b) (4)
Warnings and Precautions, Hepatotoxicity	Described hepatotoxicity (b) (4)	Revised description of hepatotoxicity and mitigation strategies. Added recommended language for REMS.
Warnings and Precautions, TURALIO REMS Program	(b) (4)	Revised to include recommended language for REMS, such as a bulleted list of the notable requirements.

Section	Proposed Labeling	Approved Labeling
Adverse Reactions, Clinical Trials Experience	…	Added the duration of exposure.
	…	Revised the list of adverse reactions that led to dose reduction/interruption and discontinuation.
	(b) (4)	Modified the list of adverse reactions to only include adverse reactions that occurred at a specified rate greater than placebo. Revised the most common list based on this modification.
	(b) (4) .	Reorganized the information into three tables: adverse reactions, hepatic laboratory abnormalities and other laboratory abnormalities and listed the categories and individual reactions or abnormalities within each category in decreasing order (as specified in 21 CFR 201.57 (c)(7)).
Drug Interactions, Clinically Important Drug Interactions	(b) (4)	Changed subsection title (b) (4)
Specific Populations	(b) (4)	Removed (8.1).
	…	Increased the recommended duration to avoid breastfeeding after the last dose (8.2).
	…	Shortened the recommended duration for use of effective contraception after the last dose for male patients with female partners of reproductive potential (8.3).
	(b) (4)	Removed (8.6).
	Listed 8.6 Hepatic Impairment and 8.7 Renal Impairment.	Reordered these subsections to list 8.6 Renal Impairment and 8.7 Hepatic Impairment. Revised recommended dosage modifications for renal and hepatic impairment.
Clinical Pharmacy, Pharmacodynamics	…	Added a description of the exposure-response relationship for serum transaminase concentrations.

Section	Proposed Labeling	Approved Labeling
Clinical Pharmacology, Pharmacokinetics	Included a tabular summary of the available clinical pharmacology data.	Reorganized the information summarized in the table to list the information under the recommended headings as described in the guidance: Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products — Content and Format and included additional parameters and variability typically found in labeling.
	Included detailed description of specific populations with no clinically meaningful effect on the pharmacokinetics of pexidartinib.	Revised for clarity and brevity.
	(b) (4)	Revised to describe drug interactions using text.
Nonclinical Toxicology	Summarized the information under multiple headings.	Edited for clarity and brevity.
Clinical Studies	(b) (4)	Omitted (b) (4) with exception of the effect of TURALIO on range of motion. Added NCT number in accordance with best labeling practices.
Patient Counseling Information	…	Reorganized the counseling topics to reflect the content found in the related sections of the labeling.

11.2. Patient Labeling

The Medication Guide for TURALIO was reviewed and revised by the FDA's Patient Labeling Team and Review Team. Revisions were made throughout the Medication Guide for consistency with the prescribing information and current labeling policies and practices. For details, refer to the Patient Labeling Team's review filed with NDA 211810.

12. Risk Evaluation and Mitigation Strategies (REMS)

In accordance with Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA), FDA will require that Daiichi Sankyo develop and comply with a REMS for pexidartinib (TURALIO).

FDA uses a variety of strategies to minimize risks associated with drugs and therapeutic biologics. The primary risk management tool is communicating through FDA-approved product labeling, which includes a summary of the essential information needed by health care providers for the safe and effective use of the drug. The Applicant determined that labeling was insufficient to ensure that the benefits of pexidartinib outweigh the risks and included a proposal to implement a Risk Evaluation and Mitigation Strategy (REMS) in the NDA submission.

The clinical review team and the Division of Risk Management (DRISK) agreed that a REMS with ETASU is necessary for the safe use of pexidartinib at this time. The goal of the TURALIO REMS program is to mitigate the risk of serious and potentially fatal liver injury by:

1. Ensuring that prescribers are educated on the following:
    a. Approved indication for TURALIO
    b. The risk of serious and potentially fatal livery injury associated with the use of TURALIO
    c. The need for liver monitoring at baseline and periodically during treatment with dose modifications as described in the Prescribing Information
    d. The need to counsel patients about the risk of serious and potentially fatal liver injury, liver monitoring at baseline and periodically during treatment with TURALIO as described in the Patient Guide and to report signs and/or symptoms of liver injury to the prescriber during therapy
2. Ensuring that prescribers adhere to the requirement of baseline and periodic monitoring as described in the Prescribing Information
3. Enrollment of all patients in a registry to further assess the safe use and acute, chronic and irreversible hepatotoxicity of TURALIO.

The REMS will consist of a communication plan, ETASU A (healthcare prescribers who prescribe the Turalio are specially certified), ETASU B (pharmacies that dispense Turalio are specially certified), ETASU E (patients using Turalio will be monitored), ETASU F (each patient using Turalio will be enrolled in a registry), an implementation system, and a timetable for submission of assessments.

Broadly speaking, the REMS will be considered successful if patients are being appropriately monitored for liver toxicity and dose modifications occur as per the Prescribing Information. It is expected that prescribers of pexidartinib will be specialized oncology practitioners, who are well accustomed to the importance of monitoring patients for therapy-related toxicities

through regular laboratory evaluation. However, given that pexidartinib is the first systemic therapy approved for this indication and that it has a novel mechanism of action and toxicity profile compared to other oncology drugs, at this time the FDA considers labeling and a communication plan alone insufficient to ensure the benefits outweigh the risk of liver injury for pexidartinib.

The primary purpose of ETASU F (patient registry) is to gather information about the incidence and severity of liver toxicity in users outside of a clinical trial setting. Although adverse event reporting systems and other database-driven systems (e.g. FAERS, Sentinel) could be used to get some information about the incidence of serious toxicity in patients who are prescribed pexidartinib, these systems are insufficient to characterize the frequency of events (which requires a denominator) occurring in this very rare and geographically diverse patient population. The FDA considers a registry the only way to assess whether the product labeling, physician education, and monitoring strategy are adequate to ensure the risk of hepatotoxicity has been appropriately minimized to ensure the safe and effective use of the drug and to gather information about the impact of chronic exposure to pexidartinib on liver function. The registry will also enable the Applicant to more easily identify patients who may wish to participate in the planned post-marketing study to fulfill PMR 3673 – 1 (see Section 13 of this review). It is expected that after a sufficient number of users have been exposed to pexidartinib for a sufficient period of time (e.g., several hundred patients with 10 years of follow up), the FDA will have a better understanding of post market safety concerns.

The need for the REMS or modifications to the REMS can be re-evaluated periodically to determine whether changes to the REMS are necessary to reduce burden or more appropriately ensure safety. For example, if there are more reports of severe hepatotoxicity or deaths than expected and evidence of insufficient monitoring in the patient status or liver adverse event reporting forms, FDA may modify the REMS to require that evidence of monitoring be submitted as a condition of prescribing the drug. Or, if the post-training knowledge assessments or other data indicate that prescribers have gained familiarity with the drug and the liver adverse event reporting forms show that providers are taking appropriate actions to reduce the risk of hepatotoxicity, the FDA may determine that the REMS is no longer necessary.

The REMS plan was not finalized at the time of this review, although all major elements had been agreed to by the FDA and the Applicant. Refer to the DRISK review, the final action letter, and the final REMS memo for details of the REMS program.

13. Postmarketing Requirements and Commitment

During the review of the NDA, FDA and Daiichi Sankyo reached agreement on the postmarketing commitments (PMCs) and postmarketing requirement (PMRs) listed below.

Post-marketing Requirement (PMR)

- **PMR 3673 – 1:** Conduct a long-term trial to further evaluate the risk of hepatoxicity in adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery, who are receiving pexidartinib. The trial will include laboratory, imaging, and pathologic assessments of patients who experience liver toxicity due to exposure to pexidartinib. The trial should enroll patients with an AST or ALT > 3 x ULN with concomitant bilirubin >2 x ULN, an isolated bilirubin > 2 x ULN (excluding those with Gilbert's syndrome), or an isolated AST or ALT > 10 x ULN. The trial should evaluate the mechanism of action of liver injury based on liver biopsy information, including a detailed assessment of changes in resident macrophage phenotype, based on marker status, as well as detailed characterization of other immune cell infiltrates. Submit cumulative, integrated safety analyses after 5 and 10 years of follow-up from an adequate number of patients to characterize the long-term risk of hepatic failure with pexidartinib. These safety evaluations should be adequate to inform labeling of patient populations at highest risk and to provide evidence-based dose modifications and monitoring recommendations.

- **PMR 3673 – 2:** Complete a pharmacokinetic trial to determine an appropriate dose of pexidartinib to minimize toxicity in patients with moderate hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072123.pdf

- **PMR: 3673 – 3:** Complete a pharmacokinetic trial to determine the effect of a low-fat meal on the bioavailability of pexidartinib in accordance with the FDA Guidance for Industry entitled "Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology found at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM631941.pdf

- **PMR: 3673 – 4:** Complete a pharmacokinetic trial to determine the effect of a moderate CYP3A4 inhibitor on the exposure to pexidartinib in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies- Study design, Data Analysis, and Clinical Implications" found at

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.

Post-marketing Commitment (PMC)

- **PMC 3673 – 5:** Submit the final trial report and results from the ongoing DDI Study PL3397-AU126 evaluating the effect of pexidartinib on the exposure of midazolam (a CYP3A4 substrate) and tolbutamide (a CYP2C9 substrate).

- **PMC 3673 – 6:** Complete a pharmacokinetic trial or PBPK modeling to determine the effect of a moderate CYP3A4 inducer on the exposure to pexidartinib following single and multiple doses of pexidartinib in accordance with the FDA Guidance for Industry entitled "Clinical Drug Interaction Studies- Study design, Data Analysis, and Clinical Implications" found at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf.

- **PMC 3673 – 7:** Given the abundance of the ZAAD-1006a metabolite in human plasma following exposure to pexidartinib, assess the potential for off-target effects of ZAAD-1006a using in vitro screening assays (panels of kinases and receptors).

14. Division Director (DHOT)

John K. Leighton, Ph.D.

15. Division Director (OCP)

Nam Atiqur Rahman, Ph.D.

16. Division Director (OB)

Rajeshwari Sridhara, M.D.

17. Acting Associate Division Director (Clinical)

Ashley Ward, M.D.

18. Office Director (or Designated Signatory Authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

Marc Theoret, M.D.

19. Appendices

19.1. References

Works Cited

Cassier PA, G. H. (2012). Efficacy of imatinib mesylate for the treatment of locally advanced and/or metastatic tenosynovial giant cell tumor/pigmented villonodular synovitis. *Cancer*, 1649-1655.

Cohen PE, N. K. (1999). Macrophages: important accessory cells for repoductive function. *J Leukoc Biol*, 765-772.

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Gelderblom H, C. C.-N. (2018). Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*, 639-648.

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Kramer DE, F. F. (2009). Pigmented villonodular synovitis of the knee: diagnosis and treatment. *Journal of Knee Surgery, 22*(3), 243-254.

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West RB, R. B. (2006). A landscape effect in tenosynovial giant cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proceeding of the National Academies of Science, 103*, 690–695.

19.2. Financial Disclosure

Table 118. Covered Clinical Study (Name and/or Number): ENLIVEN Trial

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 333		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 119. Covered Clinical Study (Name and/or Number): PLX108-01

Was a list of clinical investigators provided?	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 196		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements?	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided?	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 86		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

Executive CAC Minutes Amended to include the review of the final carcinogenicity reports in mouse and rat that supported the Committee's determination.

19.3.1. Executive CAC Final Study Minutes

Date of Meeting: April 16, 2019

Committee: Karen Davis Bruno, PhD, OND IO, Chair
Ron Wange, PhD, OND IO, Member
Paul Brown, PhD, OND IO, Member
Tim McGovern, PhD, OND IO, Member
Terry Miller, PhD, DAIP, Alternate Member
Whitney Helms, PhD, DHOT, Pharm/Tox Team Leader
Elizabeth Spehalski, PhD, DHOT, Presenting Reviewer

The following information reflects a brief summary of the Committee discussion and its recommendations.

NDA #: 211810
Drug Name: Pexidartinib (capsule)
Sponsor: Daiichi Sankyo

19.3.2. Mouse Carcinogenicity Study

The Applicant conducted a 26-week carcinogenicity study in transgenic Tg.rasH2/CByB6F1 mice. Mice were dosed at 10, 30, and 100 mg/kg daily via oral gavage. Two control groups (vehicle of (b) (4)% PLX3397-HCl (w/w), (b) (4)% Poloxamer 407 (w/w)/ (b) (4)% (b) (4) in deionized water and DI water) were included. The Committee concurred with the Applicant's proposed doses based on decreases in RBC and WBC and bone marrow depletion at 200 mg/kg/day in a dose-range finding study. No statistically significant increases in mortality or neoplastic lesions occurred in animals dosed with pexidartinib.

Observations and Results

Mortality

- Unremarkable, checked twice daily
- There were 3 early deaths, one 30 mg/kg male on Day 23, one control female on Day 124, and one 100 mg/kg female on Day 137. All remaining main cohort animals survived until termination on Day 183 or 184. The positive control animals were euthanized on Day 78-80 per the protocol.

Clinical Signs

Test article related discoloration of the fur (from dark to light brown/cream/gray) on various body surfaces were noted in both sexes at all doses, with dose-dependent onset and duration. Checked daily.

Body Weights

Body weight gain was higher at 10 and 100 mg/kg (18.2% and 30.5% compared to controls) in males and at 30 and 100 mg/kg (17.6% and 58.2%) in females. Mice were weighed weekly through Week 13 and biweekly thereafter.

Feed Consumption

Unremarkable, measured weekly

Gross Pathology

- Discoloration of fur (See Clinical Signs)
- 100 mg/kg males: small testes (23 animals), testicular discoloration (pink/red/tan, 16 animals)

Histopathology

Peer Review: Yes

Neoplastic:

Unremarkable. The incidence of tumors in different organs (pulmonary, hemangiosarcoma, and other tumors) in the negative control, vehicle control, and PLX3397-treated groups fell within the historical range for both sexes, except for Harderian Gland carcinoma in 30 mg/kg males, which exceeded the historical control range of 0-1 by 1 (Table 120).

