EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 June 2020
EMA/CHMP/431740/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Turalio

International non-proprietary name: pexidartinib

Procedure No. EMEA/H/C/004832/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

AE	Adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukaemia
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BCS	Biopharmaceutics Classification System
BID	twice daily
BPI	Brief Pain Inventory
bpm	beats per minute
C	cycle
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CMA	Critical material attribute
CPP	Critical process parameter
CQA	Critical quality attribute
CR	Complete response
CRF	Case report form
CSF-1	colony-stimulating factor-1
CSF-1R	colony-stimulating factor-1 receptor
CSR	Clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DBIL	direct bilirubin
DI	dose intensity
DMC	Data Monitoring Committee
DoE	Design of experiments
DOR	Duration of response
ECG	electrocardiogram
eDISH	evaluation of Drug-Induced Serious Hepatotoxicity
EQ-5D-5L	Euro Quality of Life five dimensions five level questionnaire
FMEA	Failure mode effects analysis
GC	Gas chromatography
GCT-TS	Giant cell tumour or the tendon sheath
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IND	Investigational New Drug
INR	International Normalised Ratio
IPC	In-process control
IR	Infrared
ISS	integrated summary of safety
IST	investigator-sponsored trials
ITT	Intent-to-treat
JP	Japanese Pharmacopoeia
KF	Karl Fischer titration
KIT	proto-oncogene receptor tyrosine kinase
LDH	lactate dehydrogenase
LDPE	Low density polyethylene
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging

ms	millisecond
NDA	New Drug Application
NF	National formulary
NMR	Nuclear magnetic resonance
NMT	Not more than
NOR	Normal Operating Range
NRS	Numeric rating scale
ORR	Objective response rate
PAR	Proven Acceptable Range
PBO	placebo
PD	Progressive disease
PDy	pharmacodynamics
PFS	Progression-free survival
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PP	Per-protocol
ppm	Parts per million
PRO	Patient-reported outcomes
PROMIS	Patient-reported Outcomes Measurement System
PSD	Particle size distribution
PT	preferred term
PVNS	pigmented villonodular synovitis
q.s.	*quantum sufficit*
QbD	Quality by design
QC	Quality control
QTPP	Quality target product profile
RECIST	Response Evaluation Criteria in Solid Tumours
RH	Relative humidity
ROM	range of motion
RP2D	recommended Phase 2 dose
rpm	Revolutions per minute
SAE	serious adverse event
SAP	statistical analysis plan
SAQ	Surgical Assessment Questionnaire
SBP	systolic blood pressure
SD	Stable disease
SMQ	standardized MedDRA queries
SOC	system organ class
SEM	Standard error of the mean
StdDev	Standard deviation
TAMC	Total aerobic microbial count
TBIL	total bilirubin
TDM	Therapeutic drug monitoring
TEAE(s)	treatment-emergent adverse event(s)
TGCT	tenosynovial giant cell tumour
TVS	tumour volume score
TYMC	Total combined yeasts/moulds count
ULN	upper limit of normal
US	United States of America
USP	United States Pharmacopoeia
UV	Ultraviolet
WBC	white blood cell count
XRPD	X-Ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Daiichi Sankyo Europe GmbH submitted on 8 March 2019 an application for marketing authorisation to the European Medicines Agency (EMA) for Turalio, through the centralised procedure falling within the Article 3(1) and point 4 of Annex I of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 May 2017.

Turalio was designated as an orphan medicinal product EU/3/15/1457 on 19 March 2015 in the following condition: Treatment of tenosynovial giant cell tumour, localised and diffuse type.

The applicant applied for the following indication: Turalio is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), also referred to as giant cell tumour 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.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0044/2019 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active substance status

The applicant requested the active substance pexidartinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received protocol assistance from the CHMP on the development for the indication on 24 July 2014 (EMEA/H/SA/2808/1/2014/III), 26 May 2016 (EMEA/H/SA/2808/2/2016/PA/I), 23 March 2017 (EMEA/H/SA/2808/1/FU/1/2017/PA/III; EMEA/H/SA/2808/2/FU/1/2017/PA/I) and 14 September 2017 (EMEA/H/SA/2808/1/FU/2/2017/PA/I). The protocol assistance pertained to the following quality, non-clinical and clinical aspects:

- Quality: Appropriateness of proposed starting materials and genotoxic impurity control strategy. Completeness of the proposed drug substance and finished product specification attributes. Discriminatory sufficiency the proposed dissolution methodology. Acceptability of submitting limited drug product stability data in the anticipated MAA.
- Non-clinical: Adequacy of the completed and proposed non-clinical program to support a MAA. Acceptability to submit the outcome of the 2-year carcinogenicity study during the MAA procedure. Proposed pharmacology and toxicology plans to characterize the nonclinical profile of ZAAD-1006a, an N-glucuronide metabolite of pexidartinib, including a 13-week non-clinical toxicology study of ZAAD-1006a in cynomolgus monkeys
- Clinical: Adequacy of the proposed clinical pharmacology program to support a MAA. Design of the planned randomized, double-blind, placebo-controlled single phase 3 clinical study PLX108-10 in 120 patients with PVNS or GCT-TS for whom surgical resection is associated with potentially worsening functional limitation or severe morbidity to support a MAA, including inclusion and exclusion criteria, primary endpoint (proportion of patients who achieve MRI (centrally-read) responder criteria as defined by RECIST version 1.1 at the Week 25 visit) and secondary efficacy endpoints, dose selection, duration of treatment (placebo controlled for 24 weeks, followed by an open-label extension for at least 24 weeks), dose adjustment algorithms, safety data, and statistical analyses.
- Acceptability of proposed risk mitigation procedures for future TGCT clinical studies, as well as for the future label to address the risk of liver effects. Design of a proposed dose escalation trial (PL3397-A-A303) to provide support for handling the risk of cholestatic hepatitis, including primary and secondary endpoints.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jean-Michel Race Co-Rapporteur: Janet Koenig

The application was received by the EMA on	8 March 2019
The procedure started on	28 March 2019

The Rapporteur's first Assessment Report was circulated to all CHMP members on	18 June 2019
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	25 June 2019
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	2 July 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 July 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	10 October 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	26 November 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	26 November 2019
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 December 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 February 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	17 March 2020
The Scientific advisory group (SAG) on oncology experts were convened to address questions raised by the CHMP on The CHMP considered the views of the SAG as presented in the minutes of this meeting.	4 March 2020
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	26 March 2020
The applicant submitted the responses to the CHMP List of Outstanding Issues on	28 April 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	18 May 2020
The Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on	22 May 2020
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 May 2020
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for refusing the granting of a marketing authorisation to Turalio on	25 June 2020

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tenosynovial giant cell tumour (TGCT), also referred to as giant cell tumour of the tendon sheath (GCT-TS) or pigmented villonodular synovitis (PVNS), is a rare, non-malignant neoplasm that can involve the bone, soft tissue, synovium or tendon sheath of small or large joints (Monaghan et al. 2001) and that typically presents in young and middle-aged adults of both sexes with no specific comorbidities.

2.1.2. Epidemiology

TGCT is a rare pathology. The more frequent localised-type disease affects persons in the 4th and 5th decades, while the diffuse-type form often occurs earlier (before 40 years of age). The incidence of TGCT appears to be similar worldwide. The prevalence of TGCT, including localized- and diffuse-type disease, is estimated as 3.4 in 10,000 in the European Union (EU), the sum of a 90.2% surgical cure rate with one year prevalence and 9.8% recurrence rate with 41 year average life time prevalence in localised-type disease (incidence rate 0.45 in 10,000), and of complete prevalence of 1.15 in 10,000 with diffuse-type disease (Ehrenstein et al. 2017). Patients usually present between the ages of 20 and 60 years and are most often diagnosed when presenting with pain and swelling at the affected joint.

2.1.3. Biologic features

TGCTs predominantly consist of mononuclear and multinucleated giant cells. Expansion of the tumour mass appears to be driven by the presence hyperexpression of colony stimulating factor-1 (CSF-1) by a small proportion of cells within the tumour. Most cells in the tumour mass are inflammatory, non-neoplastic cells that do not express CSF-1 but are attracted to the tumour because of their expression of the receptor CSF1-R. CSF-1 can promote the survival of attracted macrophages. Recurrent translocations in TGCTs involve COL6A3 and CSF1 genes (West et al. 2006) or involve other genes that induce expression of the CSF1 and IL-34 genes.

2.1.4. Clinical presentation, diagnosis and prognosis

Clinical examination finds a soft palpable mass in superficial locations, sometimes associated with heat and periarticular effusion or oedematous swelling. Thus, clinical examination is nonspecific but may be suggestive in: young adults; typical location, especially in a mass in the soft-tissue of the hand or foot; single-joint disorder with slow progression and no other sign suggestive of synovial pathology (such as polyarthritis, gout, haemophilic arthropathy), in which case aetiological assessment should be completed by biological work-up to rule out differential diagnoses and imaging. A definitive diagnosis is made from pathologic evaluation; however, features highly suggestive of the disease may be found on radiographic imaging, particularly MRI, which is indispensable to diagnosis and surgical planning.

The two distinct types of TGCT are (WHO 2013) are giant cell tumour of the tendon sheath (GCT-TS) and pigmented villonodular synovitis (PVNS). The signs and symptoms as well as the prognosis and treatment of TGCT vary depending upon the location and the subtype.

The localised type of TGCT, also known as GCT-TS, is usually a benign neoplasm, most commonly occurring in the digits. The initial sign is often a painless swelling. The tumour grows slowly over time. Sometimes, they cause pain. Unlike the diffuse type, these tumours are unlikely to cause destructive changes to the joint or surrounding areas and are less likely to recur after surgical treatment.

The diffuse type of TGCT, also referred to as PVNS, is a locally aggressive neoplasm most commonly affects large joints (particularly the knee, ankle, hip, elbow or shoulder). The tumour is widespread (diffuse) in the affected joint and affects it entirely. In most patients, only one joint is involved (mono-articular disease). Rarely, the two joints that connect the jaw bones to the skull (temporomandibular joints) or the joints that connect vertebrae (spinal facet joints) can be affected.

Symptom progression is slow; intervals between first signs and diagnosis are long, months to years. Acute forms have been reported, related to torsion and necrosis of a nodule.

The initial symptoms are usually pain and swelling of the affected joint. Stiffness of the joint can also occur. Usually, these symptoms have a gradual onset and may be minimal due to the slowly progressive nature of the disease. As the tumour mass grows and gradually expands within the intraarticular space and the surrounding tissue, symptoms such as pain, stiffness, swelling and reduced range of motion (ROM) of the affected joint can become severe and result in marked functional limitation. PVNS can progress to cause arthritic damage, degeneration of the joint and damage to the surrounding cartilage and bone, causing chronic, debilitating disease and significant functional impairment of the affected joint.

2.1.5. Management

Currently, surgical resection is the standard of care for TGCT. Resection may be total or subtotal, depending on the disease history (primary or recurrent), clinical status, diffuse or localized type, extension, location and progression (Schwartz 1989).

Localized-type TGCT is in most instances managed by direct excision of the tumour nodule. All reports show excellent or good clinical results with surgical treatment (Mankin 2011, Ottaviani 2011).

Patients with diffuse-type TGCT often have more extensive involvement and a smaller likelihood of success with surgery. The surgical management of these tumours is more complex and involves total synovectomy excision (Ogilvie-Harris 1992, De Visser 1999), joint replacement or, in very rare cases, amputation. Total arthroscopic or open synovectomy are the two possible options for synovectomy. Arthroscopic synovectomy reduces morbidity compared to open synovectomy, but it is associated with a higher risk of incomplete. Thus, open excision is preferred in patients with a locally advanced disease. For patients with a diffuse TGCT when total resection is not feasible or would induce severe morbidity, treatment options comprise subtotal resection with adjuvant therapy. After initial surgery, the disease recurs in about half of the patients, and in most patients after second surgery, so that in a number of situations surgery may be futile or risk high morbidity and loss of function, e.g., amputation. The goal is to prevent total joint replacement or amputation and to preserve function as much as possible.

Anti-inflammatory and analgesic medications, including opioids, are commonly used as supportive therapy.

Radiation therapy (RT) is the most widely used adjuvant therapy. RT (external or intra-articular, also known as isotopic synoviorthesis) seems to reduce recurrence in diffuse-type TGCT, especially when synovectomy was partial. Moderate dose external beam RT offers a high chance of local control. RT is not expected to lead to functional improvement and may be associated with accelerating degenerative arthritis.

No anti-tumour medicinal products are approved for this disease. NCCN guidelines (version 1.2019) recommended the adjuvant use of imatinib in diffuse-type TGCT, after subtotal resection for inoperable tumours. In a retrospective series of 29 TGCT patients treated with imatinib, an objective response was observed in 5, and stabilization in 20 patients on control MRI, out of 27 patients assessed, half of whom had non-operated TGCT. Symptomatic improvement was noted in 16 of 22 patients (73%) who were assessable for symptoms. In an uncontrolled study of nilotinib, the response rate was 6% among enrolled 33 patients.

About the product

Pexidartinib (PLX3397) is an orally active small molecule receptor tyrosine kinase inhibitor that selectively inhibits the CSF-1 receptor (CSF-1R) as well as the kinase receptors KIT and FLT3-ITD.

The applicant applied for the following indication: "Turalio is indicated for the treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), also referred to as giant cell tumour 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."

Further to the CHMP assessment of the application, the applicant revised and restricted the indication to "Turalio is indicated as monotherapy for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability."

Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the view that the strength of evidence was not convincing to support the claim that the product will fulfil unmet needs, considering that the tumour growth is slow and that its treatment needs to be well tolerated long-term.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as an immediate release size 0 hard capsule containing 217.5 mg pexidartinib hydrochloride as active substance, equivalent to 200 mg of the free base form.

Other ingredients are:

Capsule contents: poloxamer, mannitol, crospovidone, and magnesium stearate.

Capsule shell: hypromellose, titanium dioxide, black iron oxide and yellow iron oxide.

The product is packaged in polyamide/aluminium/polyvinylchloride/polyethylene laminate aluminium/aluminium blisters with embedded desiccant.

2.2.2. Active substance

General information

The chemical name of pexidartinib hydrochloride is 5-[(5-chloro-1*H*-pyrrolo[2,3-b]pyridin-3-yl)methyl]-*N*-{[6-(trifluoromethyl)pyridin-3-yl]methyl}pyridin-2-amine monohydrochloride corresponding to the molecular formula $C_{20}H_{15}ClF_3N_5$. It has a relative molecular mass of 454.28 g/mol and the following structure:

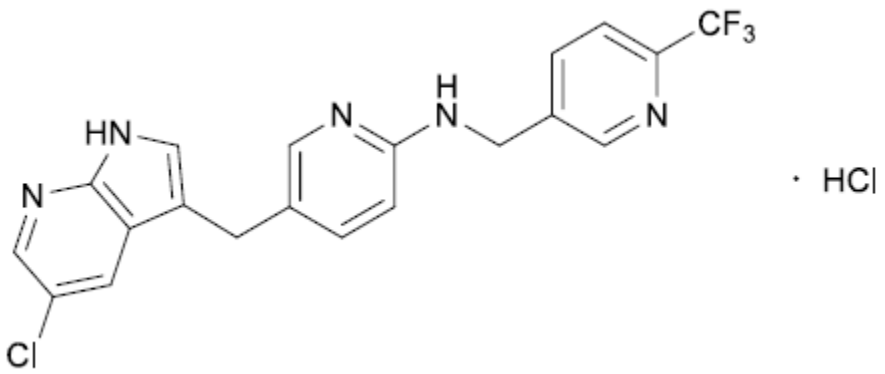


Figure 1: active substance structure

The chemical structure of pexidartinib hydrochloride is inferred from the route of synthesis, including the structures of raw materials and was elucidated by a combination of ^{1}H and ^{13}C NMR spectroscopy, high resolution mass spectrometry, infrared spectroscopy, UV/vis spectroscopy and elemental analysis. The solid-state properties of the active substance were adequately investigated. The desired polymorph is routinely produced by the manufacturing process and is the most thermodynamically stable form.

The active substance is a white to off-white slightly hygroscopic crystalline solid. Pexidartinib hydrochloride is achiral and exhibits pH-dependent aqueous solubility.

Manufacture, characterisation and process controls

Pexidartinib hydrochloride is synthesized in four main stages using well-defined starting materials with acceptable specifications.

The process is convergent, linking starting materials in convergent fashion. The choice of starting materials has been justified and is in line with the 2016 CHMP scientific advice. The synthetic process has remained essentially the same throughout development, with some modifications to reagents, solvents and reaction conditions being made to improve the process over time.

Active substance critical quality attributes (CQAs) were defined, based on the active substance properties. Risk assessments were carried out using failure mode effects analysis (FMEA) methodology to assess potential critical material attributes (CMAs) and critical process parameters (CPPs) throughout the process.

A series of multivariate experiments were conducted by design of experiments (DoE) to evaluate suitable ranges for parameters with a high risk of impacting quality, or where interactions could be foreseen. Additional single factor studies were carried out to further enhance process understanding for factors where interactions could be ruled out. Critical steps were identified, and suitable controls were introduced to guarantee the quality of the active substance, including both proven acceptable ranges (PARs) and normal operating ranges (NORs) for relevant parameters.

For each step, the carry-over of the potential impurities has been extensively described including spiking studies and analysis of impurity fate and purge. Limits for impurities in starting materials, intermediates and the active substance have been set accordingly.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The synthetic process was analysed to see if there were any risk factors for formation of nitrosamines including the use of any nitrosating agents. No such risk factors were identified. The risk evaluation as concerns the active substance is acceptable.

The active substance is packaged in double LDPE bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), identity (IR, XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.), assay (HPLC) and particle size distribution (laser diffractometry).

The active substance specifications are based on the active substance CQAs. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. The limits for particle size distribution were tightened at the request of CHMP for alignment with batches used in pivotal clinical studies.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data of the active substance manufactured from pilot to production scale and used throughout the clinical and development programs are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from three pilot scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: appearance, polymorphic form, impurities, chloride content, water content, assay, and particle size distribution. The analytical methods used were the same as for release and are stability indicating as determined by forced degradation studies. In addition, microbial limits were tested using compendial methods on an annual basis. No significant changes were

observed to any of the measured parameters and no trends were observed. The potential formation of a theoretical genotoxic impurity was investigated and it was found not to be detectable after storage.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. No increase in impurity content was observed which indicates that pexidartinib is photostable.

Samples were also exposed to high temperature conditions and to accelerated conditions in an open dish. The active substance is stable to heat, and only slight degradation was observed in the open dish study – a small increase in impurities was observed but levels were still within the release specification limits.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container without special storage conditions.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The finished product is an immediate release hard capsule with a white opaque body and a dark green opaque cap imprinted with "T10" in white ink.

The finished product is designed as an immediate-release solid dosage form containing 200 mg of Pexidartinib (free base form) and capable of meeting the finished product specification. In addition, the finished product quality should be retained throughout the proposed shelf life. A capsule formulation was selected as the proposed dosage form.

The quality target product profile (QTPP), was based on the ease of administration of the dosage form and potential flexibility in daily dose adjustments for the intended patient population. The 200 mg capsule strength was used in the pivotal clinical studies. The critical quality attributes (CQAs) deemed to be essential to achieving the QTPP.

Pexidartinib HCl is considered to be a BCS class II compound exhibiting low pH-dependent solubility and high permeability. Polymorphic form and particle size distribution could have an impact on finished product dissolution. The active substance manufacturing process routinely produces the most thermodynamically stable polymorph which is tested in the active substance release specification. In addition, it was demonstrated that there is no change to the polymorphic form during formulation. The limits for the active substance particle size distribution have been set in line with the batches used to manufacture finished product used in pivotal clinical trials.

All selected excipients are well-known and widely used in pharmaceutical industry and comply with relevant Ph. Eur. standards. There are no novel excipients used in the finished product formulation. Compatibility studies indicate that protective packaging is needed to avoid degradation.

Development of the dissolution method was adequately conducted and reported. Discriminatory power was investigated for various relevant parameters. However, the originally proposed specification was too wide and would allow non-compliant batches to pass. A major objection was raised by CHMP on the dissolution method with regards to discrepancy in batch comparisons. In response, the applicant tightened the specification and was able to adequately demonstrate and justify the differences in dissolution performance. In addition, the *in vitro* dissolution profiles of clinical batches were presented which demonstrated the *in*

vivo relevance of the dissolution method. In summary, the concerns of CHMP were adequately addressed and the discriminatory capability of the dissolution method has been demonstrated for the revised specification.

The development of the manufacturing process was conducted following Quality by Design (QbD) principles. Risk assessments were conducted using various methodologies (Principle Hazard Analysis (PHA) and Failure Mode Effects Analysis (FMEA)) and used, along with prior knowledge to establish relationships between the product CQAs and potentially critical material attributes (CMAs) and potentially critical process parameters (CPPs). Risk rankings were based on a combination of probability, severity and detectability and all factors with a medium to high risk were further investigated experimentally in a series of multivariate and univariate experiments. These studies allowed the criticality of the process variables to be understood, CMAs and CPPs were established and some proven acceptable ranges (PARs) to be defined.

The control strategy was established at the end of process development and is considered to be acceptable.

The primary packaging is aluminium/aluminium polyamide/aluminium/polyvinylchloride/polyethylene-laminate blister with embedded desiccant, sealed with aluminium/polyethylene-laminate. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process is considered to be a standard manufacturing process consisting of blending, granulation, encapsulation and packaging.

Major steps of the manufacturing process have been validated using a traditional three-batch validation approach. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process pharmaceutical form. The PARs for relevant unit operations have been set in line with development data and suitable target set-points have been defined. For some non-CPPs, normal operating ranges have been defined in line with equipment and process capability. Overall, the control strategy is considered suitable to ensure the quality of the finished product.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identity (UV, HPLC), uniformity of dosage units (Ph. Eur.), assay (HPLC), related substances (HPLC), water content (KF), dissolution (UV), and microbiological quality (Ph. Eur.).

The limits for water content, impurities, and dissolution have been justified in line with batch data. The slightly higher limits for impurities at shelf-life are justified by the stability data.

The potential presence of elemental impurities in the finished product has been assessed using a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Given the oral route of administration, class 1 and 2A elements were considered. Batch analysis data on 3 batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that no control for any elemental impurity is required.

A risk evaluation was provided to assess the potential presence of nitrosamines in the finished product. Possible presence of nitrosating agents and amines in different excipients was checked and no risk was identified. The capsules contain some secondary and tertiary amines which could potentially be nitrosated by low concentrations of nitrite present in process water. The applicant has committed to testing the capsules for nitrosamine content. In addition, the packaging consists of blisters containing nitrocellulose. Therefore, the applicant should consider the possibility of formation of nitrosamines during the printing and heat-sealing operations. These two issues are still outstanding at the time of negative opinion and should be addressed in case the applicant is going to pursue an EU marketing authorisation for the product.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for finished product used throughout clinical development, including the 3 production-scale primary registration batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production scale batches of finished product stored for up to 24 months under long term conditions (25ºC / 60% RH), 12 months under intermediate conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product were manufactured using the proposed commercial manufacturing process but were stored in less protective blisters. In addition, stability studies were started on 3 batches of product stored in the proposed commercial desiccant embedded aluminium/aluminium blisters. Data after 3 months under long term conditions, 3 months under intermediate conditions and for up to 6 months under accelerated conditions was provided.

Samples were tested for appearance, impurities, assay, water content, dissolution and microbiological quality. The analytical procedures used are stability indicating. In the stability studies in the PCTFE/PVC/Alless protective blisters, the amount of one impurity and of water increased over time, more so under accelerated conditions such that the impurity was higher than the specification after 6 months. No significant changes were observed to the other measured parameters. Comparative data from the batches stored in the commercial packaging showed no increase in impurities or water, indicating that it is sufficiently protective.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product was shown to be photostable.

Samples were exposed to accelerated conditions in an open dish or to dry heat, both of which had an adverse impact on quality after only 2 weeks. A freeze-thaw cycling study (-20 to 40ºC) had no adverse impact and demonstrates that temperature excursions during shipping and storage will have no adverse impact on quality.

Based on available stability data, the proposed shelf-life of 30 months without special storage conditions is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues considered not to have an impact on the Benefit/Risk ratio of the product. These relate to outstanding information on the possible presence of nitrosamines due to the capsule shells and packaging material, which should be addressed if the applicant was to pursue an EU marketing authorisation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the proposed SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development program of pexidartinib was designed in accordance with ICH M3 guideline. A full non-clinical program was performed in two different species (rat and dog). Pexidartinib has been assessed in rat up to 6 months and in dog up to 9 months. An additional 13-week monkey study was performed with pexidartinib to characterize ZAAD-1006a the major human metabolite; monkey was the only relevant species. Pexidartinib was also assessed through a standard battery for safety pharmacology (CNS, respiratory and cardiovascular system), a standard battery for genotoxicity, two carcinogenicity studies and a full program for reprotoxicity potential in rat and in rabbit. Safety pharmacology and pivotal toxicology studies were completed in accordance with Good Laboratory Practice (GLP).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics (PD) were investigated *in vitro* and *in vivo*. *In vitro*, concentration-response relationship of inhibition of the target protein CSF1R was obtained.

In an unusual approach the applicant also screened for off-target activity of pexidartinib within the primary PD programme. In particular, the screen only included various protein and lipid kinases and not the routine panel of receptors, enzymes etc. which is usually used for off-target screens (such a screen was done within the secondary PD programme). It turned out that pexidartinib beside CSF1R also inhibited the kinases KIT and FLT3 with high affinity. More than ten further kinases were also noticeably inhibited by micromolar concentrations of pexidartinib, see following table; the most strongly inhibited kinases are highlighted (Table 1).

Table 1: Selected inhibition data for PLX3397 lot number (Lot No.) tested at a single concentration (Conc. [µM]) against 226 kinases. Duplicates (PCT RESP1, PCT RESP 2) and averages (AVG PCT Result) are listed.

