Taiwan Food and Drug Administration

Assessment Report

Trade Name：圖拉留膠囊 200 毫克/ TURALIO (pexidartinib) capsules 200 mg

Active Ingredient：Pexidartinib

License Number：MOHW-PI 028293

Applicant：台灣第一三共股份有限公司

Approval Date：2022/5/27

Indication：

無法透過手術或其他治療[如局部放射線治療]改善，且具嚴重後遺症或嚴重功能受限的症狀性腱鞘巨細胞瘤(TGCT)成人病人。

Adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery or other treatment modality (such as local radiotherapy)

Background Information

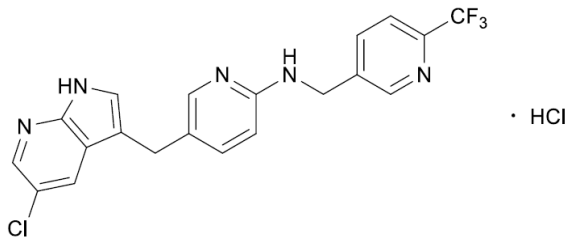
Trade Name	圖拉留膠囊 200 毫克/ TURALIO (pexidartinib) capsules 200 mg
Active Ingredient(s)	Pexidartinib
Applicant	台灣第一三共股份有限公司
Dosage Form & Strengths	膠囊劑 200 mg
Indication	無法透過手術或其他治療[如局部放射線治療]改善，且具嚴重後遺症或嚴重功能受限的症狀性腱鞘巨細胞瘤(TGCT)成人病人。 Adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery or other treatment modality (such as local radiotherapy)
Posology	400mg twice daily
Pharmacological Category **ATC Code**	L01EX15

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug Substance

The drug substance, pexidartinib hydrochloride, is chemically designated as 5-[(5-chloro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)methyl]-*N*-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyridin-2-amine monohydrochloride and has the following structure:



It is an off-white to white solid. The molecular formula and the molecular weight are $C_{20}H_{15}ClF_3N_5 \cdot HCl$ and 454.28, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of pexidartinib hydrochloride has been confirmed by elemental analysis, UV spectroscopy, IR spectroscopy, NMR spectroscopy and MS.

The drug substance specification includes tests for appearance, identification, organic impurities, residual solvents, water content, residue on ignition, particle size distribution and assay.

2.1.2 Drug Product

TURALIO capsules are immediate release capsules for oral use. Each capsule contains 200 mg pexidartinib which is equivalent to 217.5 mg pexidartinib hydrochloride. The excipients used in the drug product formulation comply with the compendial monographs.

The drug product specification includes appearance, identification, related substances, uniformity of dosage units, dissolution, assay and microbiological quality. Analytical methods are described well and validated.

Stability studies of the drug product under long term condition (25°C/60% RH) and accelerated condition (40°C/75% RH) have been carried out.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Pexidartinib hydrochloride is an oral, small-molecule, selective inhibitor that targets CSF1R, KIT, and FLT3-ITD. By targeting the CSF-1/CSF-1R pathway, pexidartinib is developed to treat tenosynovial giant cell tumor (TGCT).

Biochemical assays demonstrated that pexidartinib was a selective dual inhibitor of CSF1R and KIT but less potent against FLT3. Cell-based studies further showed that pexidartinib potently inhibited the catalytic activities of CSF1R, KIT, and FLT3-ITD. The CSF1R-inhibiting effects of pexidartinib had been further confirmed in a mouse model of cell growth in vivo. No relevant off-target inhibitory activity by pexidartinib was noted in a screening assay.

In a battery of safety pharmacology studies, pexidartinib did not show significant adverse effects on the CNS and respiratory system in rats at doses up to 200 mg/kg (approx. 2.4-fold MRHD based on BSA). Regarding cardiovascular function, pexidartinib inhibited hERG current with an IC50 value of 0.7 μmol/L, approx. 27-fold unbound Cmax at MRHD. At concentrations up to 3 μmol/L, pexidartinib did not prolong action potential repolarization in isolated rabbit Purkinje fibers. The in vitro IC50 of pexidartinib on calcium channel current was 0.2 μmol/L, approx. 7.7-fold unbound Cmax at MRHD. The in vivo cardiovascular effects of pexidartinib had been evaluated in dogs, and no

pexidartinib-related effects on the ECG parameters, heart rate, and body temperature were noted at doses up to 1000 mg/kg (approx. 41.7-fold MRHD based on BSA), consistent with the finding in the dog repeated-dose toxicity studies. However, changes in hemodynamic parameters in dogs at doses ≥ 50 mg/kg (approx. 2.1-fold MRHD based on BSA) were considered potentially undesirable pharmacodynamic effects.