Table 120. Incidence of Non-Splenic and Non-Pulmonary Tumors in Mice

MALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR Incidence Range
Dose Level (mg/kg/day)	0 (Negative Control)	0 (Control)	10	30	100	
Number Examined	25	25	25	25	25	
Harderian Gland, adenoma	1	1	0	0	0	0-2
Harderian Gland, carcinoma	0	0	1	2	0	0-1
Hepatocellular adenoma	0	0	0	0	1	0-1
Thyroid, cystadenoma	1	0	1	0	0	0-1
FEMALES						
	Group 1	Group 2	Group 3	Group 4	Group 5	HCR Incidence Range
Dose Level (mg/kg/day)	0 (Negative Control)	0 (Control)	10	30	100	
Number Examined	25	25	25	25	25	
Harderian Gland, adenoma	1	0	0	0	1	0-4
Harderian Gland, carcinoma	1	1	0	1	1	0-2
Hepatocellular adenoma	0	0	0	0	1	0-2
Thymoma	0	0	0	1	0	0-3

(Excerpted from the Applicant's submission)

Non Neoplastic:

Table 121. Non-Neoplastic Histological Findings in Mice (Carcinogenicity)

Sex		Male					Female				
Dose (mg/kg/day)		- Ctrl	0	10	30	100	- Ctrl	0	10	30	100
# Examined		25	25	25	25	25	25	25	25	25	25
Bone marrow, femoral and sternal											
Decreased cellularity	Minimal				18	3				15	13
	Mild				3	21				8	6
Skin, mammary and ventral											
Mucinous degeneration	Minimal			1	7				6	5	2
	Mild			3	13	8			2	19	13
	Moderate				4	14				1	10
	Marked					3					
Mineralization, subcutaneous	Minimal		1	1	8	6				1	5
	Mild				4	2					
Spleen											
Pigmentation, hemosiderin	Minimal			18	1			3	12	5	
	Mild			2	21	9			7	16	
	Moderate					16			1	2	24
Testes											
Degeneration, atrophy, and increased interstitial cells, bilateral	Moderate					24					
	Marked					1					
Epididymides											
Oligospermia, bilateral	Moderate					24					
	Marked					1					

Toxicokinetics

- Exposure increased in a less than dose-proportional manner in males and in a greater than dose-proportional manner in females
- At 10 mg/kg, there was an increase in exposure in males compared to females

Table 122. Summary of Mean Toxicokinetic Data for PLX3397 in Mice (Carcinogenicity)

Group	Dose (mg/kg/day)	Day	Gender	AUClast (ng*h/mL)	Dose-Normalized AUClast	Cmax (ng/mL)	Cavg (ng/mL)	Dose-Normalized Cmax	AUCinf (ng*h/mL)	%AUCextrap (%)	Tmax (h)	T1/2 (h)	AR
3	10	1	Male	240000	24000	21300	9990	2130	NC	NC	4	NC	NA
3	10	1	Female	119000	11900	19000	7820	1900	NC	NC	4	NC	NA
3	10	177	Male	301000	30100	24500	12500	2450	NC	NC	4	NC	1.25
3	10	177	Female	82700	8270	15100	5620	1510	134000†	38.5	0.5	5.51†	0.693
4	30	1	Male	587000	19600	52300	24400	1740	593000	1.09	2	3.66	NA
4	30	1	Female	599000	20000	50400	24900	1680	602000	0.595	2	3.24	NA
4	30	177	Male	632000	21100	49300	26300	1640	647000	2.33	2	4.51	1.08
4	30	177	Female	474000	15800	47800	19700	1590	474000	0.0964	2	2.4	0.791
5	100	1	Male	1740000	17400	109000	72300	1090	NC	NC	8	NC	NA
5	100	1	Female	1940000	19400	127000	80900	1270	NC	NC	4	NC	NA
5	100	177	Male	1420000	14200	84600	59100	846	NC	NC	8	NC	0.818
5	100	177	Female	1410000	14100	91400	58900	914	NC	NC	4	NC	0.728

AR = accumulation ratio
NA = not applicable
NC = not calculable due to limited data in the terminal elimination phase
Note: Units for dose-normalized AUClast and Cmax are [(ng*h/mL)/(mg/kg)] and [(ng/mL)/(mg/kg)], respectively
†Denotes an approximation due to %AUCextrap >20%

(Excerpted from the Applicant's submission)

19.3.3. Rat Carcinogenicity Study

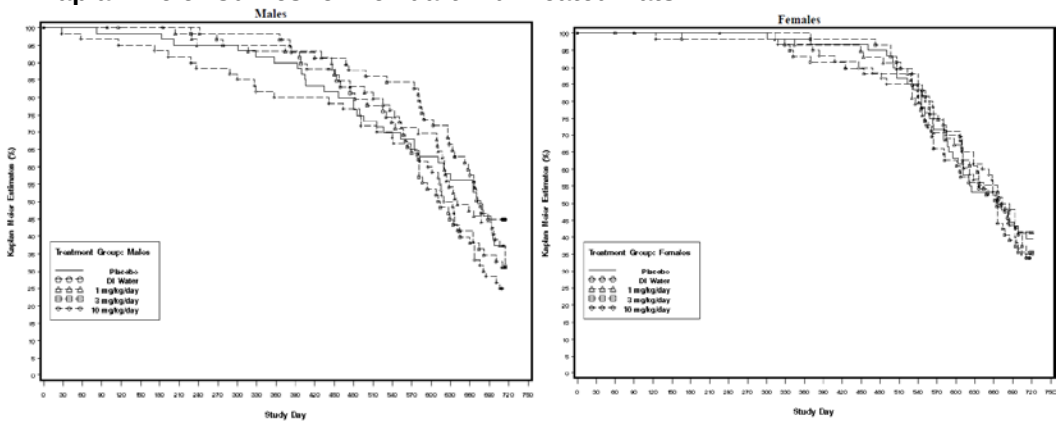
The Applicant conducted a 2-year carcinogenicity study in Sprague Dawley rats. Rats were dosed at 1, 3 and 10 mg/kg daily via oral gavage. Two control groups (vehicle of 65% PLX3397-HCl (w/w), (b)(4)% Poloxamer 407 (w/w)/ (b)(4)% (b)(4) in deionized water and DI water) were included. The Committee recommended these doses based on decreases in lymphocyte counts in females and microscopic evidence of bone marrow depletion in males at doses of 20 mg/kg/day in a dose-range finding study. No statistically significant increases in mortality or neoplastic lesions occurred in animals dosed with pexidartinib.

Observations and Results

Mortality

- Unremarkable, checked twice daily
- To avoid survival reaching unacceptable low limits, the primary necropsy for the males started on Study Day 708 because the survival in the 10 mg/kg/day group had reached 15. All male groups were terminated early because more than 100 weeks of treatment had been completed. Similarly, the primary necropsy for the females started on Study Day 716 once the survival in the water group reached 20. All female groups were terminated early. Early termination of the in-life activities was discussed with and approved by the FDA.

Figure 14. Kaplan-Meier Curves for Pexidartinib-Treated Rats



(Excerpted from the Applicant's submission)

Clinical Signs

Unremarkable, performed weekly

Body Weights

Unremarkable, recorded once weekly

Feed Consumption

Unremarkable, recorded once weekly

Gross Pathology

Table 123. Macroscopic Findings in Rats at Scheduled Necropsy (Carcinogenicity)

Sex	Male					Female				
Dose (mg/kg/day)	Placebo	0	1	3	10	Placebo	0	1	3	10
# Examined	22	25	21	18	15	23	20	24	21	21
Adrenal gland										
mottled	3	3	4	1	7					
Kidney										
Rough surface	1	1	1	3	7					
Liver										
discolored (dark red)	3	5	8	7	9	3	3	9	7	10
Thyroid										
enlarged	1	1		2	4			5	2	1
Testes										
soft	1			1	3					
small				1	5					

Histopathology

Peer Review: Yes

Neoplastic:

There was an increased incidence of pheochromocytomas in the adrenal medulla of the low and high dose male rats, but there was no dose relationship and incidence were within the range of the (b) (4) historical controls and not statistically significant when compared to DI water (benign pheochromocytomas) or placebo (malignant pheochromocytomas) controls.

Table 124. Incidence of Pheochromocytomas in Male Rats

Dosage (mg/kg/day):	Placebo	DI Water	1	3	10	Historical Control Mean% Incidence (study incidence % range) (Appendix 9)
Adrenal medulla [a]	**60**	**60**	**60**	**60**	**60**	
Pheochromocytoma, benign	3	6	14	5	8	
Pheochromocytoma, benign, multiple	1	1	1	1	5	
Total Pheochromocytoma, benign (single and multiple)	**4 (6.7%)**	**7 (11.7%)**	**15 [b] (25.0%)**	**6 (10.0%)**	**13 [b] (21.7%)**	**9.9% (1.7-32.3%)**
Pheochromocytoma, malignant	1	0	0	1	3	
Total Pheochromocytoma, malignant	**1 (1.7%)**	**0 (0.0%)**	**0 (0.0%)**	**1 (1.7%)**	**3 (5.0%)**	**0.8% (0-9.2%)**
Total Number of Animals with Pheochromocytoma, benign and malignant	**5 (8.3%)**	**7 (11.7%)**	**15 [b] (25.0%)**	**6 (10.0%)**	**15 [b,c] (25.0%)**	**10.8% (1.7-41.5%)**
Pheochromocyte, focal hyperplasia	**5 (8.3%)**	**6 (10.0%)**	**5 (8.3%)**	**7 (11.7%)**	**8 (13.3%)**	**NA**

[a] Number of tissues examined from each group.
[b] Statistically significant from Placebo control group at $p<0.01$ for common tumors
[c] Statistically significant from DI Water control group at $p<0.01$ for common tumors
NA = Not available

(Excerpted from the Applicant's submission)

Non Neoplastic

Table 125. Non-Neoplastic Histological Findings in Rats (Carcinogenicity)

Sex		Male					Female				
Dose (mg/kg/day)		Placebo	0	1	3	10	Placebo	0	1	3	10
# Examined		60	60	60	60	59	59	60	60	60	58
Aorta											
Alteration, tunica intima	Minimal	4	3	2	7	19			2	2	21
	Mild					7					4
Kidney											
Chronic progressive nephropathy	Minimal	23	20	19	22	13	5	3	8	11	17
	Mild	14	9	12	11	12	1			1	3
	Moderate	6	8	9	11	15					3
	Marked	1	1	2	4	10					1
	Severe			1		4					
Lymph node, mesenteric											
Increased mast cells	Minimal	2	3	9	8	11	2	2	6	13	16
	Mild			1	5	8			3	3	16
	Moderate				2	4				1	6
	Marked					1					2
	Severe										1
Skin											
Myxomatous change	Minimal					12					24
	Mild					3					7
Spleen											
Pigment, brown	Minimal	16	5	14	10	11	16	16	11	9	13
	Mild	4	6	5	16	25	4	11	12	25	20
	Moderate	3	1	4	5	6	4	3	14	15	12
	Marked	1			1		4	2	4	1	5
	Severe	1									
Thyroid gland											
Increased colloid	Minimal		4	2	4	10		7	9	5	12
	Mild		2	2	1	4			1	4	2
	Moderate					1				1	1
Testes											
Degeneration, seminiferous tubules (bilateral)	Minimal	3		1		3					
	Mild	1		3	2	4					
	Moderate		2	1	2	2					
	Marked			2	2	7					
	Severe	2				1					
Tongue											
Myxomatous change	Minimal				13	26		1	1	7	23
	Mild					18					26
	Moderate					1					2

Toxicokinetics

- Exposure to PLX3397 increased with dose and was generally dose proportional
- There was little drug accumulation

Table 126. Summary of Mean Toxicokinetic Data for PLX3397 in Rats (Carcinogenicity)

Dosage (mg/kg/day)	AUC0-24 hr (ng•hr/mL)			Cmax (ng/mL)		
	Day 0	Day 92	Day 175	Day 0	Day 92	Day 175
Males						
1	1770	4980	4570	276	361	306
3	5770	13,100	12,800	996	1230	1120
10	24,100	46,100	36,000	3550	4500	3400
Females						
1	1780	3220	3770	249	390	367
3	8340	10,900	12,900	963	1280	1340
10	34,800	39,300	47,200	4150	4120	4530

(Excerpted from the Applicant's submission)

19.3.4. Executive CAC Recommendations and Conclusions

Mouse study:

- The Committee concurred that the carcinogenicity study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 6-month mouse study in either males or females.

Rat study:

- The Committee concurred that the carcinogenicity study was adequate, noting prior approval of the protocol.
- The Committee concurred that there were no drug-related neoplasms in the 2-year rat study in either males or females.

19.4. OCP Appendices (Technical Documents Supporting OCP Recommendations)

19.4.1. Population Pharmacokinetic Analyses

The goal of population PK analysis (popPK) was to develop a population pharmacokinetic (PK) model to assess sources of variability (intrinsic and extrinsic covariates) of pexidartinib in healthy volunteers and patients.

The population PK model included 9 clinical trials, comprising 159 healthy subjects, 123 patients with pigmented villonodular synovitis (PVNS) and 93 patients with other tumor types. Among 375 patients in the pooled analysis, 299 had normal renal function (creatinine clearance (Clcr>= 90)), 67 had mild renal impairment (Clcr>=60 & Clcr <90), and 9 had moderate renal impairment (Clcr>=30 & Clcr <60).

The popPK analysis was conducted by the sponsor and evaluated by the reviewer. The PK of pexidartinib was characterized by a two-compartment model with sequential zero- and first-order absorption with a lag time and linear elimination. The residual error model was described by a proportional error model. A full covariate modeling approach was implemented to investigate the effects of covariate on pexidartinib. Parameter estimates of full covariate model based on reviewer's evaluation were provided in Table 127. The full model included effects of weight, creatinine clearance, race, bilirubin, AST, study population (healthy or patients) on CL/F as well as an effect of weight volume of distribution. No signs of model misspecification were identified in the goodness-of-fit plots (Figure 15). Prediction-corrected visual predictive check showed that the final model adequately described the observed PK profile of pexidartinib across different clinical studies (Figure 16). Bootstrap analyses demonstrated consistency in parameter estimates and indicated the robustness of the model. The effects of all evaluated covariates on the pexidartinib clearance were illustrated in the forest plot based on 100 bootstrap results of full covariate model (Figure 17).

No intrinsic or extrinsic factors appear to have clinically relevant effects on pexidartinib clearance. The effects of weight, Asian race, AST and total bilirubin on clearance were not statistically significant. Female subjects were estimated to have 18% lower clearance than male subjects. The post hoc pexidartinib CL were similar between subjects with normal liver function and subjects with mild hepatic impairment (Figure 18).