Conc. [µM]	Assay	PCT RESP 1	PCT RESP 2	AVG PCT Result
0.029	ABL1	-23.0	-20.0	-21.5
0.029	BRAF	22.5	32.7	27.6
0.029	BTK	-26.0	-21.0	-23.5
0.029	CAMK1D_(CaMKI_delta)	14.0	24.5	19.2
0.029	CDK7/CyclinH/MNAT1	-20.0	-20.0	-20.0
0.029	CLK1	-22.0	-15.0	-18.5
0.029	CSF1R_(FMS)	65.0	79.0	72.0
0.029	FLT3	77.0	82.0	79.5
0.029	FRK_(PTK5)	-17.0	-17.0	-17.0
0.029	IGF1R	-16.0	-12.0	-14.0
0.029	KIT	31.0	39.0	35.0
0.029	MAPK1_(ERK2)	-36.0	-23.0	-29.5
0.029	PIK3CA/PIK3R1_(p110a/p85a)	34.0	22.0	28.0
1	AURKB_(Aurora_B)	19.0	21.0	20.0
1	BRAF	20.0	21.0	20.5
1	CAMK1D_(CaMKI_delta)	16.0	10.0	13.0
1	CSF1R_(FMS)	90.0	93.0	91.5
1	FLT3	61.0	61.0	61.0
1	KIT	55.0	52.0	53.5
1	MAPK14_(p38_alpha)	14.0	26.0	20.0
1	NTRK3_(TRKC)	18.0	18.0	18.0

PCT: percent. negative values indicate activation ("negative inhibition")

For some of these kinases the IC_{50} values of inhibition by pexidartinib were determined. The results indicated that pexidartinib is a potent inhibitor of CSF1-R (IC_{50} = 17 nM/Ki 1.89 nM), KIT (IC_{50} = 12 nM/Ki 2.03 nM) and FLT3-ITD (IC_{50} = 38 nM) while exhibiting less potent activity against FLT3 (IC_{50} = 160 nM) and KDR (IC_{50} = 210 nM). Thus, the potency of pexidartinib on CSF1-R and KIT at the enzyme level was relatively similar. Besides testing direct kinase inhibition in cell-free systems, the applicant also assessed phosphorylation and proliferation in intact cells of several lines. In the absence of an established model for tenosynovial giant tumour cells, the applicant used engineered permanent cell lines, mostly different kinds

of leukaemia, made responsive to CSF1 or KIT. In these artificial systems, pexidartinib had the desired effects. Effects and cellular potency of pexidartinib on CSF1-R, KIT and FLT3 inhibition were investigated in human cancer cell lines. Pexidartinib inhibited phosphorylation of CSF1-R in human THP-1 cells (IC_{50}= 6.8 nM) and inhibited proliferation and phosphorylation of mutated FLT3 in MV-4-11 cells (IC_{50} = 26 nM) but does not significantly block autophosphorylation of ligand stimulated wild type FLT3 in RS4;11 cells (IC_{50} = 1.5 µM). Cellular potency was confirmed on CSF1-R, KIT and mutated FLT3 by inhibition of driven cancer cell growth. Indeed, pexidartinib inhibited CSF1-R in BCR-FMS/BA/F3 cells (IC_{50} = 10 nM), KIT in BCR-KIT/BA/F3 cells (IC_{50} = 120 nM) and in M-07e human cells (IC_{50} = 99 nM), and ITD-FLT3 (IC_{50} = 150 nM) in MV-4-11 human cells. Two transformed murine cell lines (M-NFS-60 and Bac1.2F5) were used to determine cellular potency on CSF1-R driven cancer cell growth and demonstrated an inhibition of CSF1-R phosphorylation by pexidartinib (IC_{50} = 440 nM, M-NFS-60; IC_{50} = 220 nM, Bac1.2F5; > 20-fold IC_{50} in BCR-FMS/BA/F3 cells).

For the *in vivo* primary PD programme the applicant also used an artificial model, a xenograft tumour in mice consisting of permanent leukaemia cells made dependent on CSF1 by suitable genetic manipulation. No relevant animal models for TGCT are established to confirm the entire pharmacodynamic profile of pexidartinib.

Secondary pharmacodynamic studies

Pexidartinib was assessed for its off-target activity on neurotransmitter-related, immunological factors, steroids, ion channels, second messengers, prostaglandins, growth factors/hormones, brain/gut peptides, and enzymes transporters, ion channels and enzymes. In the panel of off-target binding assays, pexidartinib (10 µM) did not affect control-specific binding by greater than 50% at any of the 71 different receptors, ion channels or transporters tested. No correlation with potential clinical off targets was provided by the Applicant regarding the results.

The results indicate a low risk for off target activity with pexidartinib at therapeutic plasma concentrations (clinical unbound Cmax = 39 nM).

Safety pharmacology programme

Central nervous system

The CNS/neurobehavioral safety profile was assessed in rats. In a Modified Irwin Battery assay in female rats, pexidartinib (20, 60, 200 mg/kg, oral route) did not induce any adverse neurobehavioral effects at the oral doses of 200 mg/kg. However, in a repeated-dose toxicology study in dogs some animals displayed severe neurological symptoms so that the animals were euthanized. Furthermore, a rabbit in the TK group of a reprotoxicity study showed similar symptoms and was euthanized after being noted with clonic convulsion, laboured respiration, and impaired use of the hindlimbs. Moreover, one female monkey received pexidartinib at 1 mg/kg for 13 weeks showed a hydrocephalus in the cerebrum with neuronal cell loss in the cortex of the cerebellum.

Respiratory system

The respiratory effects of pexidartinib were investigated in the rat using head-out plethysmography. After single oral gavage administration of pexidartinib (20, 60, 200 mg/kg, oral route) in female rats, there was no effect on respiratory rate, tidal volume or minute volume through 200 mg/kg. However, no PK measurement have been performed. It could be supposed that exposure at 200 mg/kg in rats is around 3-4 fold the clinical intended exposure at the recommended human dose (800 mg/day), considering TK measurements at D0 in 4-week toxicity in rat.

Cardiovascular system

Three safety pharmacology studies addressed the potential adverse cardiovascular or cardiac electrophysiological effects of pexidartinib. In the hERG assay, pexidartinib was evaluated in stably transfected HEK293 cells at concentrations of 0.1, 0.3, 1 and 3 µM, which produced concentration-dependent inhibition of hERG tail current from 8.6 to 82.2%. The IC50 for hERG blockade was 0.7 µM. The Applicant has presented no correlation between measured IC50 and the expected unbound Cmax at the intended clinical regimen (800 mg/day). The presented IC50 value is approximately 18-fold above clinical plasma concentrations (unbound Cmax 39 nM). In an isolated rabbit Purkinje fiber study, pexidartinib was evaluated at 0.1, 1 and 3 µM, no pexidartinib-related prolongation of action potential duration was observed. In vivo safety pharmacology (telemetry) studies were performed in conscious dogs. Oral dosing of pexidartinib (0, 50, 300 and 1000 mg/kg) had no effects on electrocardiographic parameters except for observed decreases in left ventricular contractility (LV dP/dtmax) and arterial pulse pressure, when compared to controls in dogs. No test article-related effects were noted for QTc interval up to the maximum dose tested (1000 mg/kg). Later in development, an investigative (non-GLP) safety pharmacology study was conducted to examine the potential binding of pexidartinib to hCav1.2 whose inhibition has been negatively correlated with risk for QT prolongation. Pexidartinib was tested at 0.03, 0.3, 1, 3 µM which produced concentration-dependent inhibition of hCav1.2 current by 5.2 to 88.5 %. The IC50 for hCav1.2 blockade was 0.2 µM.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies were conducted.

2.3.3. Pharmacokinetics

Concentrations of pexidartinib in mouse, rat, rabbit, dog and monkey plasma (EDTA), and its major metabolite ZAAD-1006a in monkey plasma were determined by validated methods (2.5 to 50000 ng/mL) of mass spectrometry (LC MS/MS) or by high performance liquid chromatography (HPLC) using ultraviolet (UV) detection following solid phase extraction or liquid-liquid extraction. Methods were validated for sensitivity, selectivity carryover, linearity, accuracy, repeatability, precision, sample dilution analysis, and sample stability. Validation reports for these methods have been provided. Absorption, distribution, metabolism and excretion were analysed by measuring radioactivity in samples of plasma, tissues, and excreta from animals dosed with 14C-pexidartinib using liquid scintillation counting (LSC) and by quantitative whole-body autoradiography.

The single-dose pharmacokinetics of pexidartinib were investigated in mice, rats, dogs, and monkeys following IV or oral administration. However, few data allow an interspecies comparison.

Absorption

Pexidartinib was rapidly absorbed after a single oral dose, with mean Tmax in plasma ranging from 0.5 to 5 h in mice, rats, dogs and monkeys, which is similar to Tmax in humans (mean 2.5 h). Mean oral bioavailability was high in rat (> 90%) and high in dog at low dose 30 mg/kg as capsule formulation (80%) but low at higher doses 80 mg/kg (12%). Pivotal repeated dose toxicity studies have been performed by oral gavage and TK parameters measured. Oral bioavailability was not reported in monkeys or in humans. Feeding conditions did not significantly affect the single dose oral PK profile of pexidartinib in male monkeys. In general, pexidartinib AUCs following repeated daily oral dosing in mice, rats, rabbits and dogs were not different from those measured on Day 1 in all species. There were no significant sex differences in pexidartinib exposures. In all five species, the pexidartinib Cmax and AUC values were lower than proportional to the administered oral doses.

Distribution

Pexidartinib (2, 10 and 75 µM) showed strong protein binding in mouse (99.9% and 99.8%), rat (99.5% and 98.3%), dog (99.8% and 99.7%), and pooled human plasma (99.9% and 99.8%). The blood to plasma ratios in rat, dog, monkey, and human increased with the pexidartinib concentrations (50, 500, and 5000 ng/mL).

The tissue distribution of total radioactivity in pigmented rats following single oral administration of ^{14}C-pexidartinib was evaluated by quantitative whole-body autoradiography (QWBA). Pexidartinib-driven radioactivity was widely and rapidly distributed to most tissues with highest tissue concentrations between 1- and 8-hours. Bile, liver, uveal tract, pancreas and adrenal gland contained some of the highest concentrations of radioactivity observed. By 336 h, radioactivity was present only in the uveal tract and the entire eye for both male and female rats (both studies), and in the female adrenal gland, the male nasal turbinates, and thyroid (second study), indicating the elimination of radioactivity was virtually complete by 336 h. Radioactivity was observed in central nervous system (CNS) tissues at 1 h and 8 h. Pexidartinib can penetrate into the CNS and neurological and behavioural effects were seen in a few animals, the mechanism underlying these findings and the relevance for humans are unclear. This findings on the CNS are reflected in the Section 5.3 of the proposed SmPC.

Remarkably high tissue concentrations are reached in the liver (which may contribute to toxicity to this organ) and in the uveal tract of the eye. Accordingly, higher tissue levels were found in pigmented as compared to unpigmented skin. In the uveal tract and in the thyroid gland pexidartinib persists remarkably longer than in other organs.

No studies were submitted addressing placental transfer and transfer into milk of pexidartinib.

Metabolism

Pexidartinib is extensively metabolised in the liver and excreted via bile. In humans, CYP3A4 and UGT1A4 appear to be the main metabolising enzymes, but other CYP and UGT isoforms also play a role. Liver metabolism was studied *in vitro* (cultured hepatocytes) in several species, but *in vivo* metabolism was fully investigated in rats only. A circulating main metabolite in humans, the glucuronide ZAAD-1006a, is not found in the plasma of mice, rats and dogs, i.e. the species which were used for most toxicology studies. The only animal species with relevant ZAAD-1006a plasma levels after oral administration of pexidartinib

was the cynomolgus monkey. Thus, the applicant tested ZAAD-1006a in some special toxicology studies (see toxicology section below).

Part of the metabolic pathways of pexidartinib involves cleavage of the secondary amine and consecutive oxidation of the resulting 2,5-dimethyl pyridine derivate (M12); a similar pathway was also detected in humans (formation of human M1 requires removal of the pyridine moiety). Pyridine is known to be hepatotoxic, probably because it forms reactive intermediates during oxidation. Thus, formation of M12 may contribute to the observed hepatotoxicity of pexidartinib. M12 is exclusively found in urine and is a major part (around 70%) of the radioactivity excreted via urine (taken from Table 6-2 of the Study Report). Thus, M12 appears to be created in larger amounts and thereby could exert toxic effects in the liver. According to its chemical structure, M12 is formed by oxidation via several different CYP enzymes so that increased formation in subjects carrying certain CYP genotypes is unlikely. However, the Applicant has not discussed M12 as partly responsible for the observed hepatic toxicity of pexidartinib. The mechanism of liver toxicity remains unknown (see below).

The metabolism of pexidartinib was investigated in vitro in hepatocytes of rat, dog, and human but no data are provided for mice or monkey. In vivo, the metabolism pathways were identified only in rat; there are no metabolism data in dog, rabbit, mouse, monkey and human. No information on metabolism pathways in dog, monkey, mice and rabbit were provided.

Pexidartinib has a high potential for PK drug interactions because it inhibits several drug metabolising enzymes and drug transporters. In-vitro studies revealed that the compound is a strong inhibitor of CYP3A4 and 3A5 and a weaker inhibitor of other CYPs (2D6, 2C8, 2C9, 2C19). Furthermore, UGT1A4 is moderately inhibited by micromolar concentrations of pexidartinib. Regarding transporters, MATE1, MATE2K, OATP1B1, OATP1B3 and OATP2B1 were moderately affected by micromolar concentrations of pexidartinib. On the other hand, enzyme induction was not observed with pexidartinib.

Excretion

The total amount of radioactivity recovered in bile and urine from male bile duct-cannulated rats indicated that a minimum of 71% dose was absorbed. For intact rats, the predominant elimination route for pexidartinib was faecal excretion. For bile duct-cannulated rats, the predominant elimination route was biliary excretion. The overall mean recovery of excreted radioactivity was 96.5% by 120 h post-dose.

2.3.4. Toxicology

The nonclinical safety profile of pexidartinib (including its major human metabolite, ZAAD-1006a) has been characterized *in vitro* and *in vivo* toxicological studies in rats, dogs and monkeys. The toxicological profile of pexidartinib has been evaluated in single and repeat-dose toxicity studies in rats, dogs, and monkeys, genotoxicity studies, carcinogenicity in rats and mice, reproductive and developmental toxicity studies in rats and rabbits, repeat-dose toxicity studies in juvenile rats, and other special toxicity studies including DILI prediction, evaluation of potential toxicity for various pexidartinib impurities and a phototoxicity study. Pexidartinib was given by oral gavage once a day, unlike the intended clinical administration route (twice daily).