Single-dose toxicity studies in rats and dogs at the respective doses up to 200 and 1200 mg/kg/day had shown no adverse effects of pexidartinib except for the treatment-related emesis at ≥ 200 mg/kg/day in dogs. In the repeated-dose studies, the toxicity of pexidartinib was generally dose- and time-dependent. In the 6-month study in rats, pexidartinib-related adverse changes occurred in the kidney, liver, male and female reproductive tissues, spleen, thymus, and chronic inflammation of the paw and vascular inflammation. The NOAEL in the rat 6-month study was 0.5 mg/kg/day in male rats, which was 0.013-fold MRHD based on AUC, and was not established in female rats. In the 9-month study in dogs, pexidartinib-related adverse effects were observed in the male reproductive organs at ≥ 30 mg/kg/day and showed partial recovery after a 16-week recovery period. The exposure at NOAEL in the dog 9-month study was 0.029- and 0.201-fold MRHD (AUC-based) for male and female dogs, respectively.

Pexidartinib showed no genotoxicity and was non-carcinogenic in vivo. Also, pexidartinib had no phototoxic potential. The reproductive and developmental toxicity was assessed in a standard battery of studies. In a FEED study in rats, male-associated lower fertility and copulation/conception indices and higher pre- and post-implantation loss with decreased viable embryos were observed at the highest dose tested. The NOAELs for male fertility and early embryonic development were approx. 0.35- and 0.29-fold MRHD (based on AUC), respectively. Besides, pexidartinib was teratogenic in rats and rabbits. In the EFD studies in rats and rabbits, minimal maternal toxicity occurred; however, decreased fetal survival (rabbits) and fetal malformations, including the visceral and skeletal malformations/anomalies, in both species were observed at the highest dose tested. The NOAELs for embryo-fetal development in rats and rabbits were approx. 0.346- and 0.446-fold MRHD (based on AUC), respectively. In a PPND study in rats, the parameters assessed were not affected, and the NOAEL was 0.293-fold MRHD (based on AUC).

Lastly, activity and the potential toxicity of the N-glucuronide metabolite, ZAAD-1006a, were also assessed. In vitro kinase assay showed ZAAD-1006a was less potent than pexidartinib, on CSF1R, KIT, FLT3, and FLT3-ITD. In a 13-week toxicity study in monkeys, no ZAAD-1006a-related changes were noted. ZAAD-1006a and pexidaritinib showed structure alert at the same structural sites in one in silico assay. Since there are no

genotoxic and carcinogenic concerns of pexidartinib in vitro and in vivo studies, the genotoxic and carcinogenic risks of ZAAD-1006a are also considered minimal.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following oral administration, pexidartinib peak exposure occurred after approximately 2.5 hours. The C_{max} and $AUC_{0\text{-}inf}$ values for pexidartinib are dose proportional over the dose range of 200 mg to 2400 mg. ZAAD-1006a (a N-glucuronide metabolite) appears in plasma within a median T_{max} of 4.5 hours after a single 400 mg oral dose of pexidartinib. The absolute bioavailability of pexidartinib has not been determined. Following a single 400 mg dose, standard high-fat and high-calorie meal increased mean C_{max} and $AUC_{0\text{-}inf}$ of pexidartinib by 98% and 110%, respectively, compared to fasted conditions. Both pexidartinib and ZAAD-1006a accumulate upon BID dosing of pexidartinib (mean Rac=3.6 and 4.6, respectively) based on the pop PK analysis.