The post hoc pexidartinib CL in subjects with mild or moderate renal impairment were about 20% lower compared to subjects with normal renal impairment (Figure 19). The dedicated study also suggests the pexidartinib exposure in patients with mild, moderate or severe renal impairment is about 40% higher compared to patients with normal renal impairment. In study PLX108-01 and PLX108-10, among 60 patients with mild or moderate renal impairment, 29 (48%) patients had dose interruption or dose reduction caused by AE and 10 (17%) patients had dose reduction caused by AE. These percentages are comparable to that observed in patients with normal renal impairment in study PLX108-01 and PLX108-10. Although a higher rate of dose reduction was not observed in patients with mild or moderate renal impairment in the clinical trials, the serious potential liver toxicity and significant exposure-safety relationship for ALT-elevation and AST-elevation calls for caution in adjusting dose in patients with organ impairment. Based on the "exposure-matching" principle and totality of evidence collected from popPK analysis and dedicated study, reduction to 600 mg total daily dose is recommended in patients with mild to severe renal impairment. The efficacy is unlikely to be compromised in these patients as the exposure with 600 mg total daily dose is expected to be similar to the exposure with 400 mg BID in patients with normal renal function.

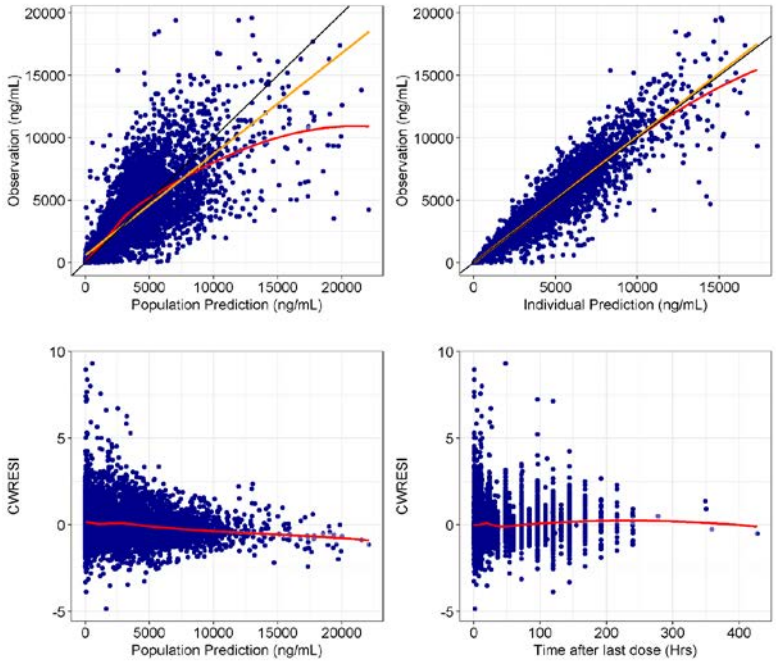
Table 127. Parameter Estimates of the Final PopPK Model

		Bootstrap		
Parameter	**Estimate**	**Median**	**CV**	**95% CI**
LNCL	1.85	1.85	3.4	(1.73, 1.97)
LNV2	4.49	4.51	1.4	(4.39, 4.62)
LNV3	4.72	4.72	1.3	(4.62, 4.85)
LNQ	3.01	3.03	3.3	(2.83, 3.2)
LNKA	1.92	1.94	13.7	(1.25, 2.37)
LNLAG	-0.946	-0.939	-3.3	(-1.03, -0.898)
LND1	0.206	0.203	37.2	(-0.03, 0.277)
FORMU PHASE1 ON F1	-0.157*	-0.157	0.0	(-0.157, -0.157)
Covariate effects				
CLCR ON CL	0.149	0.137	57.0	(-0.0217, 0.296)
ASIAN ON CL	0.158	0.164	90.1	(-0.133, 0.451)
AST ON CL	0.0311	0.0329	89.7	(-0.0271, 0.078)
TBIL ON CL	0.0266	0.0268	107.8	(-0.0334, 0.0856)
HEALTHY ON CL	1.62	1.38	10.2	(1.08, 1.62)
SEX ON CL	-0.212	-0.205	-21.8	(-0.288, -0.116)
WT ON CL	-0.11	-0.111	-96.3	(-0.306, 0.0789)
WT ON V2	0.753	0.689	37.7	(0.232, 1.23)
MILD HEP	1.01	1.03	7.6	(0.866, 1.17)

		Bootstrap		
Parameter	**Estimate**	**Median**	**CV**	**95% CI**
Random effects				
IIV CL	0.0725	0.0691	17.3	(0.0489, 0.0915)
IIV V2	0.28	0.314	28.0	(0.187, 0.52)
IIV CL_V2	0.0694	0.0697	27.5	(0.0326, 0.0989)
IIV CL_V3	0.0193	0.0147	141.7	(-0.0299, 0.0695)
IIV V3	0.246	0.234	45.0	(0.0666, 0.504)
IIV V2_V3	-0.064	-0.0664	-75.3	(-0.173, 0.0239)
IIV Q	0.446	0.444	31.8	(0.191, 0.749)
IIV KA	1.35	1.19	31.3	(0.455, 1.86)
Phase 1 F1	0.0655	0.0631	42.5	(0.0167, 0.108)
IOV1_F1	1.89	1.96	22.5	(1.12, 2.9)
IOV2_F1	0.0651	0.0652	21.3	(0.0441, 0.0972)
PR0P1	0.0877	0.0871	7.7	(0.0725, 0.0996)
PR0P2	0.0383	0.0377	5.1	(0.0338, 0.0419)

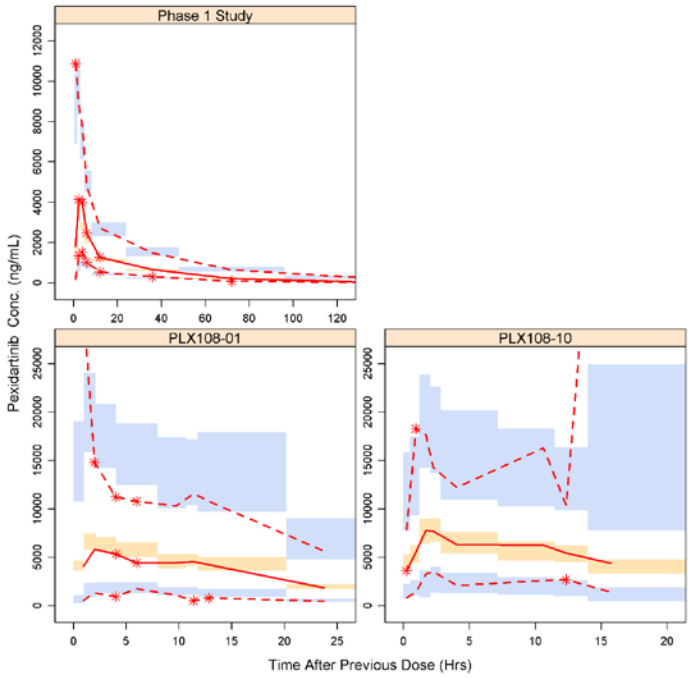
Source: Reviewer's Analysis based on "ds 0102pkpdallf3.xpt"

Figure 15. Goodness-of-Fit Plots of the Final Model



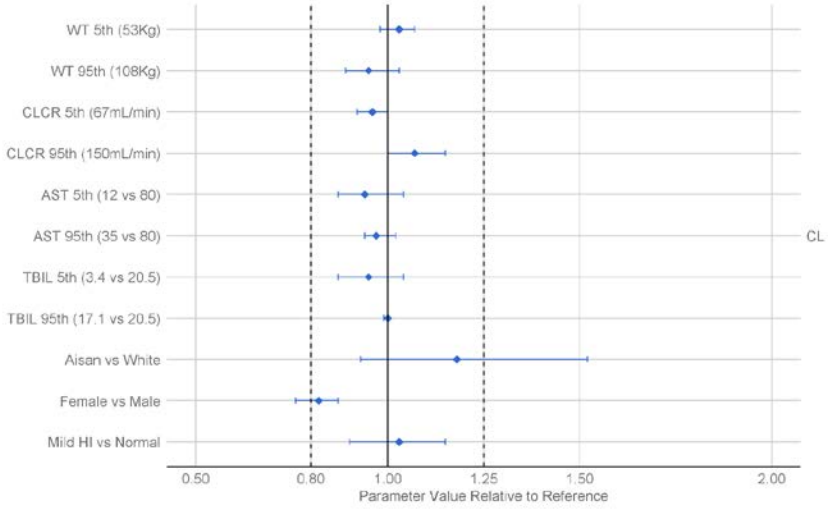
Source: Reviewer's Analysis based on "ds 0102pkpdallf3.xpt"

Figure 16. Visual Predictive Checks of Pexidartinib Concentration-Time Data



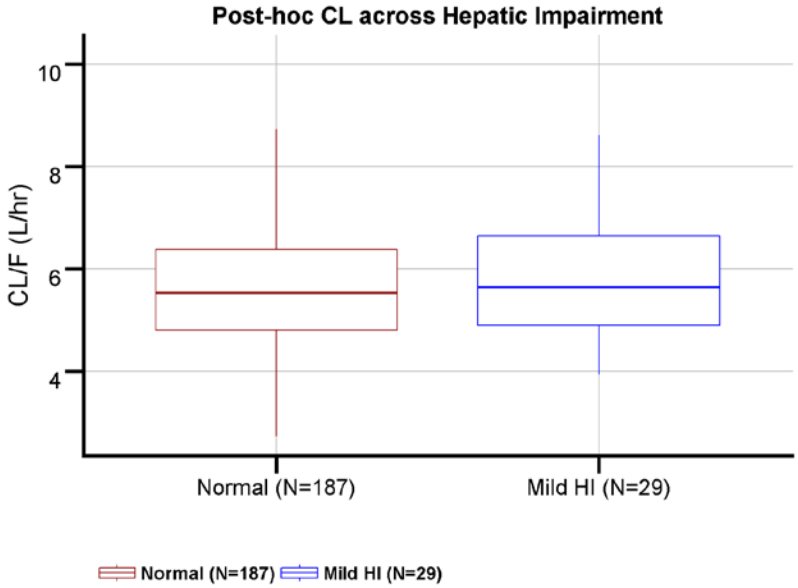
Source: Reviewer's Analysis based on "ds 0102pkpdallf3.xpt"

Figure 17. Covariate Effects on Pexidartinib Pharmacokinetic Parameters



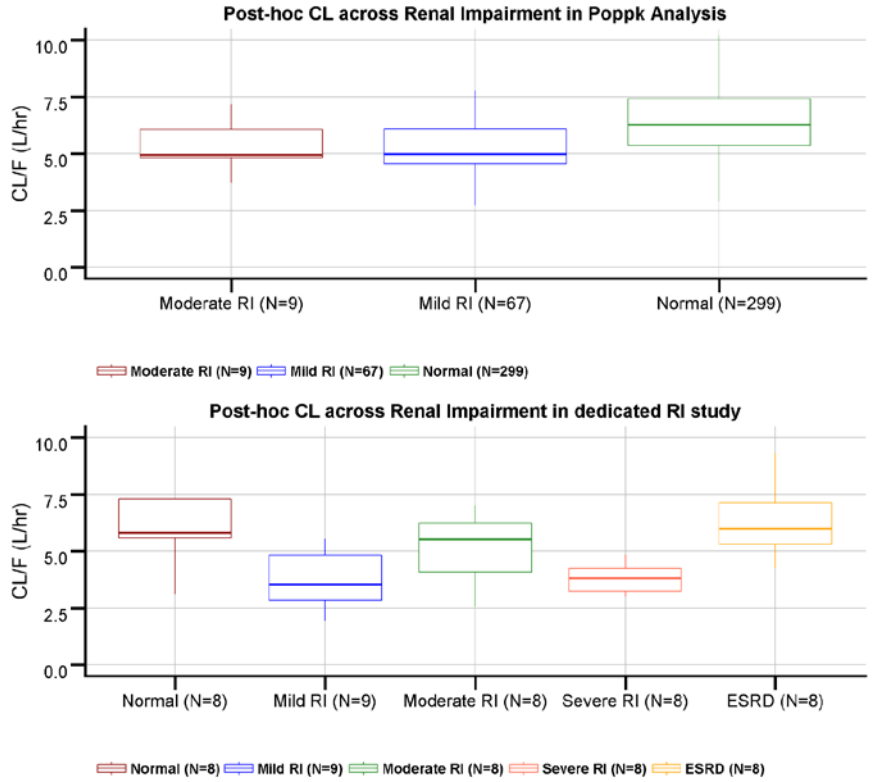
Source: Reviewer's Analysis based on "ds 0102pkpdallf3.xpt"

Figure 18. Comparison of Post Hoc CL Across Hepatic Function



Source: Reviewer's Analysis based on "ds 0102pkpdallf3.xpt"

Figure 19. Comparison of Post Hoc CL Across Renal Function



Source: Reviewer's Analysis based on "ds 0102pkpdallf3.xpt"

19.4.2. Exposure-Response Analyses

1) Methods and Data

Exposure-response analyses were conducted by the Applicant to explore the relationship between exposure of pexidartinib and efficacy and safety in patients who received pexidartinib.

Efficacy data was available in 61 patients in the treatment group and 30 patients in the placebo group who switched to treatment in Part 2 from study PLX108-10, among them 20 patients doesn't have evaluable response, and another 6 patients have no pexidartinib exposure data. Therefore exposure-ORR relationship was evaluated in 65 patients with available pexidartinib exposure and response.

Exposure safety analyses were performed to investigate whether the adverse events related to hepatic function could be attributed to the variability in pexidartinib. The markers of hepatoxicity include time to first ALT more than 3-fold the ULN, first AST more than 3-fold the ULN and first TBIL more than twice the baseline. The exposure-safety analyses were conducted in 212 patients including 128 patients from study PLX108-01 and 84 patients from study PLX108-10.

The primary exposure metrics for exposure-efficacy assessment are individual predicted average, trough concentration for pexidartinib over the first 2 weeks. The primary exposure metrics for exposure-safety assessment are individual predicted average, trough concentration for pexidartinib over the first week. Graphical quartile analyses were used to investigate the exposure-ORR and exposure-AE relationships.