Two single dose studies, three non-pivotal studies and nine pivotal repeat-dose toxicity studies were performed in CByB6F1-Tg(HRAS)2Jic mice, Sprague Dawley rats, Beagle dogs and Cynomolgus monkeys, from 28 day and 39 weeks. The duration of studies is acceptable in the frame of ICH M3 guideline.

Pexidartinib was usually administered in 10% PEG400 in de-ionized water formulations. The identified target organs of pexidartinib were similar between rat and dog, consistent though the nonclinical development (short- and long-term studies) and are bone marrow, lymphoid organs and hematopoietic systems, bone, kidney, male and female reproductive organs and liver. Changes in selected haematological and serum chemistry parameters generally correlated to the myelosuppression and anaemia. Toxicity was more pronounced in rats than dog and monkey. Treatment-related toxicity was dose- and treatment duration-dependent.

Single dose toxicity

After single dose administration of pexidartinib in SD rats and after an exploratory single escalating dose administration in beagle dogs, treatment-related effects included changes in haematology parameters in rats and emesis and reduced bone marrow erythropoiesis in dogs.

Repeat dose toxicity

The repeat-dose toxicity was evaluated in a non-GLP-compliant 14-day study in SD rats and GLP-compliant studies in SD rats (up to 6 months) and in beagle dogs (up to 9 months). In general, the toxicity of pexidartinib was dose-related and time-dependent.

Key findings in rats included changes in haematology, serum chemistry, increased incidence of chronic progressive nephropathy (CPN) in males and females, thymic lymphoid depletion, regenerative anaemia, bone marrow depletion, decreased germ cells in the testes, hypospermia in the epididymides, corpora luteal haemorrhage and luteal cysts in the ovary, necrotizing inflammation and biliary cysts in the liver, and inflammatory changes including myxomatous change in the skin, chronic inflammation of the paw, and vascular inflammation. Of note are test article-related deaths as a result of subacute inflammation of the heart (besides other injuries) that occurred in the 28-day study with 14-day recovery.

Test article-related lesions in dogs given pexidartinib for up to 9 months were similar to rats: decreased germ cells in testes, hypospermia in the epididymides, anaemia and higher AST. In addition, in the 9-months study there was a test article-related minimal to mild deposition of pigment within the liver of the 6, 30, and 100 mg/kg/day group females. The pigment was brownish, deposited in the periportal areas within cytoplasm of macrophages/Kupffer cells, and was compatible with haemosiderin. The pigmentation was still present after the recovery in in the liver of one single 30 mg/kg/day female. The hemosiderin pigment in the liver and spleen is explained by the pharmacological effect of pexidartinib on red cell clearance. It is unlikely that haemosiderin contributes to the observed organ inflammation. However, since no red blood cell counts could be presented at the end of recovery, other unidentified mechanisms cannot be ruled out.

Pexidartinib-related early deaths occurred in the dog 28 day twice daily study to 2 males and 1 female given 1000/300 mg/kg/d based on abnormal faeces, emesis and neurobehavioral findings.

Effects on the CNS was also the reason for one unscheduled death in the embryo-foetal developmental study in rabbits at high dose and one female monkey received pexidartinib at 1 mg/kg for 13 weeks showed a hydrocephalus in the cerebrum with neuronal cell loss in the cortex of the cerebellum.

The reason for the observed effects on skin and eyes in the 9-months monkey study were considered to be non-adverse. However, loss of hair pigmentation and loss of skin pigmentation and clear discharge from

the eye(s) were findings that continued during the recovery period. Eye disorders were part of observed adverse drug reactions in the randomized Part 1 of the Phase 3 clinical study.

Repeated-dose toxicology studies revealed inflammatory infiltrates in several organs including liver and blood vessels in animals treated with pexidartinib.

Liver toxicity was also observed in humans. In animals, liver findings included hepatocellular hyperplasia, which could be related to extensive metabolism of pexidartinib, centrilobular hepatocellular necrosis, which could be related to cytotoxic effects of pexidarinib accumulating in the liver, and inflammatory infiltration. The latter was also observed in other organs and could be related to any direct or indirect immunomodulatory effect of pexidartinib. These morphological liver changes were accompanied by increase of AST, ALT and GGT in serum and decrease of serum albumin. The changes were partly reversible.

Toxicity of pexidartinib was dose-dependent. With few exceptions there were no exposure margins vs. human therapeutic exposure in the high-dose groups for pexidartinib (values below or just above 1). Only in the mouse carcinogenicity study, apparent safety margins for Cmax (about 10) and AUC (about 9) were observed. Similar minimal safety margins with respect to Cmax and AUC applied to the metabolite ZAAD-1006a in the single dose (mouse, rat, dog) or 13-week monkey study at the highest dose.

Genotoxicity

Pexidartinib underwent a complete genotoxicity tests battery *in vitro* and *in vivo*, with respect to gene mutations in bacteria and mammalian cells. In conclusion, pexidartinib and the metabolite ZAAD-1006a are not considered to be genotoxic.

Carcinogenicity

Carcinogenicity testing of pexidartinib was carried out in a 2-year study in rats and a 6-month study in hemizygous Tg.rasH2 mice [CByB6F1-Tg(HRAS)2Jic (+/-hemizygous c-Ha-ras)] in compliance with GLP. Neoplasms detected in the long-term study in SD rat or short-term study in hemizygous Tg.rasH2 mouse seem not to be related to the treatment of pexidartinib. All neoplastic alterations detected in the studies exhibited either no dose relationship, were within the range of the historical control incidences or were common or spontaneous neoplasms in aged rats and mice.

In rats at the NOAEL for carcinogenicity the average exposure after repeat dosing was far below that obtained in Phase III study PLX108-10. Multiples of exposures were 0.43 x and 0.27 x based on Cmax and AUClast and thus no safety factor to the human exposure exist. In the 6-month study in rats signs of chronical inflammation -partly necrotizing- of multiple organs (liver, skin, tongue, coecum, mammary gland, vascular system) were observed in the range of expected clinical exposures. The necrotizing inflammation in the liver was not reversible even with higher incidence after 16 weeks of recovery.

In mice at the NOAEL for carcinogenicity, the average exposure after repeat dosing was above that obtained in Phase III study PLX108-10. Multiples of exposures were 10.2 x based on Cmax and 9.13 x based on AUClast. Pexidartinib was not carcinogenic in mouse above (about 10 x) the expected clinical exposures.

Reproduction toxicity

A standard battery of GLP-compliant reproductive and developmental toxicity studies was conducted in SD rats and NZW rabbits in accordance with applicable ICH guidelines. In addition, dose range-finding studies were performed in rats and rabbits.

In a rat fertility and early embryonic development study, reduced male and female reproductive performance were reported at 40 mg/kg/day and correlated with adverse effects on spermatogenic parameters (motility, concentration, morphology, sperm production rate) and macroscopic findings and lower weights of epididymides and testes. In addition, higher mean litter proportions of pre- and post-implantation loss with corresponding decreased mean number and litter proportion of viable embryos were also seen at this dose level. There was no safety margin for reproduction performance and early embryonic development based on a NOAEL of 10 mg/kg/day.

The functional effects on fertility and embryonic development reported in this study correlate with treatment-related changes in testes (germ cell degeneration) and epididymides (hypospermia) observed in rat and dog repeat-dose toxicity studies, at doses as low as 20 and 30 mg/kg/day, respectively (approximately 0.6 and 0.1 times human exposure at the dose of 800 mg). In the chronic toxicity studies, findings in testes and epididymides were still observed after recovery periods encompassing an entire spermatogenic cycle in these species. According to the applicant, changes in testes and epididymides were driven by the pharmacological activity of pexidartinib (CSF-1 and SCF are involved in the regulation of spermatogenesis). In view of the cross-species concordance of the non-reversible findings on male reproductive organs in rats and dogs, the correlating effects on the male fertility in rats, the absence of safety margins, and the underlying mechanism involving the pharmacological effect of pexidartinib, a clinical relevance seems likely. Therefore, male patients treated with Turalio should be advised to have sperm samples frozen and stored before treatment. Changes in female reproductive organs were observed in repeat-dose toxicity studies conducted in rats (notably necrosis, haemorrhage, decreased number of corpora lutea; luteal cysts; decreased incidence of retained antral follicles) and dogs (notably decreased numbers of ovarian follicles) at exposure levels mostly lower than those reached in patients.

Findings observed in the reproductive tract of female dogs are reflected in the proposed SmPC section 5.3.

In embryo-foetal development toxicity studies, a teratogenic potential was demonstrated for pexidartinib in both rats and rabbits. In rats, external (localized foetal oedema) and urogenital malformations were observed at the dose of 40 mg/kg/day, which also induced some maternal toxicity (haematological effects). At the same dose level, a general decrease in the degree of ossification was reported in foetuses and attributed to the effect of pexidartinib on the activity of osteoclasts. In rabbits, pexidartinib induced malformations of the kidneys and ribs, as well as foetal deaths at the non-maternotoxic dose of 60 mg/kg/day. An increased incidence of external malformations (spina bifida, cleft lip and cleft palate) was also reported at maternotoxic dose levels in the dose range-finding study. In both species, treatment-related foetal malformations were reported at exposure levels lower than those reached in patients. Overall, there was no safety margin for adverse effects on embryo-foetal development (foetal malformations, decreased embryo-foetal survival). The foetal malformations seen in the embryofoetal developmental studies in rats and rabbits are attributed to the pharmacological action of pexidartinib. Since no safety margin to human exist, pexidartinib should be considered as a potential human teratogen.

A pre-post-natal development toxicity study conducted in rats did not demonstrate any effect on maternal animals, and on the growth and development of their offsprings. However, the clinical relevance of this study is unclear. Indeed, the NOAEL for both maternal animals and their offsprings was set at the high

dose level of 10 mg/kg/day, which induced systemic exposure levels 4- to 5-fold lower than those reached in patients.

No data are available on the excretion of pexidartinib in animal and human breast milk. However, physicochemical data suggest excretion of pexidartinib in breast milk.

In a dose range-finding juvenile animal toxicity study conducted in rats, treatment-related adverse effects were reported on the developing skeleton and on the testes at 20 mg/kg/day or more.

Other toxicity studies

Metabolites

ZAAD-1006a is an N-glucuronide metabolite of pexidartinib. It was found to be a major metabolite of pexidartinib in clinical studies. It appears to be unlikely that ZAAD-1006a would have any significant physiological effects associated with inhibition of kinases targeted by pexidartinib at the proposed clinical dose (800 mg/day) (see pharmacology section). As exploratory single-dose oral PK studies reported that mouse, rat and dog had very low plasma concentrations of ZAAD-1006a, an additional 13-week study was performed with pexidartinib in which monkey exposure to ZAAD-1006a is comparable to those observed in humans. At the highest dose tested, changes included vomiting, effects on food consumption, electrocardiography, urinalysis, haematology, blood chemistry, and histopathology were observed. These effects are considered to be non-adverse since similar effects were noted in the control group. For TK analysis, plasma concentrations of pexidartinib and ZAAD-1006a were determined on days 1, 14, 28, and 91. Cmax and AUC0-24h values increased with dose. The high inter-animal variation observed in this study is thought to be the result of multiple transformation steps of PLX3397 to its metabolite ZAAD-1006a, and this variation had no critical impact on the toxicity profile in monkeys in this study. Regarding genotoxicity studies, two *in silico* assessments were performed. ZAAD-1006a was considered to be a non-mutagen since two identical structural alerts were detected in ZAAD-1006a and pexidartinib, and pexidartinib was found not mutagenic in *in vitro* bacterial reverse mutation assays.

The submitted toxicological characterization program of ZAAD-1006a is mostly in line with the one recommended by the CHMP (see EMA/CHMP/SAWP/581081/2017) considering data collected from pexidartinib and the single species relevant to ZAAD-1006 studies. Moreover, ZAAD-1006a is a Phase 2 conjugate and it is not a chemically reactive acylglucuronide metabolite, as no carboxylic acid group is present in the chemical structure of ZAAD-1106a. There, no further toxicology study is required.

Impurities

Four pexidartinib-related compounds that were starting materials or intermediates in the pexidartinib synthetic route may have existed as impurities in the drug substance. The four genotoxicity studies in bacteria were negative. Even though only one assay has been performed (no preliminary or confirmation test), no further tests are required.

Phototoxicity

Although pexidartinib absorb in UV/vis spectrum and exhibited an affinity for melanin, it did not have any phototoxic potential in the neutral red uptake bioassay. Pexidartinib was not phototoxic.

Mechanistic studies

In silico prediction for liver toxicity and possible mechanisms were performed by DILIsym software analyses based on *in vitro* hepatotoxicity assay data, clinical data of the phase 3 study (PLX108-10), simulations of clinical hepatic exposure and simulations of hepatotoxic mechanisms. Mechanistic investigation simulations revealed that multiple mechanisms, including mitochondrial ETC inhibition, bile acid transport inhibition, and oxidative stress, contribute to the predicted hepatotoxicity with ALT elevations for pexidartinib treatment. In addition, effects from both the parent PLX3397 and the metabolite ZAAD-1006a were found to contribute to the predicted toxicity. However, hyperbilirubinaemia was under-predicted with DILIsym in this study. The under-prediction may be due, in part, to the lack of an explicit representation of cholestasis and ductopenia in the current version of DILIsym.