Pexidartinib has a mean V_z/F of 187 L following a single 400 mg oral dose in healthy subjects. Both pexidartinib and ZAAD-1006a are highly bound (>99%) to human plasma proteins and the binding rate is independent of plasma concentration. Pexidartinib is extensively metabolized by CYP3A4 and also by UGT1A4 to N-glucuronide metabolite, ZAAD-1006a. ZAAD-1006a is the major plasma metabolite and had a 10% higher exposure than the parent drug. ZAAD-1006a has minimal pharmacological activity (355-fold lower) compared to pexidartinib. The mean $T_{1/2}$ and CL/F of pexidartinib are 26.7 hours and 5.1 L/h, respectively. Following a single 400 mg oral dose of ^{14}C-pexidartinib, the majority of the radioactivity is eliminated in feces (64.8%) with approximately 27.4% in urine. Unchanged pexidartinib is the major radioactive component detected in feces, representing 44% of the administered dose. The most abundant radioactive component in urine is the inactive metabolite, ZAAD-1006a, accounting for 10.3% of the administered pexidartinib dose. Exposure-safety analysis suggest higher pexidartinib concentrations were associated with faster onset and higher incidence of elevated ALT (three-fold ULN) and AST (three-fold ULN).

2.3.2 Interaction Studies

On the basis of the *in vitro* metabolism studies, several clinical drug-drug interaction (DDI) studies and PBPK modeling were conducted to evaluate the effect of drug interactions. The DDI results that are deemed clinically relevant are summarized in the following. Coadministration of pexidartinib with itraconazole (strong CYP3A4 inhibitor), significantly increased pexidartinib C_{max} and $AUC_{0\text{-}inf}$ by ~48% and 70%, respectively. Coadministration of fluconazole (moderate CYP3A inhibitor) is predicted to increase

pexidartinib C_{max} by 41% and AUC by 67% at steady state. Concurrent administration of the general UGT inhibitor, probenecid, with pexidartinib increased pexidartinib $AUC_{0\text{-}inf}$ by ~60%. Coadministration of rifampicin (strong CYP3A inducer) decreased pexidartinib C_{max} by 33% and $AUC_{0\text{-}inf}$ by 65%. Results from Study PL3397-A-U126 indicate that pexidartinib is a moderate inducer of CYP3A4. The C_{max} and AUC of midazolam (sensitive CYP3A4 substrate) were reduced by 28% and 53%, respectively, when midazolam was administered following multiple doses of pexidartinib. Coadministration of esomeprazole decreased pexidartinib C_{max} by 55% and $AUC_{0\text{-}inf}$ by 50%.

2.3.3 Special Populations

The effect of hepatic impairment on the exposure of pexidartinib was evaluated in Studies PL3397-A-U123 and PL3397-A-U129. All volunteers received a single 200 mg oral dose of pexidartinib after an overnight fast of 10 hours. Based on NCI-ODWG criteria, mean pexidartinib $AUC_{0\text{-}inf}$ and C_{max} in subjects with mild HI B1 (=6) increased by 16% and 27%, respectively compared to subjects with normal hepatic function (Study PL3397-A-U123). Based on NCI-ODWG criteria, total pexidartinib exposure (AUC_{last} and $AUC_{0\text{-}inf}$) was approximately 43% to 47% higher in subjects with moderate HI compared to subjects with normal hepatic function (Study PL3397-A-U129).

In dedicated renal impairment Study PL3397-A-U124, healthy subjects with mild (CLCR=60-89 mL/min), moderate (CLCR=30-59 mL/min) and severe (CLCR=15-29 mL/min) renal impairment had a 65%, 30% and 43% higher pexidartinib exposure (geometric mean $AUC_{0\text{-}inf}$), respectively, compared to healthy subjects with normal renal function (CLCR ≥90 mL/ min) following a single 200 mg oral dose of pexidartinib. Based on the pop PK analysis, patients with mild (n=67) and moderate renal impairment (n=9) had ~30% higher exposure, compared to patients with normal renal function (n=299).

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The efficacy data mainly came from pivotal study PLX108-10 (ENLIVEN).

- Study design:

The double-blind, randomized, placebo-controlled, Phase III clinical study ENLIVEN (CSR No. PLX108-10), in subjects age ≥18 years with symptomatic tenosynovial giant cell tumor (TGCT) for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced disease) had 2-part. In Part 1, subjects were randomized (1:1) to receive pexidartinib or placebo for 24 weeks. Pexidartinib dose was 1000mg/day for 2 weeks then 800 mg/day. After 24 weeks, all subjects received open-label pexidartinib 800 mg/day.

Subjects who crossed over to pexidartinib in Part 2 provided efficacy and safety data for pexidartinib at a starting dose of 800 mg/d while subjects initially randomized to pexidartinib in Part 1 were to receive 1000 mg/d for the first 2 weeks of therapy, followed by 800 mg/d.