2) Exposure-ORR Relationships

Overall, there appears to be a positive trend of exposure-response relationship for ORR with shallow slope (Figure 4). However, caution should be taken when interpreting this relationship as it was based on a small sample size with one dosing regimen. The baseline covariates across all exposure quartiles in the exposure-ORR analyses appeared to be balanced except for gender (Table 128).

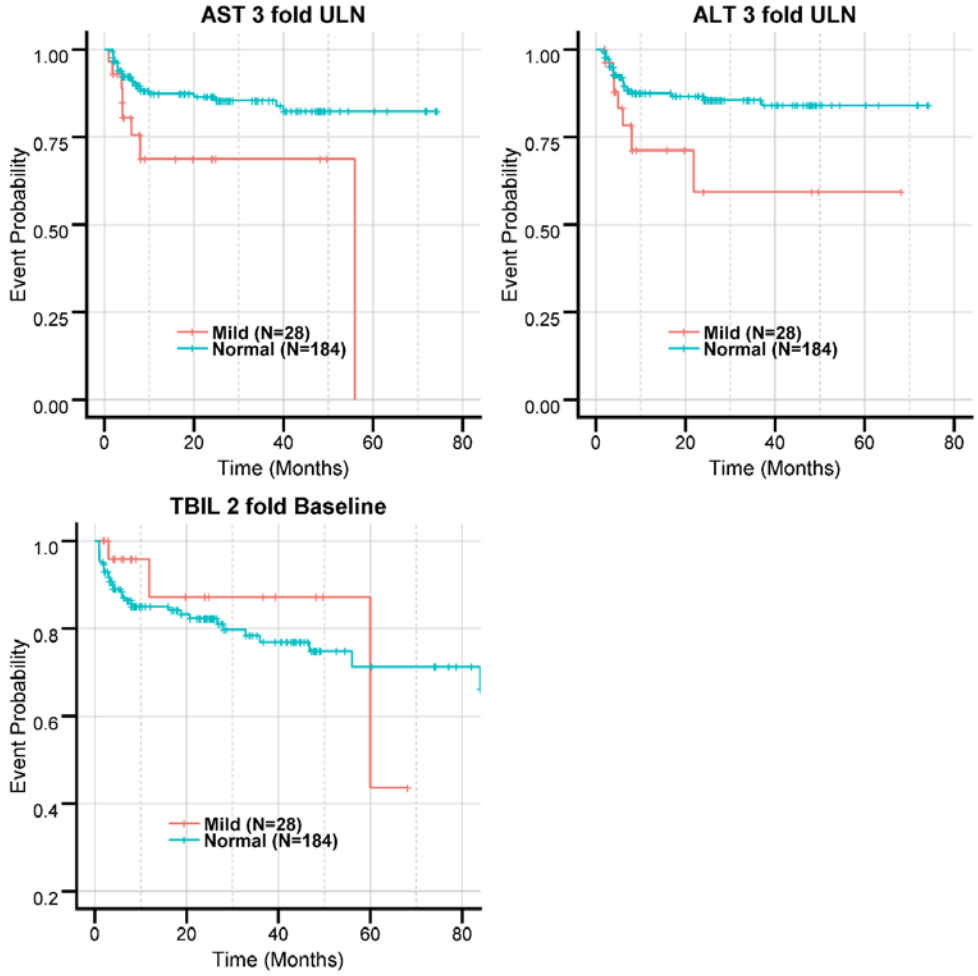
3) Exposure-Safety Relationships

Graphical quartile analyses suggest higher pexidartinib concentration during the 1st week of dosing were associated with faster onset and higher incidence of elevated ALT (three-fold ULN) and AST (three-fold ULN) (Figure 5). Statistically significant relationships were found between average pexidartinib concentration during 1st week and elevated ALT (three-fold ULN) and AST (three-fold ULN) but not for TBIL (two-fold baseline). The baseline covariates across all exposure quartiles in the exposure-AE analyses (Table 128) appear to be balanced.

Exploratory analysis was also conducted to compare biomarkers of hepatotoxicity between patients with normal liver function and patients with mild hepatic impairment. A numerically higher percentage of ALT-elevation and AST-elevation but not for total bilirubin increase was observed in patients with mild hepatic impairment compared to patients with normal function.

Graphical quartile analysis also suggested a faster onset and higher incidence of elevated ALT (three-fold ULN) and AST (three-fold ULN) in patients with mild hepatic impairment (Figure 20). Baseline AST and ALT were higher in patients with mild hepatic impairment, the other baseline covariates appear to be balanced between patients with mild hepatic impairment and patients with normal liver function (Table 129).

Figure 20. KM Curve of Time to First AST, ALT and TBIL



Source: Reviewer's Analysis based on "ds 0102aette.xpt"," adlbtgct.xpt" and "adlbntgc.xpt"

Table 128. Baseline Covariates Across Four Exposure Quartiles

Covariate	Value	Q1	Q2	Q3	Q4
A1: Number of subjects		16	16	16	17
Age		45.5 (15.1)	46 (11.2)	42.5 (11.3)	47 (12.2)
Body weight		92 (24.1)	83 (26.4)	88.8 (18.6)	74 (19.6)
Baseline AST		19.5 (42.3)	18.5 (7.1)	17.5 (4.9)	16 (4)
Baseline ALT		25 (16.9)	16.5 (18.3)	17 (9.7)	17 (8.6)
Baseline total bilirubin		7.5 (2.4)	7.5 (4.3)	6 (4.3)	6 (6.3)
Baseline CrCL		138 (29.3)	116.5 (21.9)	124 (21.4)	109 (31.2)
Baseline RECIST		16.7 (7.5)	10 (5.5)	8.6 (5.4)	7.4 (5.4)
Tumor volume score at baseline		8.8 (23)	10.5 (8.3)	6 (20.4)	6.5 (23.2)
Gender	F	4 (25%)	8 (50%)	10 (62.5%)	13 (76.5%)
Gender	M	12 (75%)	8 (50%)	6 (37.5%)	4 (23.5%)
A2: Number of subjects		53	53	53	53
Age		53 (14.6)	48 (16.6)	48 (15.3)	50 (15.1)
Body weight		75.7 (20.3)	90.5 (17.7)	75.7 (22.9)	74 (17.7)
Baseline AST		23 (13.2)	19 (25.8)	20 (9.1)	17 (9.9)
Baseline ALT		20 (15.8)	19 (17.7)	19 (15.5)	17 (12.1)
Baseline total bilirubin		6.8 (5.9)	6.8 (4.3)	8 (4.7)	6 (4.8)
Gender	F	28 (52.8%)	21 (39.6%)	30 (56.6%)	33 (62.3%)
Gender	M	25 (47.2%)	32 (60.4%)	23 (43.4%)	20 (37.7%)

A1: Exposure-ORR relationship with C_{avg} over first 2 weeks
A2: Exposure-AE relationship with C_{avg} over first 1 week
Source: Reviewer's Analysis based on "ds 0102aette.xpt" and "dsi0102resp.xpt"

Table 129. Baseline Covariates Across Hepatic Function

Covariate	Value	Mild HI	Normal
Number of subjects		28	184
Age		53 (13)	50 (15.6)
Body weight		77.6 (24.8)	79.7 (19.7)
Baseline AST		33.5 (34.2)	18.5 (6.4)
Baseline ALT		46.5 (22.8)	17 (9.8)
Baseline total bilirubin		8.8 (7.9)	6.8 (4.1)
Gender	F	15 (53.6%)	97 (52.7%)
Gender	M	13 (46.4%)	87 (47.3%)

Source: Reviewer's Analysis based on "ds 0102aette.xpt"

19.4.3. Physiological-Based Pharmacokinetic Modeling

19.4.3.1. Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report titled "Quantitative Prediction of The Potential for Pexidartinib as A Perpetrator to Cause Drug-drug Interactions by Inhibition of CYP2C8, CYP2C19, OATP1B1, P-Glycoprotein and MATE" (PBPK report #001) and "Quantitative Prediction of The Potential for Pexidartinib as A Perpetrator to Cause Drug-drug Interactions Mediated by CYP3A4 of CYP2B6, OATP1B1/3, and MATE"(PBPK report #002) to support the intended uses. Specifically, the Applicant applied the PBPK modeling approach to:

(1) Assess the effects of pexidartinib on the PK of repaglinide (CYP2C8 substrate), rosiglitazone (CYP2C8 substrate), and bupropion (CYP2B6 substrate);
(2) Assess the effects of pexidartinib on the PK of metformin (MATE1/2-K substrate) and rosuvastatin (OATP1B and BCRP substrate).

The Division of Pharmacometrics has reviewed the original PBPK reports, supporting modeling files, and concluded the following:

- The PBPK model of pexidartinib is adequate to predict the PK of pexidartinib in healthy volunteers and target cancer population.
- PBPK analyses predicted that an interaction between pexidartinib and a CYP2C8 substrate (such as repaglinide or rosiglitazone) is unlikely to be relevant. The PBPK analyses are adequate to support labeling language for pexidartinib interaction with substrates for CYP2C8.
- PBPK analyses could not be used to estimate the effects of pexidartinib on a CYP2B6 substrate (such as bupropion) due to the uncertainty of the percentage contribution of CYP2B6 to bupropion clearance in the bupropion PBPK model.
- PBPK analyses could not be used to estimate the effects of pexidartinib on substrates for drug transporters because DDI simulations using the substrate PBPK models of metformin and rosuvastatin did not capture the full spectrum of clinical DDI effects reported in the literature.

19.4.3.2. Background

Pexidartinib inhibited enzyme activities mediated by CYP2B6, 2C8, 2C9, 2C19 and 3A4 following co-incubation with human liver microsomes (0.9 to 27.6 µM). Further experiments indicated that pexidartinib is a mixed type inhibitor of CYP2B6, CYP2C9, CYP2C19 and CYP3A4, and a competitive inhibitor of CYP2C8 [Report EXP-14-AD6144]. Pexidartinib is a time-dependent inhibitor (TDI) of CYP3A4 [Report AM16-H0084-R01]. In a human hepatocyte assay, pexidartinib was shown to induce both CYP3A4 and CYP2B6 mRNA and activity [Reports 35712, TCRM-PLX-2015-01].

In vitro studies determined pexidartinib to be an inhibitor of OATP1B1, OATP1B3, MATE1 and MATE2-K [Reports OPT-2015-066, DS-014-17].

19.4.3.3. Methods

PBPK model structure and development

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V15 Simcyp Ltd., a Certara Company, Sheffield, United Kingdom). The PBPK model of pexidartinib was developed based on in vitro, human ADME study [CSR PL3397-A-115] and clinical PK data. Briefly, a first-order absorption model and a minimal PBPK model were utilized to describe pexidartinib PK. The fraction absorbed (fa) was estimated to be around 0.56 based on mass balance data that showed 44% of the dose was excreted unchanged in feces [CSR PL3397-A-115]. Parameter estimation was used to fit ka to clinical data for the 1200 mg single dose [CSR PL3397-A-121] resulting in a ka value of 0.12 h^{-1}. The unbound fraction in enterocytes (fuGut) was assumed equal to 1.

The unbound fraction in plasma (f_{up}=0.002) and blood to plasma concentration ratio (B/P=0.56) values were determined in vitro [Reports DRN-108-102, DRN-108-78]. The distribution parameters (V_{ss}=0.24 L/kg, V_{sac}=0.11 L/kg, K_{in}=0.48 h^{-1}, and K_{out}=0.05 h^{-1}) were estimated using parameter estimation and clinical data from 1200 mg SD pexidartinib [CSR PL3397-A-121]. The CL_{po} of 8.66 L/h, reported (as CL/F) for the 1200 mg single dose of pexidartinib [CSR PL3397-A-121], was used for pexidartinib perpetrator PBPK model.

Competitive inhibition models, using the in vitro K_i of 3.1 µM against CYP2C8 [Report EXP-14-AD6144], were used to simulate the interaction between pexidartinib and the CYP2C8 model substrates (i.e., repaglinide and rosiglitazone). Based on the microsomal protein concentration of 0.2 mg/mL used in the in vitro studies, the fraction unbound in microsomes (fumic) was predicted to be 0.83 (Simcyp prediction tool).

K_i values for pexidartinib for MATE and OATP1B inhibition were not available. Thus, K_i values equal to the IC_{50} value were assumed. K_i values of 5.16 µM and 13.0 µM were used for OATP1B1 and OATP1B3, respectively. A K_i value of 8.33 µM for both MATE1 and MATE2-K (averaged value from the estimated IC_{50} values for MATE1 and MATE2-K [Report DS-014-17]) was used to simulate the interaction between pexidartinib and the MATE1/2-K substrate metformin.

Simulations were also conducted using K_i values that were at least 10-fold lower than those determined in vitro to account for uncertainty associated with the determination of IC_{50}/K_i values in vitro.

The CYP2B6 Ind_{max} and Ind_{C50} values were 2.5-fold and 0.72 µM, respectively, based on the mean mRNA data; or 9.6-fold and 1.16 µM, respectively, based on the mean activity data [Report TCRM-PLX-2015-01].

In vitro data showed that pexidartinib is a competitive inhibitor, a time-dependent inhibitor (TDI) and an inducer for CYP3A4. The Applicant only considered the TDI and induction potential of pexidartinib for clinically relevant DDI. The CYP3A4 Indmax and IndC50 values were 6.03-fold and 0.32 µM, respectively, based on mean mRNA data calibrated against rifampin data [Report TCRM-PLX-2015-01). The CYP3A4 TDI parameters, K_i (inhibitor concentration causing half-

maximal inactivation) and K_{inact} values were 4.01 µM and 1.356 h^{-1}, respectively [Report AM16-H0084-R01]. The Applicant reported that the in vitro TDI and induction parameters, when incorporated in a PBPK model, would over-predicted the steady-state drug exposure. Thus, the Applicant adjusted the observed fumic value of 0.119 to a predicted value of 0.83 based on protein concentration of 0.2 mg/mL used in the in vitro studies. As the fumic value of 0.83 was applied to KI, this corresponded to a 7-fold reduction in the inactivation potency.