2.3.5. Ecotoxicity/environmental risk assessment

Table 1. Summary of main study results

Substance (INN/Invented Name): Pexidartinib / Turalio			
CAS-number (if available): 1029044-16-3 (free form); 2040295-03-0 (hydrochloride)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	logD_{OW} = 2.60 (pH = 4) logD_{OW} = 4.74 (pH = 7) logD_{OW} = 4.45 (pH = 9)	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.74	Potentially B
	BCF	201	not B
Persistence	DT50	DT_{50} (sediment) > 180 d DT_{50} (soil)>180 d	vP
Toxicity	NOEC	$NOEC_{Fish}$ = 2.73 µg/L	T
PBT-statement:	The compound is not considered as PBT nor vPvB.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	4.0 (default) 0.08 (refined)	µg/L	> 0.01 threshold Yes
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{foc} =11907 L/kg (soil) K_{foc} =19722 L/kg (soil) K_{foc} =16032 L/kg (soil) K_{foc} =34424 L/kg (sludge) K_{foc} =22605 L/kg (sludge)	
Ready Biodegradability Test	OECD 301	21 % in 28 days	Not readily biodegradable
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, 12\ °C, water}$ = 0.8–1.5 d $DT_{50, 12\ °C, sediment}$ = 232–720 d $DT_{50, 12\ °C, whole\ system}$ = 293–737 d	vP in sediment and the whole system Sediment organism test triggered

		% shifting to sediment = 72–89 % 1 relevant transformation product: Metabolite 1 $DT_{50,\ 12\ °C,\ whole\ system}$ = 127–273 d			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test	OECD 201	NOEC	0.0469	mg/L	*Pseudokirchnerilla subcapitata*
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.027	mg/L	
Fish, Early Life Stage Toxicity Test	OECD 210	NOEC	0.00273	mg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	>1000 400	mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	Whole BCF_{ss} Kinetic BCF_k Kinetic BCF_L	201 178 92	L/kg	5% lipids, BCF based on TR
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	NOEC	25.6	mg/kg	
Terrestrial Plants, Growth Test/*Brassica, Pisum*	OECD 208	NOEC	no results	mg/kg	high variation of biomass data
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/kg	
Collembola, Reproduction Test	OECD 232	NOEC	1000	mg/kg	
Sediment dwelling organism OC = 1.9 %	OECD 218	NOEC	1000	mg/kg	*Chironomus riparius*
Aerobic transformation in soil	OECD 307	 Parent (DFOP) Metabolite 1 Metabolite 2 Metabolite 3 (all SFO) $CO_{2,\ max}$ NER_{Max}	$DT_{50,\ 12\ °C}$ [d] 44–215 99.7 (geo. mean) 73.7–300 97.3–184 n/d Plateau formation 10.5 % 52.8 %		vP in all 4 soils

Pexidartinib does not pose a risk to the aquatic and sediment compartment. A final conclusion on the risk to soil organisms cannot be drawn as additional data on the toxicity to plants need to be generated. The applicant agreed to provide a new test on toxicity to plants according to OECD 208 as post-authorisation measure. Pexidartinib is not a PBT-substance, but vP and T.

2.3.6. Discussion on non-clinical aspects

The non-clinical safety profile of pexidartinib has been characterized *in vitro* and *in vivo* pharmacological, pharmacokinetic and toxicological studies primarily in rats and in dogs. This non-clinical development program is designed in accordance with ICH M3 guideline and is sufficient to support marketing authorization of pexidartinib in patients with TGCT. All pivotal studies were conducted in compliance with GLP requirements.

The primary pharmacodynamics programme submitted by the applicant was limited. It is acknowledged that non-clinical models for TGCT do not exist and that little is known about its pathophysiology, besides the fact that a small fraction of tumour cells constitutively produces CSF1, e.g. due to chromosomal rearrangement, and thereby likely drive the accumulation and proliferation of the majority of the tumour cells which express CSF1 receptors (CSF1R). It is not known whether other factors besides CSF1 play a role.

The inhibition of CSF1R is the main mode of action of pexidartinib. However, pexidartinib also inhibits KIT proto-oncogene receptor tyrosine kinase (KIT). KIT is the main off-target structure, but other kinases could potentially be inhibited. No primary pharmacology data on CSF1-R/KIT/ITD-FLT3 activity in mice, rats, dogs, rabbits or monkeys have been submitted; the relevance of animal species used in non-clinical development is questionable. The absence of selectivity of pexidartinib is contributing to the important side-effects observed with pexidartinib treatment. The findings have been listed in the proposed SmPC to inform the prescriber.

The lack of pharmacodynamic drug interactions studies is acceptable since the pharmacodynamic effects of pexidartinib do not indicate relevant potential interactions.

The PK profile of pexidartinib was investigated in single- and repeated-dose toxicity studies. Pexidartinib showed lower than dose-proportional exposure, no appreciable differences in the PK profile between male and female and no accumulation over time. Only rat ADME was well described; ADME profiles in other animals used in non-clinical program are missing and no comparison to human PK profile was reported.

High tissue concentrations of pexidartinib were found in the uveal tract of the eye, in pigmented skin and in the thyroid gland. Here, pexidartinib was retained and could accumulate and thereby induce potential long-term damage. Ophthalmological or histological changes were not observed, but an effect on visual acuity is difficult to determine in animals. In clinical data, the risk for accumulation seems to be most pronounced in the uvea. There were several reports of ocular AEs in patients treated with Turalio in the clinical trials, but there were no suitable controls so that the effect of pexidartinib on top of the spontaneous incidence of vision events cannot be determined. "Vision changes" was included in the tabular listing of AEs in Section 4.8 of the proposed Turalio SmPC. Together with "eye oedema", the frequency was given as "very common" for these eye disorders. Further measures such as recommending regular ophthalmologic examinations were not considered necessary. This toxicity will be further evaluated in a PASS trial (see RMP).

The oral route of administration was used in all toxicology studies to match the intended clinical administration route. Pexidartinib hydrochloride was given once daily, unlike the clinical proposed regimen, without PK arguments to justify the difference in the treatment regimen. Rats, rabbits, dogs, monkeys and mice were used, however, the relevance of these animal models is questionable. The identified target organs of pexidartinib were similar between rat and dog, consistent though the nonclinical development (short- and long-term studies) and are bone marrow, lymphoid organs and haematopoietic systems, bone, kidney, male and female reproductive organs and liver. The observed clinical chemistry effects are considered to be non-adverse based on the low incidence and/or lack of correlative histopathology. The relevance of the findings in the dogs after single dose administration is questionable due to limited sample size and high inter-animal variability, although emesis occurred consistently throughout all toxicology studies and bone marrow suppression may be attributed to the inhibition of the KIT proto-oncogene tyrosine kinase. Changes in selected haematological and serum chemistry parameters generally correlated with the myelosuppression and anaemia. These latter changes need to be further evaluated in human.

Toxicity was more pronounced in rats than dogs and monkeys. Treatment-related toxicity was also dose- and treatment duration-dependent.

Changes attributed to direct pexidartinib related effects were observed in liver, kidney and vascular system. Although chronic progressive nephropathy is considered a spontaneous age-related disease, the incidence and/or severity was increased with pexidartinib. Changes attributed to pexidartinib related induced stress were observed in thymus, adrenal gland, change in circulating WBC and inflammatory factors. Other findings were driven by the pharmacological activity of pexidartinib since the natural ligands of CSF1R (CSF-1) and KIT (SCF) regulate many pathways (growth and proliferation of macrophages and osteoclasts, haematopoiesis, spermatogenesis, oogenesis and folliculogenesis).

The applicant did not submit evidence whether or not the toxicological findings could be related to off-target activity of pexidartinib beyond KIT. In the absence of mechanistic explanation, the relevance of the toxicological findings remains uncertain, and accordingly they are listed in the proposed SmPC to inform the prescriber.

No effects on neurobehavioral or respiratory system were observed. However, concerns about neurotoxicity exist given the distribution in the CNS and the observed effects in repeated dose toxicity studies. The cause of the CNS-toxicity is not clear. A direct neurotoxic effect is conceivable since pexidartinib can penetrate into the brain. Immunological events may also play a role, in line with the observed inflammatory infiltrates in other organs and in blood vessels. These findings have been listed in the SmPC to inform the prescriber and user that pexidartinib may cause neurotoxic effects including cognitive disorder (section 4.8), and neurotoxic adverse events need to be further studied.

Pexidartinib produced concentration-dependent inhibition of hERG tail current with no correlated effect in a telemetry study in dogs. Although sodium channels were not tested, the demonstrated inhibition of hCav1.2 channels by pexidartinib explains the absence of QTc prolongation despite hERG blockade and explains that the risk for torsade-de-point arrhythmias is low according to current understanding so that further studies are not required.

The pathomechanism of inflammatory infiltrates into several tissues observed in the rat repeat-dose toxicity study remains unclear. At present, it could not be clarified if/which kinases are responsible for the inflammatory infiltrates and thus, there is no mechanistic explanation with relevance to humans.

The observed inflammation in the heart was due to septicaemia but no mechanistic explanation of the heart findings (increased organ weight, deposition of mucosubstances) was provided. Without understanding the mechanism, it is not possible to assess the relevance for humans and to decide if the underlying processes can have unfavourable effects in the long term. Thus, these cardiac effects have been included in Section 5.3 of the proposed SmPC to inform the prescriber about observed effects of unknown relevance.

In humans suffering from TGCT and treated with pexidartinib, circulating CSF1 levels are markedly increased, probably because of blockade of clearing by CSF1R. CSF1 in high concentrations could bind to receptors other than CSF1R (which is blocked by pexidartinib) and thereby trigger immune cell attraction and inflammatory infiltration. Circulating CSF-1 levels were not determined in animals used in the toxicology studies. Therefore, no further mechanistic considerations are possible regarding the observed inflammatory infiltration in liver and blood vessels and the hemosiderin deposition in the liver.

Whereas the liver injury events in humans were considered by the applicant to be most likely idiosyncratic in nature, their mechanism is not clear. In animals, liver findings included hepatocellular hyperplasia,

centrilobular hepatocellular necrosis, and inflammatory infiltration and were accompanied by increase of AST, ALT and GGT in serum and decrease of serum albumin. It is questionable whether the applicant's claim of a clear difference between liver effects in animals and humans is true. The liver effects of pexidartinib are complex, in humans as well as in animals, so that a clear distinction does not appear possible. Discussing potential mechanisms of the observed hepatic effects of pexidartinib in animals and humans could not provide mechanistic insights. Thus, uncertainties remain, and in the absence of known mechanisms by which pexidartinib affects the liver, defining preventive measures for avoiding liver damage during pexidartinib therapy remains difficult. This is taken into account for benefit / risk considerations.

There were no relevant exposure margins *vis-a-vis* human therapeutic exposure in the high-dose groups for pexidartinib (values below or just above 1). Only in the mouse carcinogenicity study, safety margins for Cmax (about 10) and AUC (about 9) were observed. Similar minimal safety margins with respect to Cmax and AUC applied to the metabolite ZAAD-1006a in the single dose (mouse, rat, dog) or 13-week monkey study at the highest dose. A definitive conclusion about possible risks for humans with continued treatment cannot be drawn. Monitoring in the clinical setting as part of pharmacovigilance activities should be conducted to detect any new toxicities.

Pexidartinib was found negative in a complete genotoxicity test battery *in vitro* and *in vivo*. The carcinogenic potential of pexidartinib was evaluated in a 6-month study in rasH2 mice and a two-year study in Sprague Dawley rats. Observed neoplastic lesions in the rat study could not be attributed to pexidartinib and critical points in the mice study were effects on the haematopoietic system (anaemia, bone marrow depletion). However, in the rat study, the NOAEL was far below that obtained in Phase III study PLX108-10 and no proof of bone marrow exposure or at least systemic exposure have been submitted in chromosomal aberration in mice. A reduction in PCE/ECs ratio up to 19% was observed, but in the absence of toxicokinetic data, it is impossible to assess if exposure was sufficient compared to the clinical exposure (Cmax/AUC). Section 5.3 in the proposed SmPC includes that the tested exposures in 2-year rat were well below (approximately 0.3 times of) human intended exposures. There are also uncertainties on relevance of the species used in the *in vivo* chromosomal aberration as well as of the system used for metabolic activation in the two other tests. Moreover, due to the pharmacological mode of action, which includes immunosuppressive effects, it cannot be excluded that pexidartinib may increase the risk of malignancies, which is consequently reflected in the proposed SmPC section 4.4.

Reduced male and female reproductive performance were reported in fertility study. These findings were correlated with treatment-related changes in testes (germ cell degeneration) and epididymides (hypospermia) observed in rat and dog repeat-dose toxicity studies and in ovaries (necrosis, haemorrhage, decreased number of corpora lutea; luteal cysts; decreased incidence of retained antral follicles in rats and decreased numbers of ovarian follicles in dogs) at exposure levels mostly lower than those reached in patients. It cannot be concluded with certainty that female reproductive tract findings were reversible. In the 6-month rat study, recovery females were 49-week old at the time of sacrifice and were therefore undergoing reproductive senescence at that time, which may have acted as a confounding factor during evaluation of the reversibility of female reproductive tract findings. As indicated by Dixon et al. (2014), luteal cysts are unusual lesions in mice and rats, may be associated with increased progesterone, and are induced by progesterone receptor inhibitors in rats. Interaction of pexidartinib with the progesterone receptor is considered as unlikely by the applicant since findings observed with both compounds in rats are not completely overlapping. However, this is not unexpected for compounds which have different pharmacological activities despite having one common pharmacological target. Based on literature data reporting a role for KIT in ovarian development and function, as well as expression of CSFR

in female reproductive tract and its role in fertility, inhibition of both targets may cause complex effects on the ovary. Thus, the mechanism underlying luteal cysts is not clearly elucidated. In view of the cross-species concordance of the non-reversible findings on male and female reproductive organs in rats and dogs, the correlating effects on the male and female fertility in rats, the absence of safety margins, and the underlying mechanism involving the pharmacological effect of pexidartinib, a clinical relevance seems likely. Therefore, male patients treated with Turalio are advised to have sperm sample frozen and stored before treatment and female will be advised that pexidartinib have an impact on fertility, as reflected in the proposed SmPC sections 4.4 and 4.6.