Dose interruption/reduction guideline of this study was set for hematologic AEs, liver function abnormalities, and other AEs. The resume dose after these AEs were reduce by one 200 mg capsule, until 400 mg/d.

Study population: 120 subjects (61 pexidartinib and 59 placebo) with locally advanced, symptomatic TGCT for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity were enrolled. There were 100 subjects (83.3%) completed part 1 randomized treatment, and a total of 78 subjects received at least 1 dose of open-label pexidartinib treatment. Sixty-five subjects remained on open-label pexidartinib treatment at the time of the cut off：27 Mar 2017.

Discontinuation of pexidartinib due to adverse events were 13.1% in part 1, and 6.4% in part 2. Most subjects were assessed as none or low probability of complete tumor resection (92.1%), and moderate or severe postoperative morbidity (97.4%).

- Efficacy results:

The primary endpoint was the **proportion of subjects who achieved a CR or PR at the Week 25 Visit based on centrally read MRI scans and RECIST 1.1.**
The secondary endpoint (assessed on week 25) included **Range of Motion (ROM)** assessed by independent assessors, **Tumor Volume Score (TVS)**, **PROMIS Physical function (PROMIS-PF)**, **Worst stiffness NRS, Brief pain inventory (BPI) pain NRS.**

The study had demonstrated that pexidartinib 1000 mg/day (200 mg per capsule×2 in the morning and 200 mg×3 in the evening) for the first 2 weeks then 800 mg/day (200 mg×2 BID) for a total of 24 weeks was superior to placebo in the proportion of subjects who achieved CR or PR at the Week 25 Visit based on centrally read MRI scans and RECIST 1.1 (39.3% (24/61) vs. 0%; $p<0.0001$).

In part 1, the response rate at Week 25 was significantly higher in pexidartinib group than in the placebo group (39.3% vs. 0%, $p<0.0001$). Nine subjects (14.8%) receiving pexidartinib experienced complete tumor response. In part 2 cross-over treatment, another 9 subjects (30.0%) had CR or PR at Week 25. Among the 91 subjects treated with pexidartinib in Part 1 and/or Part 2, the best overall response is 41.8% (95% CI

32.2-52.0) at the data cut off: 27 Mar 2017. In the subsequent follow-up, the median duration of response was not reached with a median follow-up of 49.6 months (Range, 9-66 months; data cut-off, 01 June 2021), which implied the durability of tumor response.

The secondary endpoints generally favored pexidartinib treatment:

	Placebo	**Pexidartinib**	**p value**	**Difference**
ROM LS mean CFB in % normal reference	6.2% (1.5-10.9)	15.1% (10.9-19.2)	0.0043	8.9 (1.6-14.8)
TVS response	0% (0-6.1)	55.7% (43.3-67.5)	<0.0001	55.7 (41.9-67.5)
PROMIS LS mean CFB; Normal average=50	-0.9 (-3.0, 1.2)	4.1 (1.8, 6.3)	0.0019	5.0 (1.9, 8.0)
Worst Stiffness NRS LS mean CFB; NRS 0 (normal) –10	-0.3 (-0.9, 0.3)	-2.5 (-3.0, -1.9)	<0.0001	-2.2 (-3.0, -1.4)
BPI-30 Pain response, ≥ 30%	15.3% (8.2, 26.5)	31.1% (20.9, 43.6)	0.032	15.9 (0.7, 30.2)

However, for PROMIS, Worst stiffness NRS, and BPI-30 pain score, the proportion of missing data is 43.3%, which could not be neglected and could affect the interpretation of these clinical-related endpoints.

In part 2 cross-over treatment, the effect size of the secondary endpoints was generally similar to those in part 1 treatment. This finding suggests that the clinical benefit with 800 mg/day (part 2 dose) is similar to the clinical benefit with initial dose of 1000mg/day for 2 weeks (part 1 dose).

2.4.2 Safety Results

The safety data mainly came from pivotal study PLX108-10 (ENLIVEN) and another study PLX108-01. PLX108-01 study is a first-in-human dose escalation study, with an TGCT extension cohort. The dosage of pexidartinib in PLX108-01 TGCT cohort is 1000 mg/day, which is higher than in ENLIVEN study. Pooled analyses of pexidartinib-treated subjects from these 2 studies were used during review.

In pooled analyses of pexidartinib-treated subjects, there was 130 TGCT patients

received pexidartinib treatment. The median exposure to pexidartinib was 43 weeks (2-211).