Reviewer Comment:

- *Based on the recommended basic model (FDA's draft DDI guidance), the calculated R1 value for CYP3A4 was 1.03 (K_i value of 10.5 µM), slightly higher than the predefined cutoff value of 1.02. Therefore, it is acceptable to include only TDI and induction potential in the Applicant's PBPK model.*
- *Pexidartinib is a substrate for both CYP3A and UGT1A clearance pathways. Based on cytochrome P450 inhibition assay [Report XT154103] and clinical DDI study with itraconazole, the Applicant proposed comparable contribution of CYP3A4 and UGT1A4 to the metabolism of pexidartinib.*
- *The simulation results of Applicant's pexidartinib PBPK model (PBPK report 002) showed a 10% decrease in CYP3A activities in the liver at steady state following multiple doses of 400 mg pexidartinib twice daily when incorporated induction and TDI parameters. Reviewer noted that since both CYP3A and UGT1A4 contribute significantly on the clearance of pexidartinib; there is uncertainty on whether to use the multiple doses PK data of pexidartinib to optimize the interaction effect of pexidartinib on CYP3A pathway. Reviewer recommends using the clinical DDI with midazolam (ongoing study) to refine the interaction parameters of pexidartinib on CYP3A.*
- *Uncertainties on the CYP3A interaction parameters precluded the use of this model to evaluate the effects of pexidartinib on a sensitive CYP3A substrate. It also added uncertainty on the prediction of effect of pexidartinib on drugs where CYP3A might be a minor but significant clearance pathway.*

PBPK model verification

Model performance was evaluated by comparing the predicted concentration-time profiles and PK parameters with clinically observed data from the 1800 mg and 2400 mg single dose studies, and 1000 mg/day and 800 mg/day multiple doses of pexidartinib.

PBPK model application

The PBPK model of pexidartinib was applied prospectively to predict the following:

- Effects of pexidartinib on the PK of repaglinide (CYP2C8/OATP1B1 substrate) and rosiglitazone (CYP2C8 substrate);
- Effects of pexidartinib on the PK of bupropion (CYP2B6 substrate);
- Effects of pexidartinib on the PK of metformin (MATE1/2-K substrate), and rosuvastatin (OATP1B and BCRP substrate).

The PBPK models for repaglinide, rosiglitazone, rosuvastatin and metformin from Simcyp's library were directly used by the Applicant. The Applicant verified the ability of these models to be used as a substrate model for a target CYP or transporter-mediated pathway by comparing the predicted DDI effects with observed clinical PK and DDI data. There is no verification of the Applicant's bupropion PBPK model.

Reviewer Comment:

- *The Applicant's bupropion PBPK model is similar to the default bupropion model in Simcyp's library (V17), except that the Applicant only included CYP2B6 and dehydrogenases mediated clearance in its bupropion model.*
- *Additional discussion on the limitations in the Applicant's substrate models (bupropion, rosuvastatin and metformin) can be found in the Results section.*

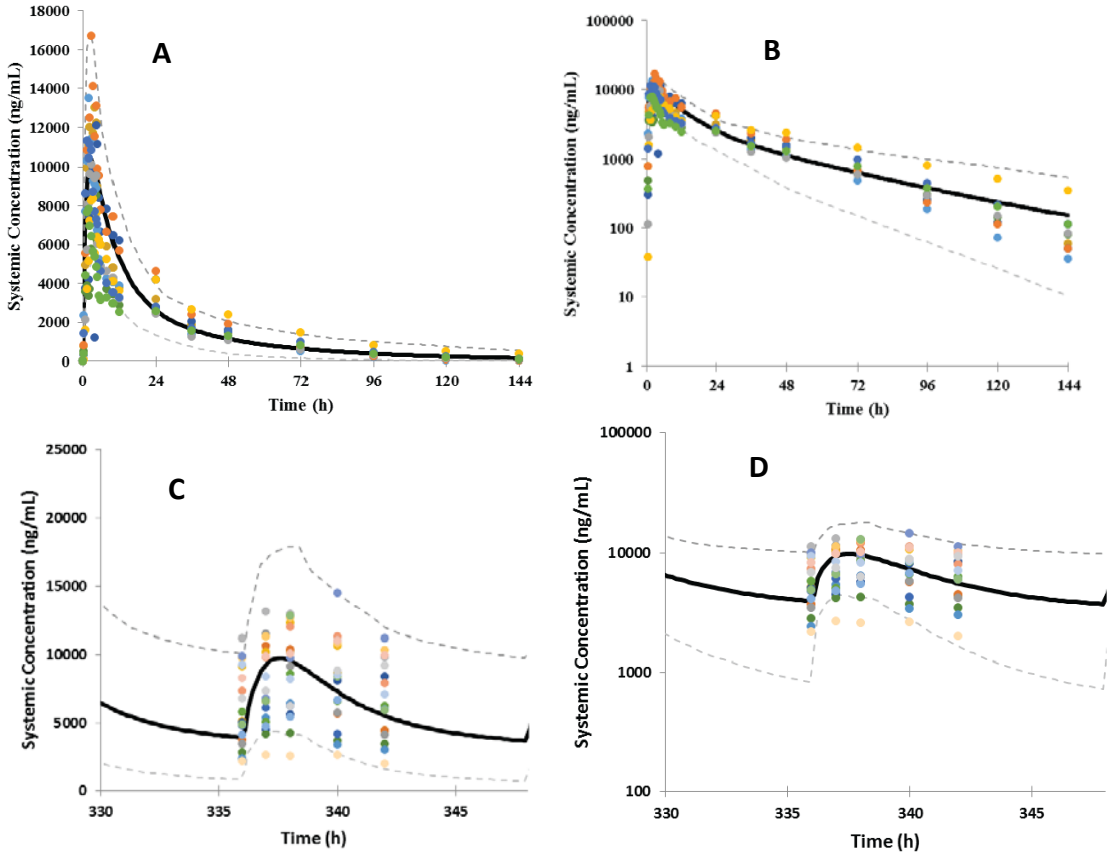
19.4.3.4. Results

Can PBPK analysis provide a reasonable description of the PK of pexidartinib?

Yes, PBPK simulations reasonably described the PK profile of pexidartinib following single dose administration in healthy subjects, and multiple dose in target cancer population. Comparison of observed PK profile versus PBPK predicted are shown in Figure 21.

There was reasonable agreement between PBPK predicted and observed exposures in healthy volunteer PK data (single 1800 mg and 2400 mg and dose levels). The predicted geometric mean values for AUC, C_{max} and T_{max} were within 15% of the observed values. The model recovers the patient PK data (1000 mg/day [Study 108-01] and 800 mg/day [PopPK-Phase 3 Study PLX 108-10] acceptably since the predicted geometric mean C_{max} and AUC values were within 2-fold of the observed parameters reported or estimated using Population PK analysis.

Figure 21. PBPK Predicted and Observed PK Profiles



PBPK predicted mean (lines) and observed (circles-individuals) plasma concentration-time profiles of pexidartinib (A) following a single oral dose of pexidartinib 1800 mg in healthy subjects and (B) log-transformed concentration profiles [Study PL3397-A-U117]; (C) last dosing interval following a 1000 mg daily dose (split 400 mg : 600 mg) for 14 days and (D) log-transformed concentration profiles [Study 108-01]. The grey dashed lines represent the 5% and 95% percentiles.
Source: PBPK_001 Report

Table 130. Comparison of PBPK Predicated and Observed C_{max} and AUC Values

	Observed			Predicted			Predicted/Observed Ratio		
Pexidartinib Dosing Regimen	**C_{max} (ng/mL)**	**AUC (ng.hr/mL)**	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC (ng.hr/mL)**	**T_{max} (h)**	**C_{max}**	**AUC**	**T_{max}**
1800 mg SD	10947	207293	2.8	9783	214746	3.1	0.89	1.04	0.91
2400 mg SD	14079	256929	3.2	13994	291081	2.7	0.99	1.13	0.85
1000 mg/day (400 mg:600 mg) day 15	8820	42800	-	11707.0	46569	-	1.33	1.09	-
800 mg/day (400 mg:400 mg) day 15	9689.7	197876.7	-	7766	100524	-	0.8	0.51	-

Predicted/Observed Ratio of geometric means. SD: single dose; $AUC_{0\text{-}114h}$ for SD; $AUC_{0\text{-}6h}$ for 1000 mg/day dose; $AUC_{0\text{-}24h}$ for 800 mg/day dose.
Source: Tables 3, 4, 5 and 6 of PBPK_001 report

Can PBPK analysis be used to estimate the effects of pexidartinib on a CYP2C8 substrate?

Yes. PBPK DDI simulations were conducted between repeated doses of pexidartinib (400 mg BID) and single dose of repaglinide (CYP2C8/OATP1B1 substrate) or rosiglitazone (CYP2C8 substrate) in the healthy volunteer population model.

Repaglinide is a substrate of CYP2C8 and CYP3A4 pathway, as well as a substrate for OATP1B1-mediated uptake. The Applicant verified the contributions of CYP2C8 and CYP3A4 pathway using the clinical DDI data with clarithromycin (CYP3A inhibitor) and gemfibrozil (dual CYP3A4 and CYP2C8 inhibitor). OATP1B1 uptake was verified by comparing observed and simulated C_{max} and AUC ratios of repaglinide for subjects of different OATP1B1 phenotypes (Kajosaari et al. 2008 [PMID: 18187595]). The reviewer explored the contributions of CYP2C8, CYP3A4 and OATP1B1 pathways on the PK of repaglinide by turning on and off each pathway in the repaglinide model (Table 131). The contribution of CYP2C8 to repaglinide clearance is approximately 60%.

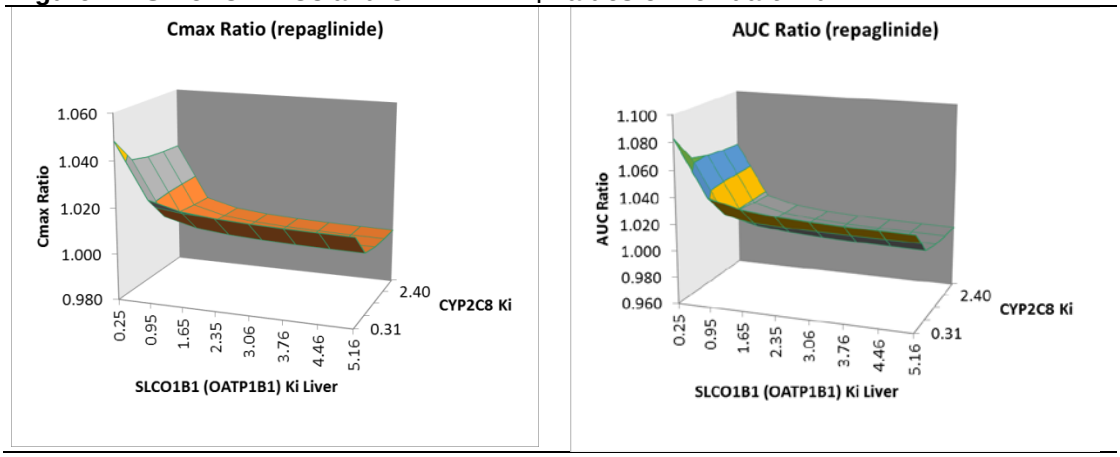
Table 131. Contributions of CYP2C8, CYP3A4 and OATP1B1

	Repaglinide PK			
DDI Scenario	**C_{max} (ng/mL)**	**$AUC_{0\text{-}tau}$ (ng.hr/mL)**	**$C_{max}R$**	**$AUC_{0\text{-}tau}R$**
Default model	2.86	5.31	1.00	1.00
Turn off CYP2C8 pathway only	4.41	10.94	1.54	2.06
Turn off CYP3A4 pathway only	3.99	8.18	1.39	1.54
Turn off OATP1B pathway only	5.87	19.99	2.05	3.76

Data presented as geometric means. C_{max} and AUC ratio of geometric means.
Source: Reviewer's analysis using the library (V17) repaglinide PBPK model following a single dose of 0.25 mg repaglinide in population representative.

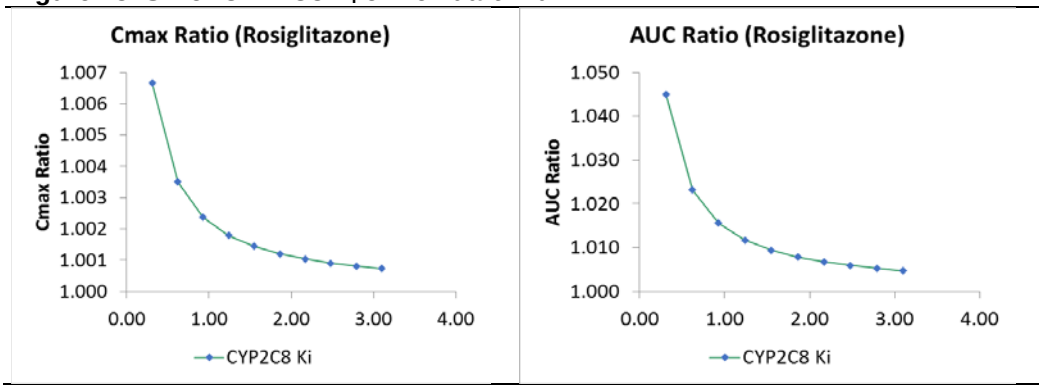
The effect of pexidartinib on the PK of repaglinide is expected to be low. The drug interaction effect in terms of predicted geometric mean (90% CI) ratios for C_{max} and AUC_{inf} were 1.00 (1.00 - 1.00) and 1.01 (1.01 – 1.01), respectively when co-administered a single dose of 0.25 repaglinide on day 14 with repeat doses of 400 mg BID pexidartinib for 15 days. To address the uncertainty associated with the in vitro interaction parameter values, 10 and 20-fold lower K_i values (0.31 µM and 0.25 µM) than those reported in vitro for CYP2C8 and OATP1B1 respectively, were applied in the simulation. The results of the sensitivity analysis showed a less than 10% difference in the predicted C_{max} and $AUC_{0\text{-}inf}$ ratio for rosiglitazone when lower K_i values for CYP2C8 and OATP1B1 were tested (Figure 22).

Figure 22. SA of CYP2C8 and OATP1B1 K_i Values of Pexidartinib



For rosiglitazone, the drug interaction effect in terms of predicted geometric mean (90% CI) ratios for C_{max} and $AUC_{0\text{-}inf}$ were 1.00 (1.00 - 1.00) and 1.00 (1.00 - 1.00) respectively, following the administration of a single oral dose of 4 mg repaglinide on day 14 with and without 400 mg BID pexidartinib administration. The result of sensitivity analysis showed that there is less than 5% difference in the predicted C_{max} and $AUC_{0\text{-}inf}$ ratio for rosiglitazone when a 10-fold lower CYP2C8 K_i value was tested (Figure 23). The fmCYP2C8 value for rosiglitazone is approximately 50%.