The findings in juvenile animals were in line with the overall toxicological profile defined for pexidartinib in repeat-dose and reproduction toxicity studies. However, findings were observed below human exposures. A product-specific waiver was granted for the development of pexidartinib for treatment of benign soft tissue sarcoma in all subsets of the paediatric population on the grounds that pexidartinib is likely to be unsafe. Therefore, no additional data were required for the present application.

In embryo-foetal development toxicity studies, a teratogenic potential was demonstrated for pexidartinib in both rats and rabbits. A pre-post-natal development toxicity study conducted in rats did not demonstrate any effect on maternal animals, and on the growth and development of their offsprings.

No data are available on the excretion of pexidartinib in animal and human breast milk. However, physicochemical data suggest excretion of pexidartinib in breast milk. In the DRF juvenile toxicity study in rats, findings were observed below human exposures. Adverse effects on the breast-fed child cannot be excluded. Therefore, pexidartinib has been contraindicated during breast-feeding.

Pexidartinib was not phototoxic.

At present, a final conclusion on the environmental risk of Pexidartinib cannot be drawn as outstanding issues need to be addressed.

2.3.7. Conclusion on the non-clinical aspects

Pexidartinib has a specific non-clinical safety profile, with notable toxicities of concern and dose-limiting toxicities at exposures close to or below clinical exposures.

Studies on the mechanism of action of pexidartinib indicated that it is not highly selective for CSF1R/FMS.

The mechanism of liver toxicity in animals and in humans is unknown; therefore, it is not possible to define preventive measures for avoiding liver damage during pexidartinib therapy. This was taken into account for benefit-risk considerations.

Toxicity findings could be of relevance for patients since no adequate safety margins could be achieved in the animal toxicity studies and since pexidartinib is intended to be administered life-long, new toxicities may occur and should be further monitored in the clinical setting.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study	Subjects treated	Population
Tier 1: Data from studies in TGCT indication		
PLX108-10 (Phase 3 ENLIVEN)	120 (91 with pexidartinib)	TGCT
PLX108-01 (Phase 1 Extension TGCT cohort)	39	TGCT
Tier 2: Non-TGCT Safety Data from studies of pexidartinib monotherapy in cancer subjects		
PLX108-01 (non-TGCT cohort)	93	Non-TGCT solid tumour
PLX108-03	20	Hodgkin lymphoma
PLX108-04	38	Glioblastoma multiforme
PLX108-05[a]	90	AML
PLX108-06	6	Prostate cancer
PLX108-13 (non-IND study)	6	KIT-mutant melanoma
PL3397-A-A103 (non-IND study)	11	Solid tumours, 1 TGCT subject
Tier 3: Non-TGCT Safety data from combination therapy studies		
PLX108-07 (+ paclitaxel)	74 (68 with pexidartinib)	Solid tumours
PLX108-08 (+ temozolomide, radiotherapy	65	Glioblastoma multiforme
PLX108-09 (+ vemurafenib)	13	BRAF-mutant melanoma
PLX108-14 (+ pembrolizumab)	78	Solid tumours
PLX121-01 (+ PLX9486)	12	Solid tumours
Tier 4: Other pexidartinib studies		
Clinical pharmacology studies (14 studies)	338	Healthy or special population subjects (not patients)
Investigator-initiated studies (8 studies)	138	Solid and haematologic tumours

Abbreviations: AE = adverse event; AML = acute myeloid leukaemia; IND = Investigational New Drug; KIT = proto-oncogene receptor tyrosine kinase; TGCT = tenosynovial giant cell tumour.

[a] Because of the higher pexidartinib doses studied in subjects with AML and the unique disease-specific AEs observed in these subjects, the results of Study PLX108-05 are presented separately in a separate column for the non-TGCT monotherapy population in Tier 2.

2.4.2. Pharmacokinetics

Sixteen (16) clinical studies and 3 popPK models were submitted to provide clinical pharmacology data. All biopharmaceutical and PK studies were performed in healthy volunteers, including volunteers with hepatic (HI) and renal function impairment (RI), and PK parameters were estimated after single doses. 1 early solid tumour patient study and 1 study in the target TGCT population included PK assessment after multiple doses.

Pexidartinib was measured in plasma and dialysate, and the glucuronide metabolite of pexidartinib, ZAAD-1006a, was measured in plasma using liquid chromatography with tandem mass spectrometry detection (LC-MS/MS).

Pooled data from Phase 1 and 3 studies were used for population PK analyses of pexidartinib and its metabolite ZAAD. Rich and sparse sampling data from healthy volunteers and patients from 375 subjects were included in the analyses. Investigation of the impact of renal impairment on the PK was conducted using rich sampling data. Overall, PK data across different doses in healthy volunteers and patients were used for model development.

Absorption

No absolute bioavailability studies have been submitted for pexidartinib.

Following oral administration over a range of doses (200 mg to 600 mg), pexidartinib peak exposure occurred after approximately (median) 2.5 hours. Pexidartinib was partially absorbed after oral administration as indicated in the mass balance study (Study PL3397-A-U115) where 44.0% of total radioactivity was excreted as unchanged pexidartinib in the faeces after administration of 400 mg ^{14}C-pexidartinib suspension, and 27.4% of radioactivity eliminated in urine. Therefore, bioavailability of pexidartinib is at least 27.4%. Consideration of elimination during 72 first hours (absorption phase) could lead to consider Fa up to 70%. However, this is below the 85% absorption threshold delimiting class I and II from class III and IV; therefore, pexidartinib is classified as a BCS class IV compound.

When pexidartinib is co-administered with esomeprazole to increase the gastric pH, maximal and total exposure of pexidartinib are reduced by approximately 47-55%.

Pexidartinib PK exhibits a multiphasic manner which is a result of a combination of multiple factors, including pH-sensitive dissolution, solubility limited absorption, its pKa allowing absorption throughout the GI tract, and enterohepatic recirculation.

- Bioequivalence

Two bioequivalence studies, providing comparison of formulation AE and AF (study PL3397-A-U114), and comparison of formulation AF optimized versus non-optimized (study PL3397-A-U116), were provided. The oral bioavailability of the fasted Phase 3 formulation (J-3397-AF) of PLX3397 HCl is approximately 17% higher than that of the fasted Phase 1 formulation (J-3397-AE).

- Influence of food

Effect of food was tested in three studies, PLX108-11, PL3397-A-U114 and PL3397-A-U121. In the 3 studies examining the effect of a high-fat meal on the bioavailability of pexidartinib with various formulations and single doses, absorption was delayed and the exposure (Cmax and AUC) to pexidartinib was approximately doubled. Metabolite to parent ratio appeared stable for the different doses and did not

change with fasted or fed status. With 400mg under low-fat conditions resulted in 56% higher Cmax and 59% higher total exposure (AUC), compared to the fasted state.

Distribution

Pexidartinib was distributed widely throughout the body, with apparent volume of distribution (Vz/F) values ranging from 200 to 570L, and for fasted healthy subjects ranged from 178.3-210.8 L at 200-600 mg in study PL3397-A-U117. From the popPK analyses that included HV and patient data, the typical PK parameter estimates for a reference subject were 98.0L for the apparent volume of distribution of the central compartment (Vc/F) and 116L for that of the peripheral compartment (Vp/F).

Pexidartinib is highly protein bound (>99%) in human plasma; protein binding at HSA (human serum albumin) was 99.9% and at AAG (α-1 acid glycoprotein) was 89.9%, as measured *in vitro*.

Elimination

- Clearance

CL/F values in fasted subjects ranged from 5.10-9.61 L/h. CL/F increased with dose, possibly due to decreasing bioavailability with higher doses. Based on the PopPK analysis, healthy subjects appeared to have a modestly higher CL/F (26%, 95% CI: 16-36%) compared to patients with TGCT. Half-life t1/2 after single pexidartinib doses was between 24.97 hours at 200mg (with estimated 7 days to steady state) and 19.56 hours at 2400mg.

- Excretion

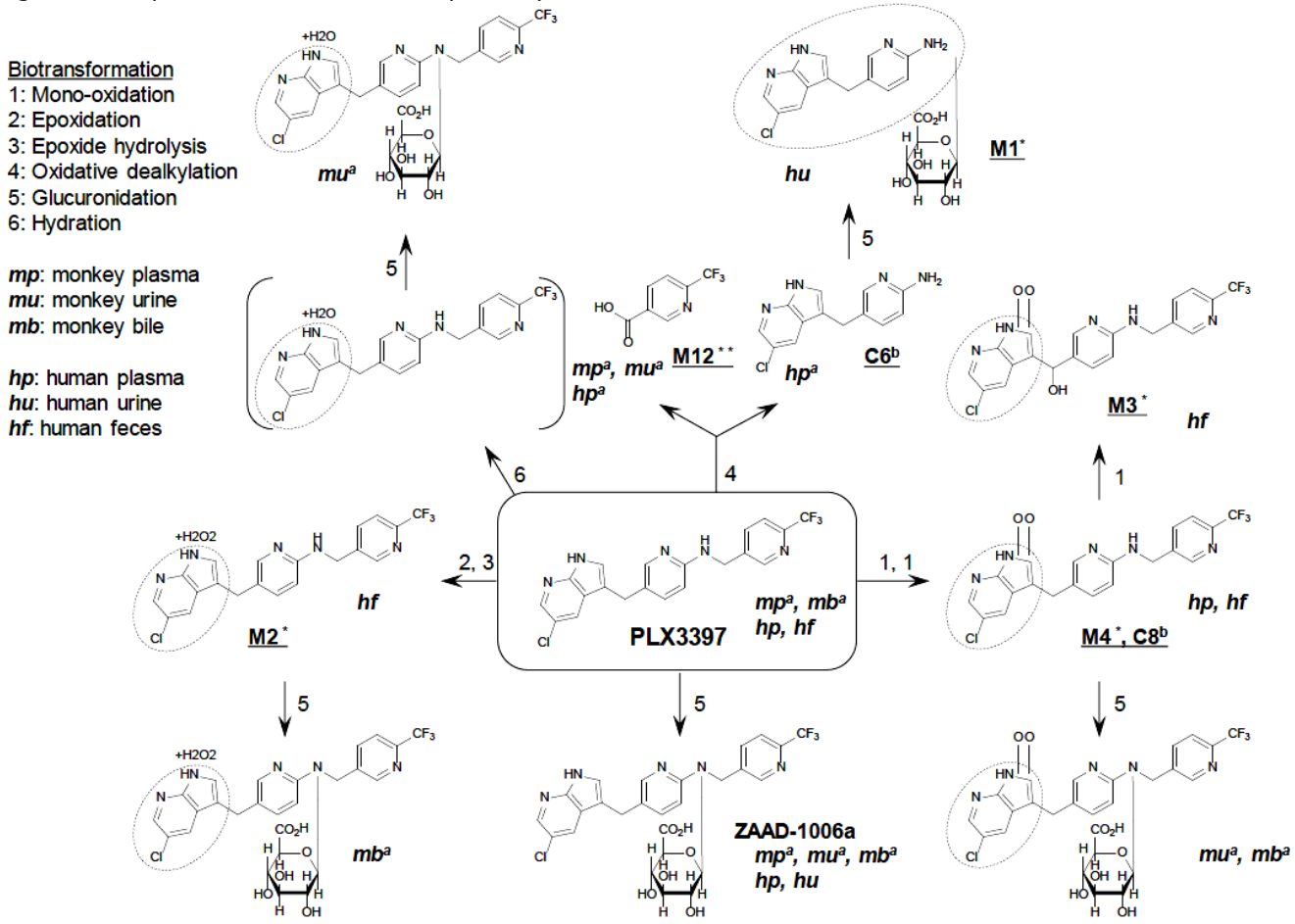
After a single oral dose of 400 mg of radiolabelled pexidartinib, 65% and 27% of radioactivity were eliminated in the faeces and urine respectively. Elimination is mostly through faeces as the unchanged drug (44% of the total administered radioactivity), with terminal half-life between 24 and 28h (mean t1/2, 27 h), and clearance around 5.6 L/h (93 mL/min). ZAAD-1006a was the most abundant component excreted in urine.

- Metabolism

Pexidartinib was highly metabolized in the body, as indicated by the presence of only 34.9% of the total radioactivity in plasma as the parent drug. In human liver microsomes, pexidartinib was mainly metabolized (oxidised) by rCYP3A4 and rCYP3A5 (100% decrease) and to a lesser extent by rCYP2D6 (65% decrease). Approximately 27% decrease was observed with rCYP2C8, rCYP2C9, and rCYP2C19. When pexidartinib was incubated with a panel of rUGTs, the primary metabolizing (glucuronidising) UGT isoform was rUGT1A4 (25% decrease).

Five detectable metabolites were identified in the mass balance study. No parent drug was detectable in the urine following oral administration; based on recovered radioactivity, the *N*-glucuronide ZAAD-1006a was the only metabolite excreted at >=10% of the dose in the urine. Of the 2 metabolites identified in plasma, the N-glucuronide metabolite, ZAAD-1006a, was the major plasma metabolite of pexidartinib (formed by UGT1A4) and had an exposure (corrected for molecular weight) that was approximately 10% higher than the exposure to the parent after single-dose administration. ZAAD-1006a was minimally active pharmacologically.