The majority of pexidartinib-treated subjects had at least 1 TEAES (99.2%), and most of which were treatment-related (97.7%). The proportion of AE≧Grade 3 were 43.1%, and the proportion of SAE were 12.3%. Among pexidartinib-treated subjects, there were high rate of treatment discontinuation (20%) and also dose reduction or interruption (53.8%). Higher dose (1000mg/day) brings higher proportion of drug discontinuation and dose reduction. The most common AEs in the TGCT population was hair color changes (73.8%), fatigue (56.9%), nausea (42.3%), arthralgia (33.8%), diarrhea (29.2%), AST increased (29.2%), dysgeusia (28.5%), pruritus (26.2%), and ALT increased (25.4%).

One fatal AEs (cardiac arrest) was noted in the pooled analyses of pexidartinib-treated subjects, which was considered unrelated to study treatment due to prior cardiac history. Most of the Grade≧Grade 3 AE, SAE, or AE resulted in dose reduction/interruption was hepatic enzyme abnormality. When exploring the hepatic AEs, across the pooled safety dataset, 38.5% pexidartinib-treated subjects had at least one hepatic disorder AEs (15.4%≧Grade 3). The most frequented reported events were AST increased (29.2%) and ALT increased (25.4%). In some cases, the hepatotoxicity was serious and prolonged, and biopsies confirmed ductopenia and/or cholestasis. The most cases of hepatotoxicity recovered after drug discontinuation (from 1 months to 7 months). Four TGCT subjects (3.1%) receiving pexidartinib experienced ALT and AST ≥3 × upper limit of normal (ULN) with total bilirubin (TBIL)> 2 ULN (3 in PLX108-10 part 1 and 1 in PLX108-01 TGCT cohort). However, these 4 subjects all had ALP increased, which suggested cholestatic liver injury rather than hepatocellular injury. Among the pexidartinib clinical program (not only TGCT but also other solid tumor), 2 cases of hepatoxicity were not reversible. One death of a subject with vaginal melanoma was observed in the context of ongoing cholestatic liver injury. Another subject, who received pexidartinib in combination with paclitaxel as neoadjuvant therapy for early stage breast cancer, developed cholestatic hepatotoxicity that persisted until a liver transplant was performed after 20 months. Generally, the frequency of hepatic related AEs was higher among 1000mg/day group than 800mg/day group.

2.5 Bridging Study Evaluation

PK part

The assessment for the impact of ethnic factor on pexidartinib PK were based on population PK analysis by pooling data from the 7 healthy volunteer studies and 5 studies (Studies

PLX108-13, PL3397-A-A103, PL3397-A-U126, PLX108-01, PLX108-10) with cancer patients studies, as well 2 studies enrolling Asian subjects with TGCT (Studies PL3397-A-J304 Part 1 and PL3397-A-A303).

The steady state pexidartinib exposure metrics ($AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$) were predicted for each patient at the dose regimen of 400 mg BID. Exposure metrics of pexidartinib were compared by race (Asian in Asian countries vs. non-Asian patients). Asian countries were defined as East Asian countries of Japan, Korea, Taiwan, China or Hong Kong in this comparison. The population PK analysis from the pooled data showed pexidartinib $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ in East Asian patients (N=48) was approximately 18% and 7% higher, respectively than non-Asian patients (N=236). In addition, pexidartinib $C_{max,ss}$ and $AUC_{0\text{-}24h,ss}$ in Study PL3397-A-A303 (Chinese and Taiwanese TGCT patients, N=25) was approximately 12% and 14% higher, respectively when compared to Study PLX108-10 (non-Asian TGCT patients, N=84). Overall, exposures of pexidartinib were slightly higher in Eastern than Western patients.

Clinical part

Study PL3397-A-U126 enrolled two East Asian with TGCT. In this study, the tumor response was 100% for East Asian after treated with pexidartinib. An ongoing study PL3397-A-A303, which is a single arm study evaluates Chinese and Taiwanese TGCT patients treated with pexidartinib 800mg/day, provided further safety data for East Asian. Up to date, there were 27 subjects enrolled in study PL3397-A-A303. Among 27 subjects, 3 had event of AST/ALT ≧ 3xULN and T-bil ≧ 1xULN. These hepatic events started within the first 8 weeks of treatment, and resume normal after treatment discontinuation.