Figure 23. SA of CYP2C8 K_i of Pexidartinib



PBPK simulations suggested that an interaction between pexidartinib and a CYP2C8 substrate is unlikely to be clinically significant.

Can PBPK analysis be used to estimate the effects of pexidartinib on a CYP2B6 substrate?

No. Limitations were found in the default bupropion library model that precluded its use as a CYP2B6 substrate for estimation of the effect of pexidartinib. Bupropion is metabolized by several clearance pathways (CYP2B6, CYP2C19, CYP3A and dehydrogenases) and has a stereoselective metabolism. These factors led to difficulties in the characterization of contributions of enzymes to the bupropion clearance. For example, the contributions of the CYP2B6 (fmCYP2B6) were assigned to be 61% and 42% respectively in the Applicant's and library bupropion PBPK model. However, in vitro data suggested that the fmCYP2B6 for R-bupropion, S-bupropion, and racemic bupropion was predicted to be 30, 10, and 21%,

respectively (Sager et al. 2016 [PMID: 27495292]). Given the uncertainty in the fmCYP2B6 value in the bupropion PBPK model, the simulated DDI results could be inconclusive. Thus, the Applicant's PBPK analysis was inadequate to assess pexidartinib effect on the PK of bupropion (a CYP2B6 substrate).

Can PBPK analysis be used to estimate the effects of pexidartinib on drug-transporter substrates?

No. Limitations were found in the default metformin library model that precluded its use as a MATE substrate for estimation of the effect of pexidartinib. Current in-house analysis of the metformin PBPK model demonstrated metformin model could not capture the full spectrum of clinical DDI effects reported in the literature. For example, the model under-predicted the effects of cimetidine and pyrimethamine on metformin at a dose level of 500 mg. Therefore, PBPK analysis could not be used to estimate the effects of pexidartinib on a MATE substrate.

There are also concerns about the default rosuvastatin library model that precluded its use as an BCRP and OATP1B1/3 substrate. Reviewer acknowledges that the rosuvastatin PBPK model can describe the rosuvastatin plasma PK data following a single or multiple dose of rosuvastatin at various dosing levels. The model also captured the increase in rosuvastatin PK following coadministration with a single dose of 600 mg rifampicin (an inhibitor for multiple transporters). However, the model underpredicted the magnitude of interaction with cyclosporine (a prototypical inhibitor of BCRP/OATP1B1) (Simonson et al. 2004, PMID: 15289793). Until additional data is available to substantiate the reason for this under-prediction, the rosuvastatin library model is not adequate for use as an OATP1B1/3 substrate model. Thus, PBPK analysis could not be used to estimate the effects of pexidartinib on an OATP1B1/3 substrate.

Conclusions

In summary, the PBPK model of pexidartinib is adequate to predict the PK profile of pexidartinib in healthy volunteers and target cancer population.

PBPK analysis predicted that an interaction between pexidartinib and a CYP2C8 substrate (such as rosiglitazone or repaglinide) is unlikely to be clinically significant. The PBPK analysis is adequate to support labeling language for pexidartinib interaction with substrates for CYP2C8 isoenzyme.

The Applicant's PBPK analyses were inadequate to assess pexidartinib effects on the PK of bupropion (CYP2B6 substrate), metformin (MATE1/2-K substrate), and rosuvastatin (OATP1B1/3 substrate) due to the limitations identified in the substrate PBPK models.

19.5. ENLIVEN Study Monitoring

Table 132 was reproduced from the ENLIVEN Clinical Study Report. References in the footnotes refer to portions of the CSR, not to this review.

Table 132. Schedule of Events- Part 1

Procedure	Day −42 to −1 [a]	P1-C1D1	P1-C1D8 ± 2d	P1-C1D15 ± 2d	P1-C1D22 ± 2d	P1-C2D1 ± 2d	P1-C2D15 ± 2d	P1-C3D1 ± 7d	P1-C4D1 ± 7d	P1-C5D1 ± 7d	P1-C6D1 ± 7d	P1 Compl [b] ± 7d	P1-Post Tx [c] ± 7d	End St/Ear. Term. ± 7d
	Screen [a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25	LD +28d	LD+12 Week/new Tx [d]
Informed consent	X													
Demog. & medical history	X													
Height, weight	X											X[e]	X[e]	
Vital signs, incl. BP, pulse, temp	X[f]	X		X		X		X	X	X	X	X	X	
Physical examination [g]	X					X			X			X	X	
ECG [h]	X	X		X								X	X	
ECHO or MUGA scanning [i]	X								X			X	X[j]	
Chemistry, hematology	X	X		X[k]		X		X	X	X	X	X	X	
Liver function tests [l]	X	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	X[l]	
Urinalysis		X							X			X	X	
Hepatitis panel	X													
Coagulation tests [m]		X										X	X	
Hormone testing [n]	X	X										X	X	
BPI Worst Pain NRS [o, p]	X	X						X		X		X	X	
Worst Stiffness NRS item [o, p]	X	X						X		X		X	X	
Most disturbing Sx assessment		X												

Procedure	Day −42 to −1 [a]	P1-C1D1	P1-C1D8 ± 2d	P1-C1D15 ± 2d	P1-C1D22 ± 2d	P1-C2D1 ± 2d	P1-C2D15 ± 2d	P1-C3D1 ± 7d	P1-C4D1 ± 7d	P1-C5D1 ± 7d	P1-C6D1 ± 7d	P1 Compl[b] ± 7d	P1-Post Tx [c] ± 7d	End St/Ear. Term. ± 7d
	Screen [a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25	LD +28d	LD+12 Week/new Tx [d]
PROMIS Physical Function Scale[o]	X	X						X		X		X	X	
Global Rating of Concept item		X						X		X		X	X	
EQ-5D-5L instrument[o]		X						X		X		X	X	
Review completed outpatient PROs		X						X		X		X	X	
Patient Global Impress. of Change item												X	X	
MRI of the affected joint[q]	X								X			X	X	X
ROM assessment[r]	X								X			X	X	
Serum pregnancy test[s]	X					X		X	X	X	X	X	X	X
Archival tumor tissue[t]	X													
PK, PDy blood sampling[u]		X		X		X		X		X				
Analgesic use assessment	X[v]	X						X		X		X	X	
Subject randomization		X												
Dispense study Tx		X		X		X		X	X	X	X			
In-clinic study Tx dosing[w]		X		X										

Procedure	Day −42 to −1 [a]	P1-C1D1	P1-C1D8 ± 2d	P1-C1D15 ± 2d	P1-C1D22 ± 2d	P1-C2D1 ± 2d	P1-C2D15 ± 2d	P1-C3D1 ± 7d	P1-C4D1 ± 7d	P1-C5D1 ± 7d	P1-C6D1 ± 7d	P1 Compl[b] ± 7d	P1-Post Tx [c] ± 7d	End St/Ear. Term. ± 7d
	Screen [a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25	LD +28d	LD+12 Week/new Tx [d]
Study Tx dosing[x]		—— Twice daily dosing through Week 24[x] ——												
Tx compliance assessment				X		X		X	X	X	X	X		
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Surgical Assessment Questionnaire	X											X	X	
Collection of surgical data[z]												X	X	X
HCRU & productivity assessment		X				X		X	X	X	X	X	X	

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BP = blood pressure; BPI = Brief Pain Inventory; C = cycle; Compl = Completion; D/d = Day; Demog. = demographics; ECG = electrocardiogram; ECHO = echocardiogram; End St./Ear. Term. = End-of-Study/Early Termination; EQ-5D-5L = EuroQol 5-dimensional descriptive system; FSH = follicle-stimulating hormone; GCT-TS = giant cell tumor of the tendon sheath; HCRU = healthcare resource use; incl. = including; LD = last dose; LH = luteinizing hormone; MRI = magnetic resonance imaging; MUGA = multi-gated acquisition; NRS = Numeric Rating Scale; P = Part; PDy = pharmacodynamic; PK = pharmacokinetic; PRO = Patient-reported Outcome; PROMIS = Patient-reported Outcomes Measurement Information System; PVNS = pigmented villonodular synovitis; ROM = range of motion; Screen = Screening; Sx = symptom; temp. = temperature; Tx = treatment

[a] Procedures performed as part of subject care within the 42-day period before the first dose of study drug may have been used for screening purposes if they conformed to protocol requirements and standards. All screening test results were reviewed prior to dosing to assess the study candidate's eligibility for inclusion.
[b] The Part 1 Completion Visit applied to subjects who were not continuing into Part 2. Those continuing into Part 2 instead had the assessments indicated at P2-C1D1 (see Table 6-2).
[c] Subjects who exited the study with radiologic disease progression underwent their last study evaluation 28 days ± 7 days after their last dose of study drug or before any new PVNS therapy, including surgery, whichever occurred first. Any planned new PVNS therapy, including the type of surgical procedure, was recorded. Subjects who withdrew from the study with radiologic progression did not undergo an End-of-Study/Early Termination MRI.
[d] Subjects who ended their study participation with no radiologic disease progression underwent post-treatment procedures 28 days ± 7 days after their last dose of study drug and a final MRI 12 weeks ± 7 days after their last dose of study drug or before any new PVNS therapy, including surgery, whichever occurred first. The latter MRI did not need to be performed if new PVNS therapy started within 4 weeks of the Post-treatment Visit. Before or at the End-of-Study/Early Termination Visit, plans for any new PVNS therapy were obtained (see Footnote z).
[e] Weight only.
[f] Vital signs were performed before any invasive procedures were carried out on the same day.
[g] In the event of early withdrawal or if the subject completed Part 1 but did not enter Part 2, a physical examination was performed at the Post-treatment Visit.

[h] A standard 12-lead ECG was performed prior to dosing. Subjects were told not to take their morning dose of study drug at home on days when an ECG was performed; instead, they brought their study drug bottle to the study site and took their morning dose upon study site instruction. At the P1-C1D1 and P1-C1D15 Visits only, the ECG was performed before and 2 hours after dosing. The 2-hour postdose ECG began within 10 minutes of the 2-hour postdose time point.
[i] ECHO or MUGA scanning was chosen by investigator preference. However, the same imaging platform must have been used throughout the study.
[j] ECHO or MUGA scanning was only repeated if more than 3 months had elapsed since the last procedure. Subjects who showed a reduced ejection fraction relative to Baseline at the last visit were followed until a stable ejection fraction was measured by 2 consecutive tests.
[k] Hematology only.
[l] ALP, ALT, AST, and total and direct bilirubin were assessed at screening, weekly during P1-C1 beginning on Day 1, on Days 1 and 15 of P1-C2, and on Day 1 of every cycle thereafter.
[m] Subjects receiving concomitant warfarin had their anticoagulation status carefully monitored for any necessary dose adjustments (see Section 6.4.8).
[n] Women who were not using hormonal contraception were tested for levels of FSH, LH, progesterone, and estradiol. Hormone testing was not required for women who had either an oophorectomy or were postmenopausal. Men were tested for levels of LH, FSH, and testosterone. Men whose testosterone level was below Baseline at the last study visit were followed until their level had stabilized or returned to Baseline.
[o] Subjects recorded responses to the BPI Worst Pain NRS item, Worst Stiffness NRS item, PROMIS Physical Function Scale, and EQ-5D-5L in the eDiary before any invasive procedures (NOTE: at the Screening Visit only, the recall period was the preceding week for the BPI Worst Pain NRS item and Worst Stiffness NRS item. The subject's response was documented in the medical notes).
[p] Subjects were reminded to complete the BPI Worst Pain NRS item and the Worst Stiffness NRS item, at least 4 of 7 consecutive days for 2 weeks prior to randomization, and prior to Day 1 of P1-C1, P1-C3, and P1-C5 and before the Part 1 Completion Visit (Week 25). In the event of early withdrawal or if the subject completed Part 1 but did not enter Part 2, this item was completed prior to the Post-treatment Visit.
[q] The investigator may have requested a centrally read blinded MRI to confirm progression, eg, if a subject's mid-study clinical profile or local radiological assessment indicated progression.
[r] A ROM assessment in the affected joint or tumor location was performed by a blinded independent third-party assessor.
[s] Women of childbearing potential had a serum pregnancy test within 14 days prior to randomization (or, where different regulations apply, within 72 hours of randomization) (Women who had documentation of at least 12 months of spontaneous amenorrhea and had an FSH level >40 mIU/mL were assessed as postmenopausal and did not need to undergo pregnancy testing).
[t] Archival surgical tissue from TGCT tumors was obtained at Screening (or whenever available) for biomarker assessment.
[u] Details on blood sampling are found in Section 6.5.2.1 (PK) and Section 6.5.2.2 (PDy).
[v] A diary of analgesic use was kept for the 2-week period before the first dose of study drug.
[w] The morning dose of study drug was administered at the study site on the days indicated; P1-C1D1 was within 3 days after randomization.
[x] Dose administration by the subject at home. See Section 6.1 for dose reduction as of P1-C1D15. Subjects took their last dose of study drug the evening before their scheduled Part 1 Completion Visit (Week 25).
[y] After the subject provided signed informed consent; AEs were monitored throughout the study via safety assessments, observation, and subject reporting (see Section 6.5.3).
[z] If surgical resection of the tumor was performed within 12 weeks after the last dose of study drug, details of the surgery and its outcome were obtained.

19.6. Additional Clinical Outcome Assessment Analyses

19.6.1. Patient-Reported Outcome Scales

Figure 24. PROMIS® Physical Function Items

PROMIS Item Bank v. 1.2 – Physical Functioning (Lower Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA10	Are you able to stand for one hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

PROMIS Item Bank v. 1.2 – Physical Functioning (Upper Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB34	Are you able to change a light bulb overhead?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA12	Are you able to push open a heavy door?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA5	Does your health now limit you in lifting or carrying groceries?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA13	Are you able to exercise for an hour?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Figure 25. Worst Stiffness NRS Item

The following question asks about stiffness at the site of your tumor.

Please rate your stiffness by circling the one number that best describes your stiffness at its worst in the last 24 hours.

0 1 2 3 4 5 6 7 8 9 10

0 = No stiffness

10 = Stiffness as bad as you can imagine

Figure 26. Brief Pain Inventory (BPI) Worst Pain Numeric Rating Scale (NRS) Item

The following question asks about pain at the site of your tumor.

Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

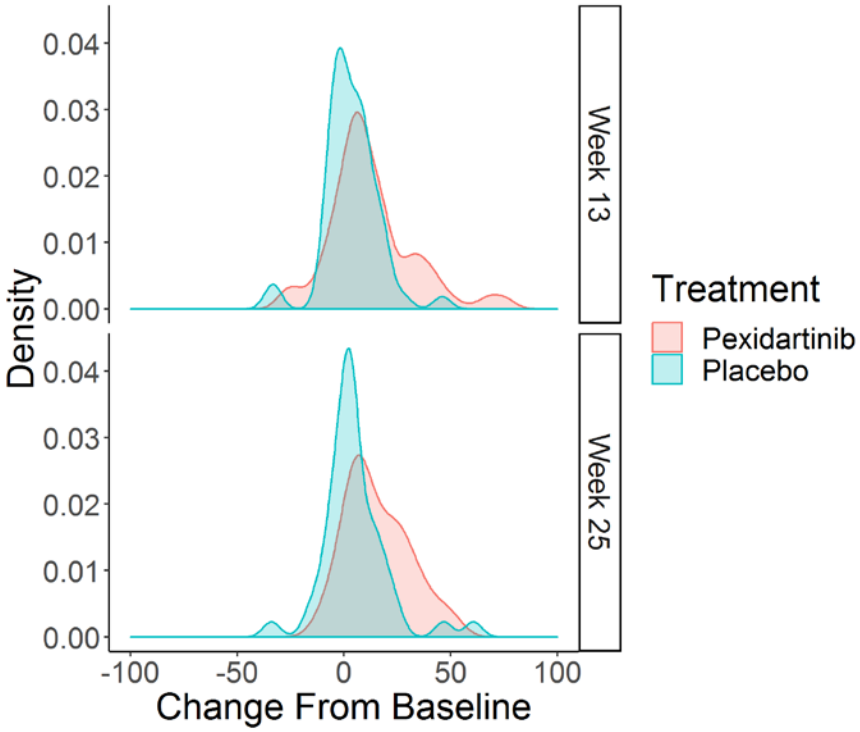
0 1 2 3 4 5 6 7 8 9 10

0 = No pain

10 = Pain as bad as you can imagine

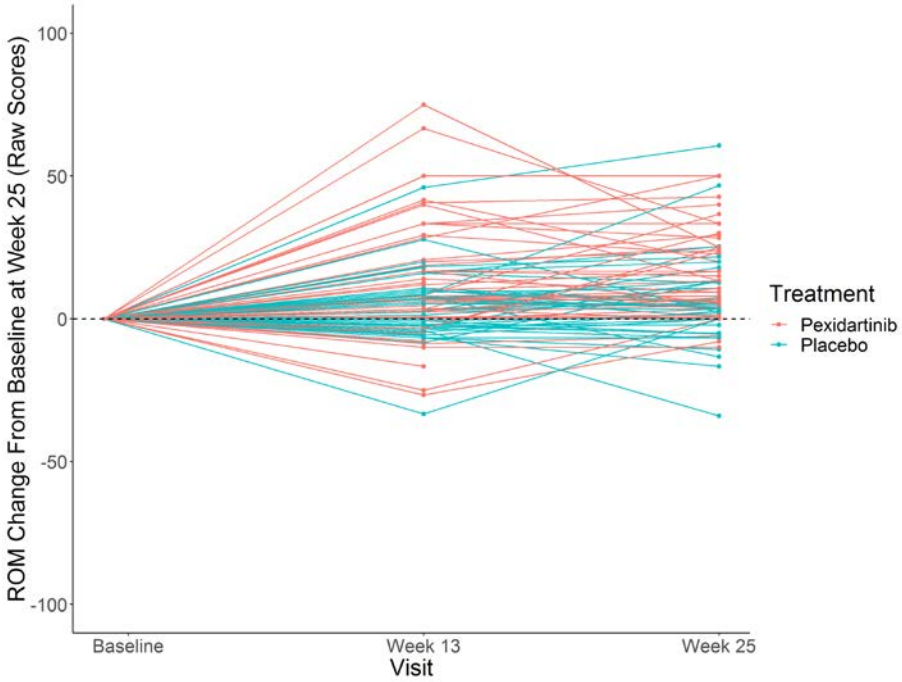
19.6.2. Range of Motion

Figure 27. ROM Change From Baseline Score by Treatment and Follow-up Visit



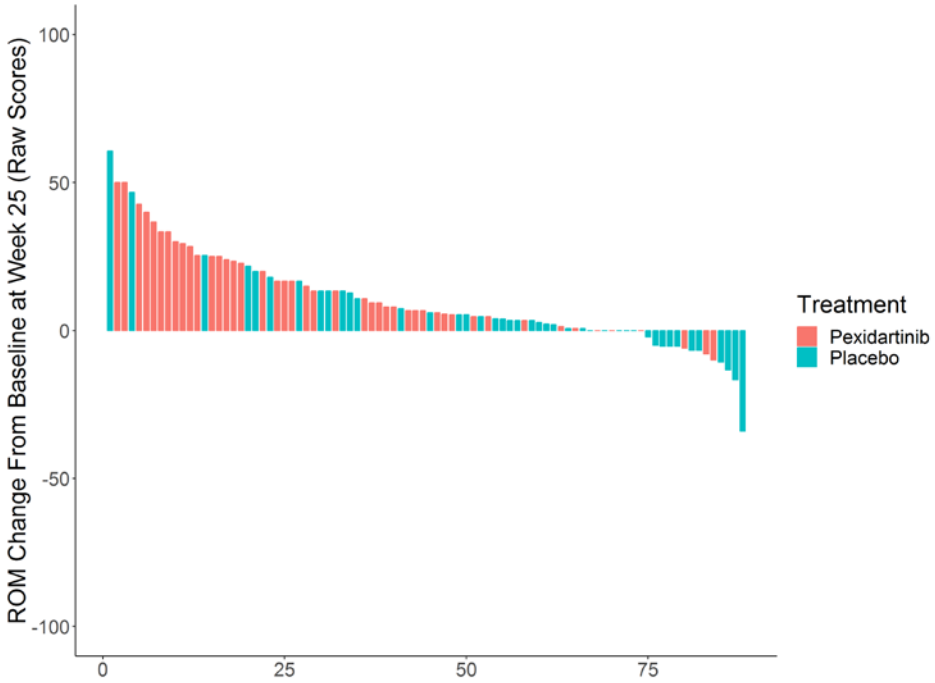
Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

Figure 28. Spaghetti Plot of ROM Change From Baseline



Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

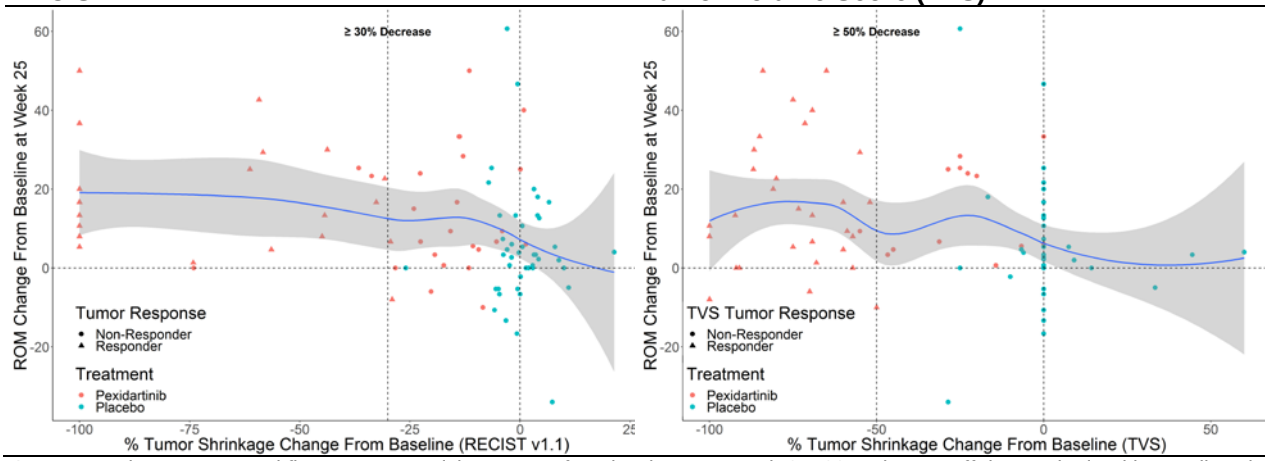
Figure 29. Waterfall Plot of ROM at Week 25 by Treatment Arm



Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

Figure 30. ROM at Week 25 by Percent Change Tumor Shrinkage

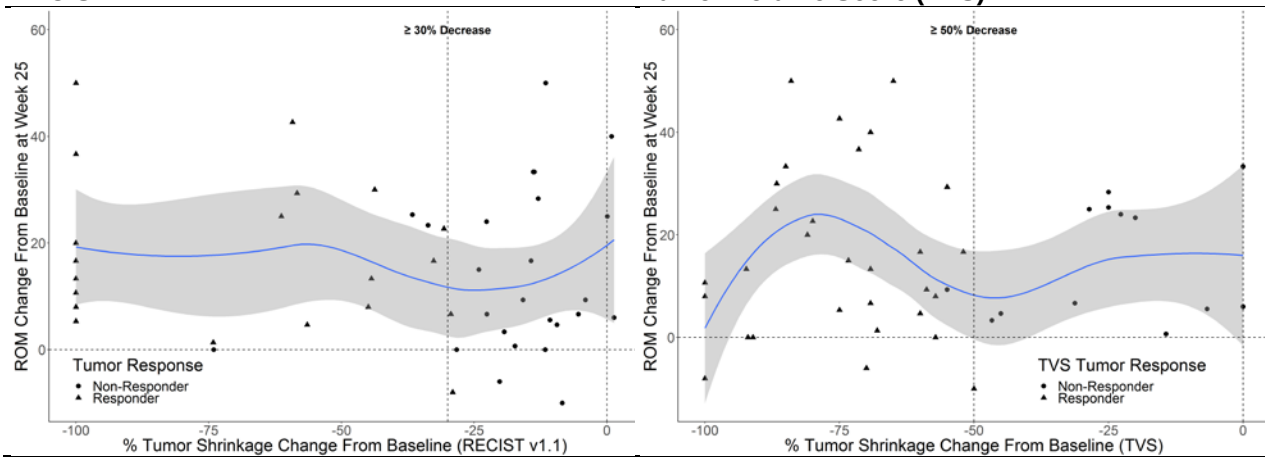
RECIST **Tumor Volume Score (TVS)**



Source: Reviewer generated figure – summarizing range of motion (ADFA, March 27, 2017 data cutoff date, submitted by Applicant) and response datasets (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

Figure 31. ROM at Week 25 by Percent Change Tumor Shrinkage

RECIST **Tumor Volume Score (TVS)**



Source: Reviewer generated figure – summarizing range of motion (ADFA, March 27, 2017 data cutoff date, submitted by Applicant) and response datasets (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

Table 133. Subgroup Analysis of ROM by Overall Response Rate

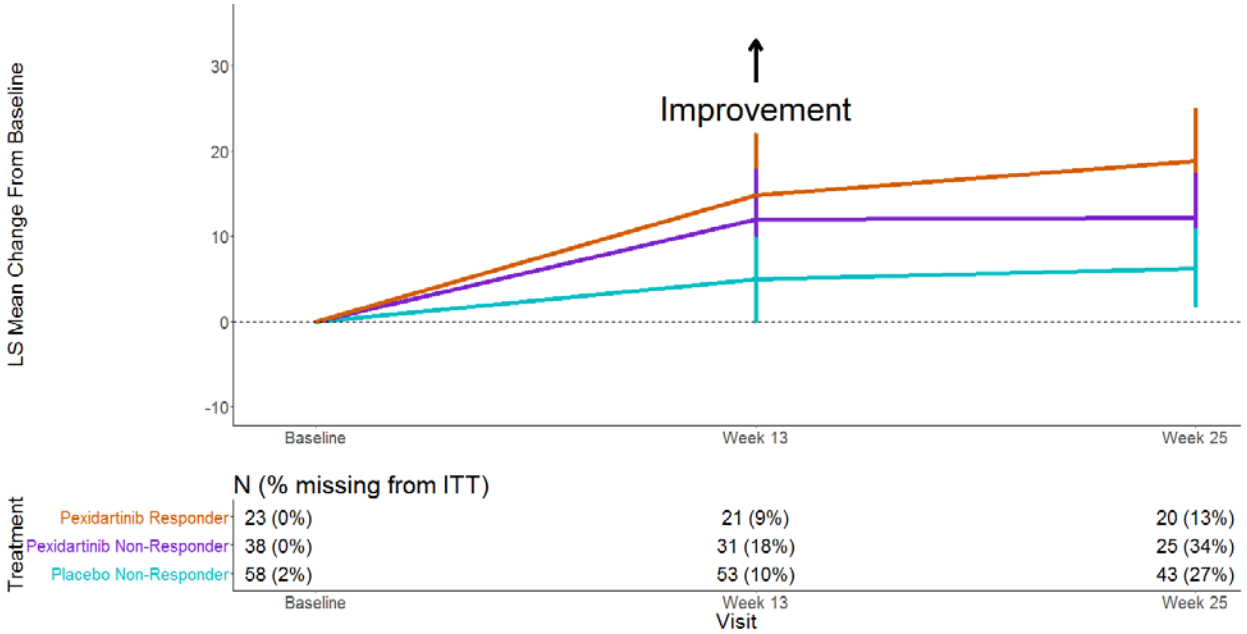
Change From Baseline at Week 25[1,2]	Pexidartinib Responder N=24	Pexidartinib Non-Responder N=37	Placebo Non-Responder N=59
LS Mean (95% CI)	18.8 (12.6, 24.9)	12.1 (6.8, 17.5)	6.5 (1.9, 10.9)
Difference From Placebo (95% CI)	12.5 (4.8, 20.2)	5.9 (-0.8, 12.6)	

Source: Reviewer generated table – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

[1] Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, joint type, treatment by visit interaction, baseline by visit interaction, treatment by joint type interaction, baseline by joint type interaction

[2] 32 (27%) patients missing at Week 25

Figure 32. Least Squares Mean Δ From Baseline Plot of ROM by ORR



Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

Table 134. Sensitivity Analysis for Missing Data of ROM Knee Only

	Pexidartinib N=34 LS Mean (95% CI)	Placebo N=39 LS Mean (95% CI)	Difference from Placebo LS Mean (95% CI)
Primary results (MMRM)[*1,2]	14.5 (9.7, 19.3)	5.5 (1.0, 10.0)	9.0 (2.5, 15.4)
FDA tipping point analysis: Delta-adjusting PMM Pexidartinib penalty = -12%	11.3 (6.3, 16.3)	5.5 (0.8, 10.3)	5.7 (-1.0, 12.6)