Figure 2: Proposed biotransformation pathway in humans



In human ^{14}C-ADME study, ZAAD-1006a was the most predominant (10.3% of the administered radioactivity) moiety in urine. M1 represented 5.4% of the administered radioactivity in urine. M2 represented 2.35 % of the administered radioactivity into faeces. M4 represented 0.822% of the administered radioactivity) into faeces.

No transporter-mediated uptake or excretion of pexidartinib was found at several tested transporters in non-clinical studies such as p-glycoprotein, Breast Cancer Resistance Protein (BCRP), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT) 1, OCT2, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, OATP2B1, and bile salt export pump (BSEP).

- Inter-conversion

Not applicable because pexidartinib has no asymmetric carbon atoms in the molecule.

- PK of metabolites

The main metabolite of interest is ZAAD-1006a: t1/2 is between 22 and 28 hours (around 38h in renally impaired patients), expecting accumulations similar to that of parent compound. ZAAD-1006a exposure,

based on Cmax and AUCs, was approximately 2- to 3-fold higher in subjects with renal impairment (mild, moderate, and severe impairment, and subjects with ESRD on regular haemodialysis) compared to subjects with normal renal function.

- Consequences of possible genetic polymorphism

The potential for the PK of pexidartinib and/or ZAAD-1006a to be affected by UGT1A4 polymorphism was investigated in an exploratory pooled meta-analysis (Study DSPI-PCS-109). UGT1A4 genotype had only a small effect, no other genetic polymorphism is expected to impact PK of Pexidartinib.

Dose proportionality and time dependencies

Dose proportionality was studied at single dose in study PL3397-A-U117. Dose proportionality was shown between 200 and 400 mg, and under proportionality was shown above 400 mg. Upon multiple dosing as a 400mg twice daily regimen, a moderate accumulation of pexidartinib (3.6-fold median AUC) was estimated in the popPK. The findings for dose proportionality for ZAAD-1006a were generally similar to those for pexidartinib, with 4.6-fold accumulation.

- Inter and Intra-individual variability

From the population PK modelling, variance parameter estimates were indicative of a moderate to high degree of unexplained interindividual variability for pexidartinib with estimates (percent coefficient of variation (%CV)) of 30 for CL/F, 56.1 for Vc/F, 48.8 for Vp/F 70.8 for Q/F, 165 for KA, and 32.6 for F1 of the Phase 1 formulation. Estimates of inter-occasion variability were 229%CV for KA and 25.9%CV for F1.

- Pharmacokinetics in target populations

For the target population, pexidartinib and ZAAD-1006a pharmacokinetics were only estimated by popPK modelling. Overall, population PK modelling showed an only small patient covariate effect, with a slightly higher CL/F.

Special populations

- Age

Table 2: Number of subjects in pexidartinib PK trials

PK Trials	**Age 65-74 (Older subjects number /total number)**	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PL3397-A-U114	0	0	0
PL3397-A-U116	0	0	0
PL3397-A-U117	0	0	0
PL3397-A-U118	0	0	0
PL3397-A-U119	0	0	0
PL3397-A-U120	0	0	0
PL3397-A-U121	0	0	0
PLX108-01	25/132 (18.9%)	9/132 (6.8%)	0
PLX108-10	5/84 (6.0%)	1/84 (1.2%)	0

- Impaired renal function

In study PL3397-A-U124, in patients with impaired renal function, exposure is increased between 1.1 and 1.65-fold (mean 1.3-fold) for pexidartinib and 2- to 3-fold higher for the metabolite ZAAD-1006a in subjects with renal impairment ranging from mild (mean CLcr = 68.73 mL/min) to severe (mean CLcr = 19.63 mL/min) and ESRD. Based on the PopPK analysis, the Applicant proposed a reduced dose of 600 mg/day, administered as a split dose of 200 mg in the morning and 400 mg in the evening in subjects with mild to severe renal impairment, including subjects with ESRD. The predicted steady state exposure of pexidartinib at this proposed dose of 600 mg/day will be similar to subjects with normal renal function receiving a dose of 800 mg/day.

Table 3: Plasma PK parameters and statistical analysis of pexidartinib in renal impairment study

Parameter (Mean [SD])	**Renal function classification by creatinine clearance (Cockcroft-Gault Formula)**					
	Normal (n = 8)	**Mild (n = 8)**	**Moderate (n = 8)**	**Severe (n = 8)**	**ESRD A (on dialysis) (n = 8)**	**ESRD B (off dialysis) (n = 8)**
Cmax (ng/mL)	1860 (755)	2830 (709)	2140 (1190)	2240 (612)	1980 (913)	1790 (737)
Tmax (h)a	1.50 (1.00, 3.00)	1.75 (1.00, 2.50)	1.75 (1.50, 2.50)	2.50 (1.00, 4.50)	2.25 (1.50, 6.50)	2.25 (1.00, 5.00)
AUClast (ng·h/mL)	35,400 (14,900)	62,600 (25,700)	44,800 (18,200)	55,900 (26,600)	31,400 (9630)	31,800 (10,600)
AUCinf (ng·h/mL)	36,500 (15,800)	66,500 (29,200)	47,100 (20,000)	51,000 (18,000)b	32,200 (10,100)	32,600 (11,200)
t1/2 (h)	29.6 (6.80)	36.3 (10.5)	36.4 (7.27)	36.5 (13.0)b	26.6 (8.16)	26.1 (8.12)

ESRD: single 200 mg dose of pexidartinib, A: followed by HD for 4 hours; B: between HD sessions)

- Impaired hepatic function

Hepatic insufficiency had no influence on pexidartinib exposure or protein binding; however, the metabolic ratio and exposure of the metabolite ZAAD-1006a increased with subjects with moderate HI.

- Sex

The difference in exposure between sexes was relatively small.

- Race

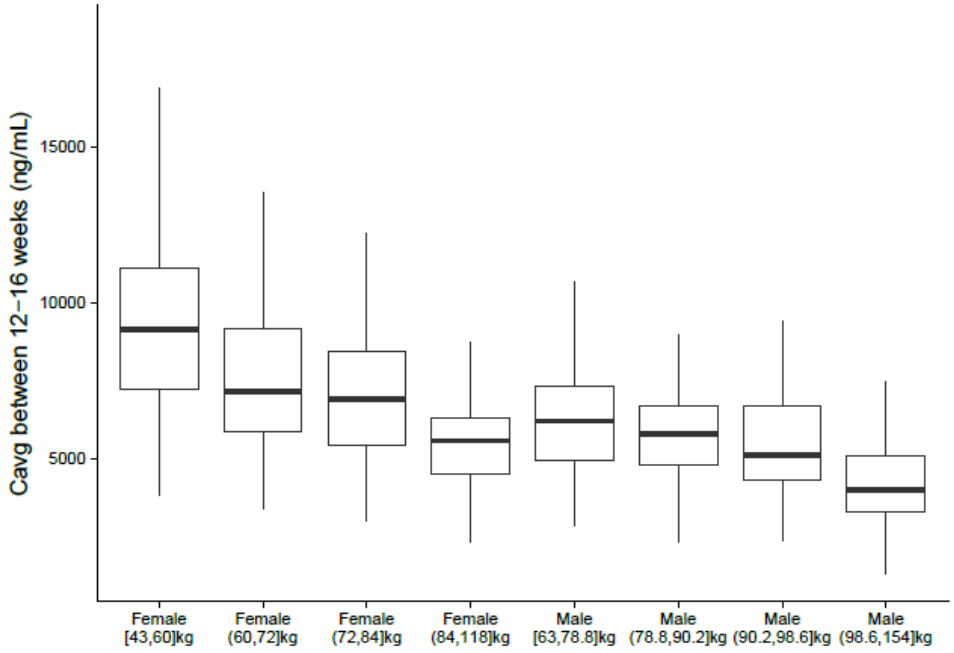
Asian subjects had a higher CL/F than non-Asian subjects. The covariate effect of race (Asian versus non-Asian) partially fell outside of the range 80% to 125%, but with a wide 95% CI.

- Weight

Covariate analysis in the PopPK analysis indicated that CL/F increased with increasing WT. When WT was at a low value of 53 kg, it resulted in a greater than 20% decrease in CL/F and an approximately 36% increase in AUC0-24,ss.

ER analyses combined for sex and weight effects revealed that median Cavg in females within the lowest BW quartile (<60 kg) was approximately 2.2-fold higher than that in males within the highest BW quartile (>98.6 kg; Figure 3).

Figure 3: Distribution of predicted Cavg by sex and body weight



Boxes depict the 25th, 50th, and 75th percentiles of the data. Vertical lines extending from the boxes (whiskers) show the 25th percentile - 1.5 × IQR and the 75th percentile + 1.5 × IQR, where IQR (interquartile range) is the distance between the 25th and 75th percentiles.

- Elderly

Age was not found to be a covariate affecting pexidartinib exposure in the PopPK analysis. Therefore, no dose adjustment is needed based on age in adult patients. The table of PK trials vs table of ages could not be found, the applicant should provide it.

- Children

Pexidartinib is not intended for use in the paediatric population; no paediatric data have been submitted.

- Exposure relevant for safety evaluations

A pooled population PK (PopPK) analysis of PK data was performed and showed that the PK of pexidartinib in healthy subjects and TGCT patients was similar, and that the multiple dose PK of pexidartinib was predictable from single dose data. The PK parameters at 400 mg after a single dose in healthy subjects and after single and multiple doses (PopPK estimates) in TGCT subjects are presented Table 4 and Table 5.

Table 4: Mean (SD) values of pexidartinib PK parameters following single and multiple doses

Dose	400 mg SD[a]	400 mg BID[b]	
		After First Dose	After Multiple Doses
Tmax (h)	2.5[c] (1.5, 8.0)	Not calculated	
Cmax (ng/mL)	4657 (1503)	3524 (1093)	8625 (2746)
AUCinf or AUC_{0-12}[d] (ng.h/mL)	87891 (31462)	21529 (5231)	77465 (24975)
Accumulation Ratio	Not applicable	Not applicable	3.6 (0.8)
$t_{1/2}$ (h)	27 (6.5)	Not calculated	
CL/F (L/h)	5.1 (1.9)	5.6 (1.6)	
Vz/F (L)	187 (50)	Vc/F = 98 L; Vp/F = 116 L	

Abbreviations: BID = twice daily; Cmax = maximum observed plasma concentration; CL/F = apparent clearance; $t_{1/2}$ = terminal half-life; Tmax = time to the maximum observed plasma concentration; SD = standard deviation.

[a] Source: Single dose PK data from Module 2.7.2, Table 6.1.

[b] Source: For the 400 mg BID regimen, PopPK predicted values in patients were reported (Module 2.7.2, Section 3.1). The multiple dose parameters indicate steady state parameter, like Cmax,ss and AUC0-12,ss.

[c] Median and range was reported for Tmax.

[d] AUC_{0-12} for BID regimen.

Table 5: ZAAD-1006a PK parameters following single and multiple doses of pexidartinib

PK Parameter (Mean [SD])	Pexidartinib 400 mg single dose	Pexidartinib 400 mg BID	
		After 1st Dose	After Multiple Doses
Tmax (h)[a]	4.5 (3.0, 8.0)	Not calculated	
Cmax (ng/mL)	3769 (1741)	4194 (2182)	13,564 (6095)
AUCinf or AUC_{0-12} (ng·h/mL)[b]	119,572 (54,743)	30,602 (12,871)	137,872 (62005)
Accumulation Ratio	Not applicable	Not applicable	4.6 (0.8)
$t_{1/2}$ (h)	26 (6.1)	Not calculated	
CL/F (L/h)	Not calculated	1.8 (0.4)	
Vz/F (L)	Not calculated	Vc/F = 24 Vp/F = 50	

Source: Module 5.3.3.1, PL3397-A-U117 CSR, Table 9.4 and Module 5.3.3.5, Report PLX3397-PMx001-ADD, Table 6.

AUC_{0-12} = area under the plasma concentration-time curve from time 0 to 12 hours postdose; AUCinf = area under the plasma concentration-time curve from time of dosing extrapolated to infinity; BID = twice daily; CL/F = apparent clearance; Cmax = maximum observed plasma concentration; CSR = clinical study report; h = hours; PK = pharmacokinetic; SD = standard deviation; $t_{1/2}$ = apparent terminal elimination half-life; Tmax = time to the maximum observed plasma concentration; Vc/F = volume of distribution of the central compartment; Vp/F = volume of distribution of the peripheral compartment; Vz/F = apparent volume of distribution.

[a] Median and range reported for Tmax.

[b] AUC_{0-12} reported for BID regimen.

Pharmacokinetic interaction studies

- *In vitro*

The non-clinical program for pexidartinib included *in vitro* studies using human biomaterials to assess e.g. plasma protein binding, metabolism and potential for DDIs. *In vitro* studies indicated that pexidartinib is likely to inhibit and induce CYP2B6 and to inhibit UGT1A1 at clinically relevant concentrations. Pexidartinib also inhibited the transport activities of MATE1, MATE2-K, OATP1B1 and OATP1B3 *in vitro*. Pexidartinib is not a substrate for active transport by OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, SMVT, OATP2B1, BCRP, BSEP, or P-gp according to non-clinical studies. No clinical studies were conducted to assess the effect of inhibition of these transporters on pexidartinib PK.

- *In silico*

Two PBPK modelling reports (Study PBPK-001 and Study PBPK-002) were submitting investigating the drug-drug interaction potential of pexidartinib with omeprazole (CYP2C19 substrate), rosiglitazone (CYP2C8 substrate), repaglinide (OATP1B1 and CYP2C8 substrate), metformin (MATE substrate), digoxin (P-gp substrate), midazolam (CYP3A substrate), and bupropion (CYP2B6 substrate). Both PBPK models were developed using the Simcyp Simulator V15 R1. The minimal PBPK model with SAC was applied in all simulations of the plasma concentration-time profiles of pexidartinib.