	PL3397-A-A303 **800mg** East Asian	PLX108-10 **800mg** Part 2	PLX108-10 **1000mg→800mg** Part 1	PLX108-10 and PLX108-01 **All doses**
	N=27	N=30	N=61	N=130
AST increased	17 (63.0%)	5 (16.7%)	27 (44.3%)	38 (29.2%)
Grade ≥3	5 (18.5%)	1 (3.3%)	6 (9.8%)	10 (7.7%)
ALT increased	16 (59.3%)	7 (23.3)	19 (31.1%)	33 (25.4%)
Grade ≥3	7 (25.9%)	2 (6.7%)	6 (9.8%)	12 (9.2%)
Blood bilirubin increased	6 (22.2%)	0	4 (6.6%)	5 (3.8%)
Grade ≥3	2 (7.4%)	0	1 (1.6%)	1 (0.8%)
GGT increased	11 (40.7%)	0	3 (4.9%)	3 (2.3%)
Grade ≥3	4 (14.8%)	0	2 (3.3%)	2 (1.5%)

AST ≥3ULN	10 (37.0%)	3 (10.0%)	18 (29.5%)	28 (21.5%)
AST ≥5ULN	6 (22.2%)	1 (3.3%)	7 (11.5%)	12 (9.2%)
ALT ≥3ULN	11 (40.7%)	4 (13.3%)	21 (34.4%)	29 (22.3%)
ALT ≥5ULN	7 (25.9%)	2 (6.7%)	14 (23.0%)	19 (14.6%)
AST or ALT ≥3ULN and TBIL ≥1ULN	3 (11.1%)	0	7 (11.5%)	9 (6.9%)
AST or ALT ≥3ULN and TBIL ≥2ULN	2 (7.4%)	0	3 (4.9%)	4 (3.1%)

2.6 Conclusion

Symptomatic tenosynovial giant cell tumor (TGCT) is not a fatal disease. However, TGCT could be associated with severe morbidity or functional limitations and not amenable to improvement with surgery. For those who could not receive surgical excision, other treatment options are external beam radiotherapy, radiosynovectomy, total knee or hip replacement, but the outcome is not promising. There is an unmet medical need for symptomatic TGCT patients who could not receive surgical excision.

From clinical trial PLX108-10 (ENLIVEN), the tumor response of pexidartinib 800mg/day therapy is statistically significantly better than placebo (39% vs. 0%). For other clinically relevant endpoints, including ROM improvement, Physical function improvement (PROMIS-PF), and stiffness improvement, pexidartinib treatment are also statistically significantly better than placebo.

The main concern for pexidartinib treatment is hepatic-related adverse events. There is dose-response relationship for hepatic-related adverse events, which was demonstrated by higher event rate for pexidartinib 1000mg/day than pexidartinib 800mg/day. For TGCT subjects, the majority of these hepatic events occurred within the first 8 weeks of treatment. Up to 58.8% of subjects who had hepatic adverse events needed treatment discontinuation or dose reduction. In study PLX108-10 and PLX108-01, there were 4 subjects experienced serious mixed or cholestatic hepatotoxicity (AST or ALT≧3ULN and TBIL≧2ULN). For east Asians, based on an ongoing study PL3397-A-A303, the incidence of hepatic adverse events was obviously higher than non-Asians. This finding could not be explained only by pexidartinib exposure, since the differences of Cmax,ss and AUC0-24h,ss are within the range of individual variants. In study PL3397-A-A303, all Asian subjects who experienced serious hepatotoxicity recovered after drug discontinuation.

Due to the concern for potential severe hepatic injury after pexidartinib treatment, the indication should be restricted to adult patients with symptomatic tenosynovial giant

cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery or other treatment modality (such as local radiotherapy). RMP is required to ensure precautious use of drug, which includes medication guide, communication plan, ETASU, and registry. Pexidartinib could only be prescribed to patients with normal liver function. All patients should have liver function monitor at regular interval (every week for the first 8 weeks of treatment, every two weeks for the third month, and monthly thereafter). Black Box Warning for hepatotoxicity should be added into the label. The sponsor should provide the complete CSR of study PL3397-A-A303 as soon as possible after the completeness of the trial.

3. Post-Marketing Requirements

(1) RMP is required, which includes medication guide, communication plan, ETASU, and registry.

(2) The sponsor should provide the complete CSR of study PL3397-A-A303 as soon as possible after the completeness of the trial.