Sources: [*]Reviewer generated table – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant),[**]Applicant analyses
[1] Estimated using MMRM with fixed effects for treatment arm, visit, baseline, region, joint type, treatment by visit interaction, baseline by visit interaction, treatment by joint type interaction, baseline by joint type interaction
[2] 32 (27%) patients missing at Week 25

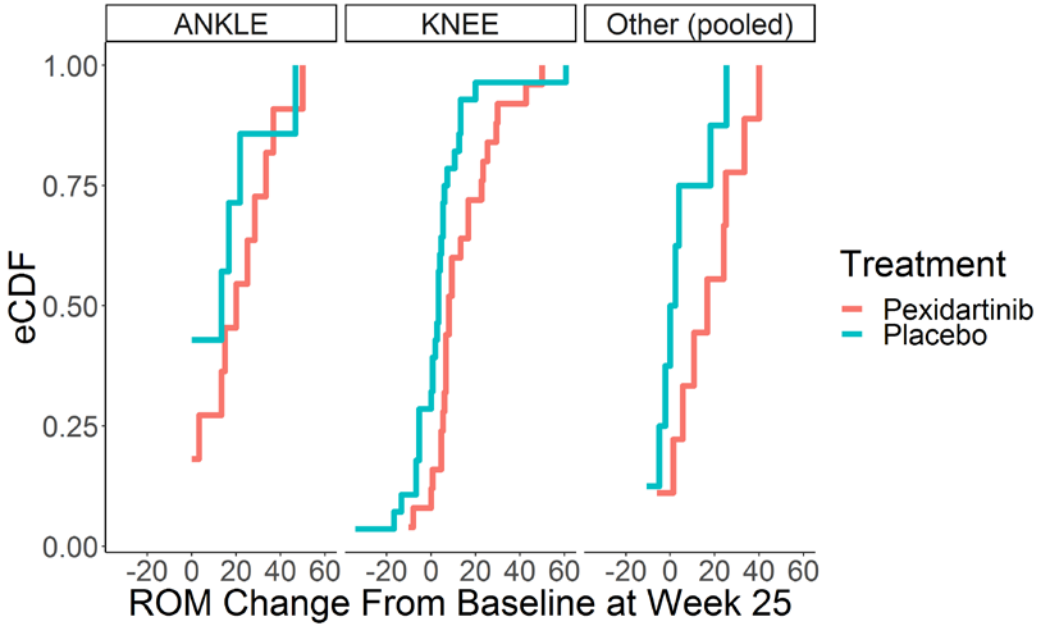
Table 135. Responder Analyses of ROM by Thresholds of Clinically Meaningful Within-Patient Change

Threshold	Pexidartinib N=61 Response Rate (95% CI)	Placebo N=59 Response Rate (95% CI)
5%	56% (43, 67)	27% (17, 40)
6.7%	46% (34, 58)	22% (13, 34)
10%	39% (28, 52)	20% (12, 32)
15%	34% (24, 47)	12% (6, 23)
20%	28% (18, 40)	8% (4, 18)
25%	21% (13, 33)	5% (2, 14)

Table 136. Responder Analyses of ROM at the Knee

Threshold	Pexidartinib N=34 Response Rate (95% CI)	Placebo N=39 Response Rate (95% CI)
5%	56% (39, 71)	26% (15, 41)
6.7%	41% (26, 58)	18% (9, 33)
10%	29% (17, 46)	15% (7, 3)
15%	26% (15, 43)	5% (1, 17)
20%	21% (1, 37)	5% (1, 17)
25%	15% (6, 30)	3% (0, 13)

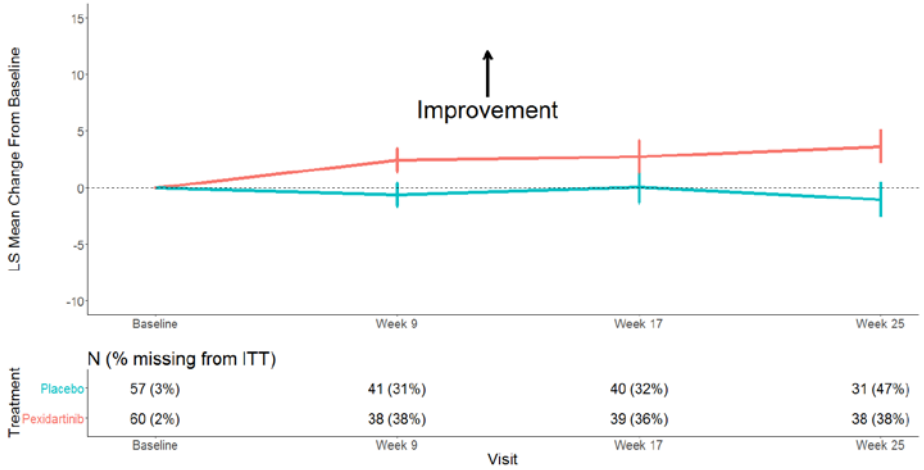
Figure 33. Empirical Cumulative Distribution Function Plot of ROM



Source: Reviewer generated figure – summarizing range of motion dataset (ADFA, March 27, 2017 data cutoff date, submitted by Applicant)

19.6.3. Physical Function

Figure 34. Least Squares Mean Δ From Baseline Plot of Physical Function



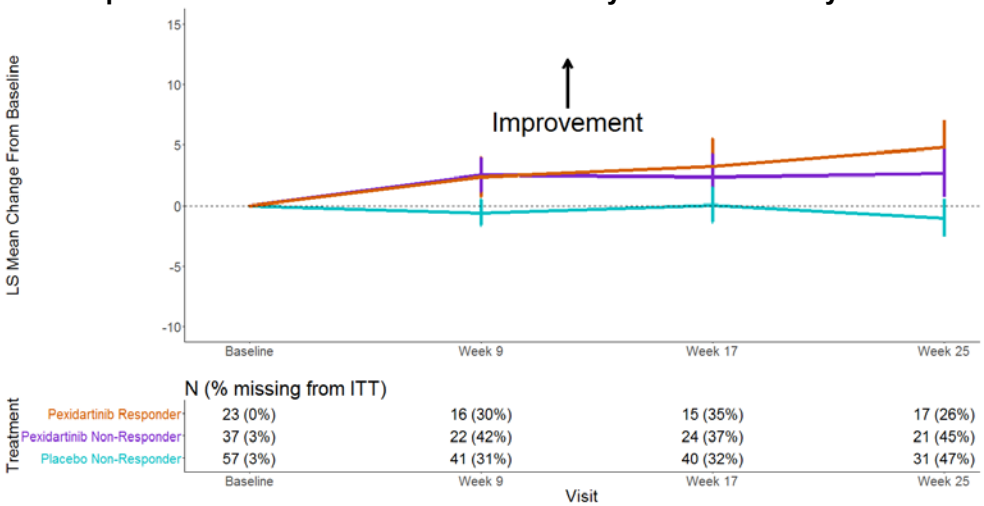
Source: Reviewer generated figure – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant)

Table 137. Subgroup Analysis of Physical Function by Overall Response Rate

Change From Baseline at Week 25[1,2]	Pexidartinib Responder N=23	Pexidartinib Non-Responder N=38	Placebo Non-Responder N=59
LS Mean (95% CI)	4.8 (2.5, 7.0)	2.6 (0.7, 4.6)	-1.1 (-2.6, 0.5)
Difference From Placebo (95% CI)	5.8 (3.1, 8.6)	3.7 (1.1, 6.2)	

Source: Reviewer generated table – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)
[1] Estimated using Mixed Model Repeated Measures (MMRM) with fixed effects for treatment arm, visit, baseline, region, treatment by visit interaction, baseline by visit interaction based on pre-specified model in SAP
[3] 51 (43%) patients missing at Week 25

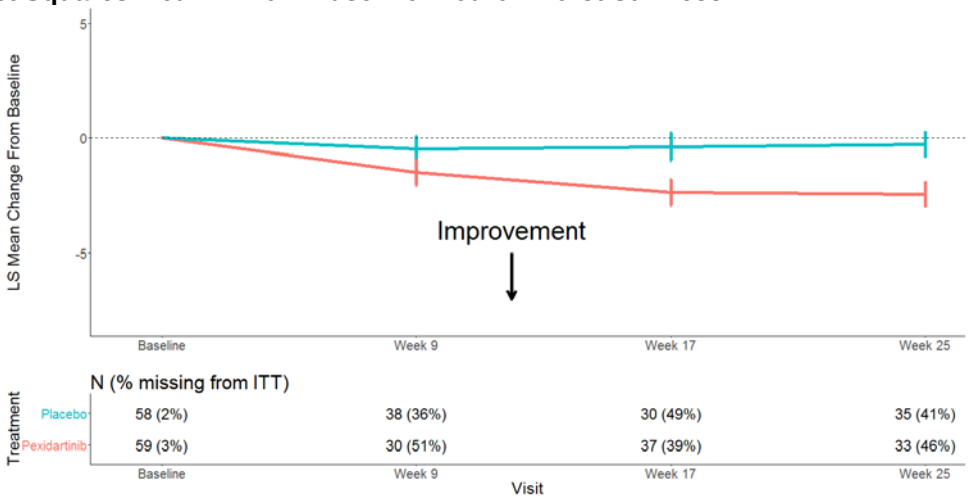
Figure 35. Least Squares Mean Δ From Baseline Plot of Physical Function by ORR



Source: Reviewer generated figure – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

19.6.4. Worst Stiffness

Figure 36. Least Squares Mean Δ From Baseline Plot for Worst Stiffness



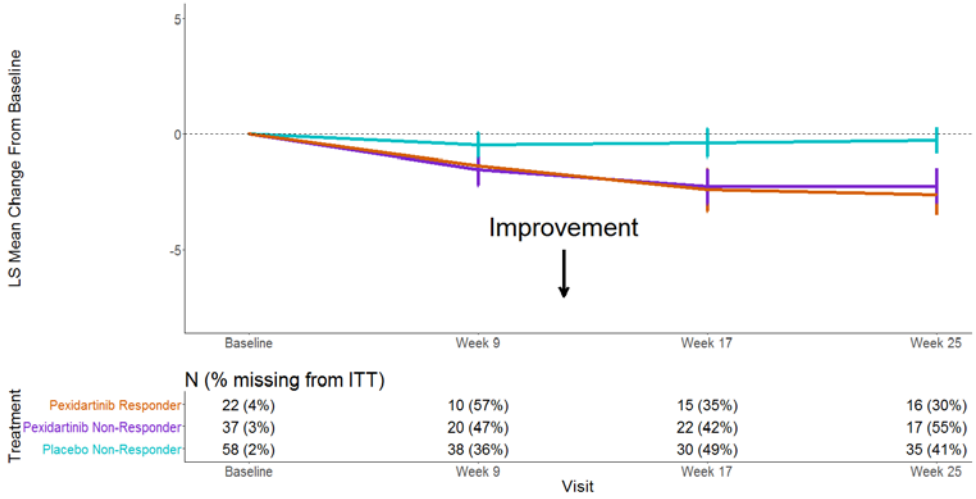
Source: Reviewer generated figure – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant)

Table 138. Subgroup Analysis of Worst Stiffness by Overall Response Rate

Change from Baseline at Week 25[1,2]	Pexidartinib Responder N=23	Pexidartinib Non-Responder N=38	Placebo Non-Responder N=59
LS Mean (95% CI)	-2.6 (-3.5, -1.7)	-2.3 (-3.0, -1.5)	-0.3 (-0.9, 0.3)
Difference From Placebo (95% CI)	-2.4 (-3.4, -1.3)	-2.0 (-2.9, -1.0)	

Source: Reviewer generated table – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)
[1] Estimated using Mixed Model Repeated Measures (MMRM) with fixed effects for treatment arm, visit, baseline, region, treatment by visit interaction, baseline by visit interaction
[2] 52 (43%) patients missing at Week 25

Figure 37. Least Squares Mean Δ From Baseline Plot of Worst Stiffness by ORR



Source: Reviewer generated figure – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)

19.6.5. BPI-30

Table 139. Subgroup Analysis of BPI-30 by Overall Response Rate

BPI-30 Response Rate	Pexidartinib Responder N=23	Pexidartinib Non-Responder N=38	Placebo Non-Responder N=59
No. Responses[2] (%)	10 (43%)	9 (24%)	9 (15%)
Response Rate 95% CI	(26%, 63%)	(13%, 39%)	(8%, 27%)

Source: Reviewer generated table – summarizing questionnaire dataset (ADQS, March 27, 2017 data cutoff date, submitted by Applicant) and ORR using response analysis dataset (ADRS, January 31, 2018 data cutoff date, submitted by Applicant)
[1] Estimated using Mixed Model Repeated Measures (MMRM) with fixed effects for treatment arm, visit, baseline, region, treatment by visit interaction, baseline by visit interaction based on pre-specified model in SAP
[2] 50 (42%) patients missing at Week 25

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/s/

NATALIYA N FESENKO
07/31/2019 10:34:20 AM

ELIZABETH I SPEHALSKI
07/31/2019 10:35:57 AM

ALEXANDER H PUTMAN
07/31/2019 10:39:47 AM

WHITNEY S HELMS
07/31/2019 10:40:59 AM

JOHN K LEIGHTON
07/31/2019 10:42:02 AM

SAFAA BURNS
07/31/2019 10:43:58 AM

JEANNE FOURIE ZIRKELBACH
07/31/2019 10:47:22 AM

YOUWEI N BI
07/31/2019 11:42:39 AM

YOUWEI N BI on behalf of JIANG LIU
07/31/2019 11:43:26 AM

XINYUAN ZHANG on behalf of YUCHING N YANG
07/31/2019 11:47:44 AM

MANUELA GRIMSTEIN
07/31/2019 11:49:16 AM

MALLORIE FIERO
07/31/2019 11:50:35 AM

PALLAVI S MISHRA-KALYANI
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CHRISTY L OSGOOD
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IBILOLA A FASHOYIN-AJE
07/31/2019 12:23:11 PM

RAJESHWARI SRIDHARA
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NAM ATIQUR RAHMAN
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MARC R THEORET
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