Pexidartinib is likely to have negligible interaction potential with substrates of CYP2C8, CYP2C19, OATP1B1 and MATE even at the highest single dose of 2400 mg or a multiple dose of 1000 mg daily dose. Pexidartinib at a single dose of 1800 mg was shown to inhibit P-gp mediated efflux of digoxin clinically (Cmax increase of 36%) and simulations showed that after single doses of 400 mg or 600 mg pexidartinib, corresponding increases of 20% and 25% were predicted. When a 1000 mg daily dose of pexidartinib is considered, the likely increase in Cmax is about 30% with a corresponding increase of about 18% in the AUC. With an 800 mg daily dose, an increase of about 27% in Cmax and 17% in AUC is predicted.

- *In vivo*

In vivo interaction studies indicated that pexidartinib is a moderate inducer of CYP3A4, a weak inhibitor of CYP2C9 (see section 4.5), but pexidartinib was not a clinically relevant inhibitor of CYP2C9 and CYP2C19 in interaction studies. Pexidartinib was a moderate inducer of CYP3A4 in the clinical interaction study.

Pexidartinib effect on other drugs (perpetrator)

Study PL3397-A-U127 aimed to determine the direct inhibitory effect of pexidartinib on the PK of omeprazole (Cytochrome 450 [CYP] 2C19) and digoxin (P-glycoprotein (P-gp)) in healthy subjects following a single dose of pexidartinib: Co-administration of pexidartinib resulted in a 37% decrease in omeprazole Cmax and a 17-23% decrease in omeprazole AUC. Similar decreases were observed for 5-hydroxy omeprazole resulting in similar metabolite-to-parent ratios (MPR). Co-administration of pexidartinib resulted in a 32% increase in digoxin Cmax and a small (8% to 9%) increase in AUCs.

Study PL3397-A-U126 aimed to determine DDIs with midazolam (CYP3A4 substrate) and tolbutamide (CYP2C9 substrate). Co-administration of midazolam with pexidartinib on Cycle 1 Day 1 (Study Day 3) resulted in a 21% decrease in area under the concentration-time curve from time 0 to the last quantifiable concentration (AUClast) of midazolam with a more pronounced decrease (52% decrease based on AUClast) observed on Cycle 1 Day 11 (Study Day 13) after multiple doses of pexidartinib. Co-administration of tolbutamide with pexidartinib on Cycle 1 Day 1 resulted in a 15% increase in the

exposure of tolbutamide based on AUClast. On Cycle 1 Day 11, when co-administered after multiple doses of pexidartinib, tolbutamide AUClast increased by 36% with no change in Cmax.

Effect of other drugs on pexidartinib (victim)

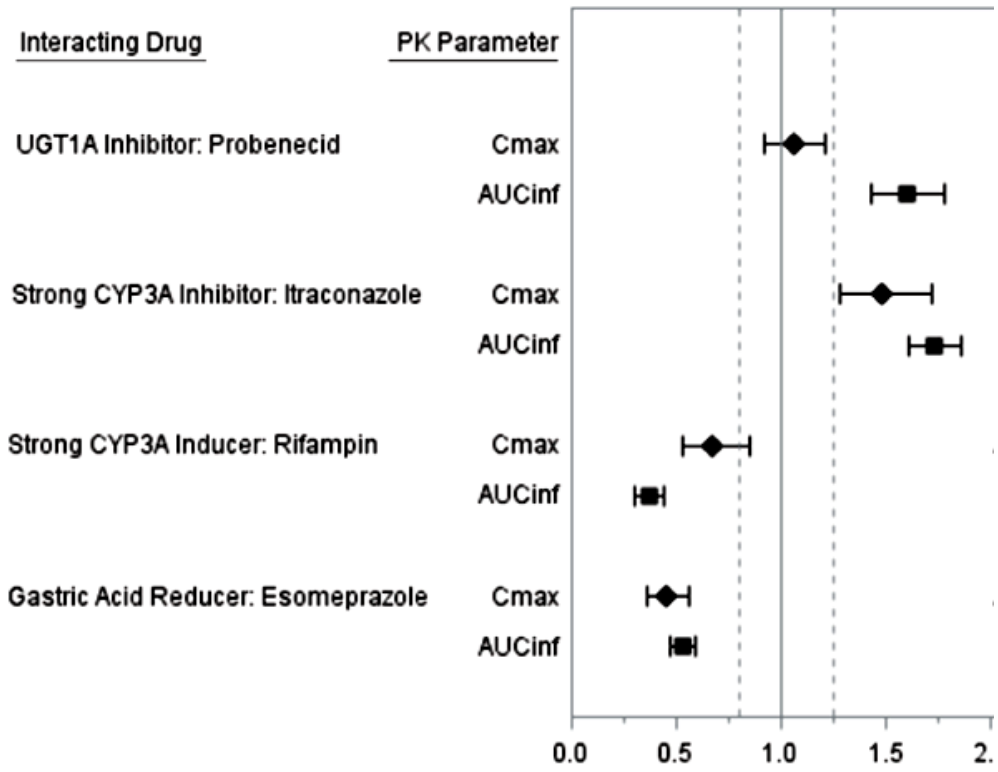
The purpose of study PL3397-AU118 was to evaluate the effects of a potent CYP3A4 inhibitor, itraconazole, on the pharmacokinetic (PK) parameters of pexidartinib and its main metabolite ZAAD-1006a, a glucuronide conjugate of pexidartinib. Compared to pexidartinib alone, co-administration of pexidartinib with itraconazole resulted in the following: For pexidartinib, Cmax increased by 48.26%, AUC0-144 increased by 70.55%, and AUCinf increased by 73.00%. For the glucuronide conjugate of pexidartinib, ZAAD-1006a, Cmax increased by 50.50%, AUC0-144 increased by 93.59%, and AUCinf increased by 97.08%. There was no change in metabolite-to-parent ratio for Cmax, but for AUCs increased by approximately 15%. There were no changes in Tmax or t1/2 with itraconazole administration.

The purpose of study PL3397-A-U122 was to assess the effect of probenecid, a general UGT inhibitor, on the PK of pexidartinib and its major metabolite, ZAAD-1006a: Cmax, AUClast, and AUCinf of pexidartinib increased approximately by 6% (Cmax) to 60% (AUCs) in the presence of probenecid compared to when pexidartinib was administered alone. For ZAAD-1006a, mean AUC increased by more than 2-fold, compared to pexidartinib alone (approximately 114% increase). Mean metabolite to plasma ratios for AUC, adjusted for molecular weight, increased by about 42% in the presence of probenecid and decreased by about 7% for Cmax.

Study PL3397-A-U119 evaluated the effects of a potent CYP3A4 inducer, rifampin, on the pharmacokinetic (PK) parameters of pexidartinib and its major metabolites. The peak and total (Cmax and AUCinf) exposure to pexidartinib was decreased in the presence of rifampin, an inducer of CYP3A4 enzyme, compared to a single dose of pexidartinib alone (approximately 33% and 64%, respectively). All subjects had lower AUC values for ZAAD-1006a with co-administration of rifampin. The mean Cmax of ZAAD-1006a (pexidartinib metabolite) was higher when rifampin was co-administered with pexidartinib, although most subjects (13 of 16) had a reduction in Cmax. The metabolite to parent ratio for AUC increased when pexidartinib was co-administered with rifampin indicating more rapid metabolism following co-administration with rifampin.

The effect of concomitant medication on the exposure of pexidartinib is shown in Figure 4.

Figure 4: Geometric mean ratio relative to reference with 90% CI



Abbreviations: AUCinf = area under the plasma concentration-time curve from time of dosing extrapolated to infinity; CI = confidence interval; Cmax = maximum observed plasma concentration. Solid black dots represent the geometric least squares mean ratio of the PK parameter when pexidartinib was administered with the concomitant medication to when pexidartinib was administered alone; whiskers represent the 90% CI.

2.4.3. Pharmacodynamics

Mechanism of action

Pexidartinib (PLX3397) is a selective inhibitor of the colony stimulating factor 1 receptor (CSF1R). This receptor is also known as feline McDonough sarcoma (FMS) kinase. CSF1R is a tyrosine kinase transmembrane receptor for colony stimulating factor 1 (CSF-1), which also known as macrophage colony stimulating factor 1 (M-CSF). CSF1R is also the receptor for interleukin (IL)-34.

Physiologically, CSF-1 is a homodimeric growth factor that regulates survival, proliferation, motility, and differentiation of cells of the mononuclear phagocytic lineage. Mononuclear phagocytes from many different tissues including bone marrow, blood, peritoneal cavity, pulmonary alveoli, and liver are capable of exhibiting a proliferative response to CSF-1.

Expansion of the TGCT tumour mass appears to be driven by the presence of abundant CSF-1 expressed by a subset of neoplastic cells within the tumour. The majority of cells in the tumour mass are non-neoplastic inflammatory cells that do not express CSF-1 but are attracted to the tumour site because of their expression of the receptor CSF1R.

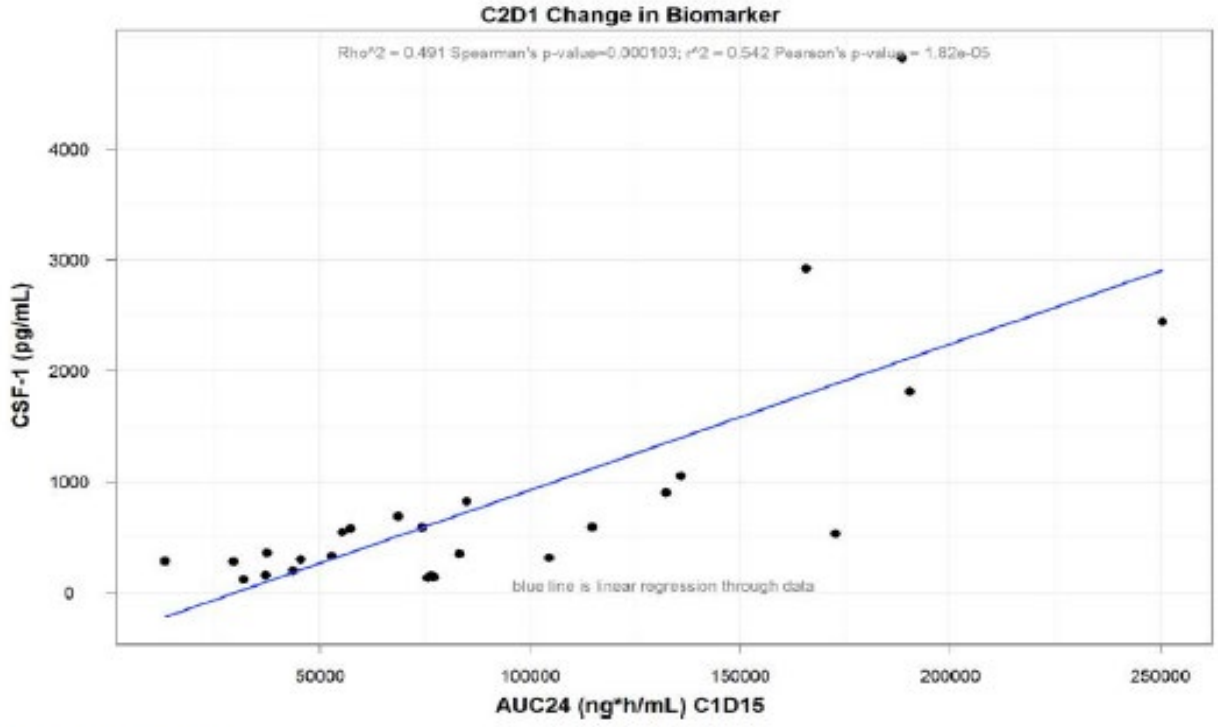
No clinical mechanism of action studies were submitted. Based on non-clinical studies, pexidartinib demonstrated potent activity against CSF1R and KIT catalytic activities, with IC50 values of 17 nmol/L and 12 nmol/L and inhibition constant (Ki) values of 1.89 nmol/L and 2.03 nmol/L, respectively. In contrast, pexidartinib was >10-fold less potent against FLT3 and KDR and exhibited minimal effects on the catalytic activities of FLT1, LCK, TRKA, TRKC, and BTK. IC50 values of the major metabolite ZAAD-1006a against recombinant human CSF1R, FLT3 and KIT were 6040, 10300 and >50000 nmol/L, respectively. IC50 values of PLX3397 HCl and ZAAD-1006a against recombinant human FLT3-ITD were 38 and 7300 nmol/L, respectively.

Primary pharmacology

- Dose-escalation phase in Study PLX108-01

Serum CSF-1 levels increased in all patients after initiation of pexidartinib dosing, as would be anticipated from Fms inhibition, resulting in reduced clearance of the ligand. Importantly, higher plasma pexidartinib exposures were associated with higher elevations of CSF-1 (Figure 5), supporting a concentration-dependent pathway inhibition with the highest CSF-1 concentration requiring the highest pexidartinib exposure. Higher pexidartinib exposures were also associated with larger decreases from baseline in urinary NTX concentrations, suggesting a concentration-dependent effect of PLX3397 on osteoclast inhibition. Clinically relevant increases in adiponectin were also observed, with 2-to 3-fold increases from baseline generally observed in patients treated at dose levels of 900 mg/day and higher.

Figure 5: Relationship between pexidartinib exposure and serum CSF-1 concentrations



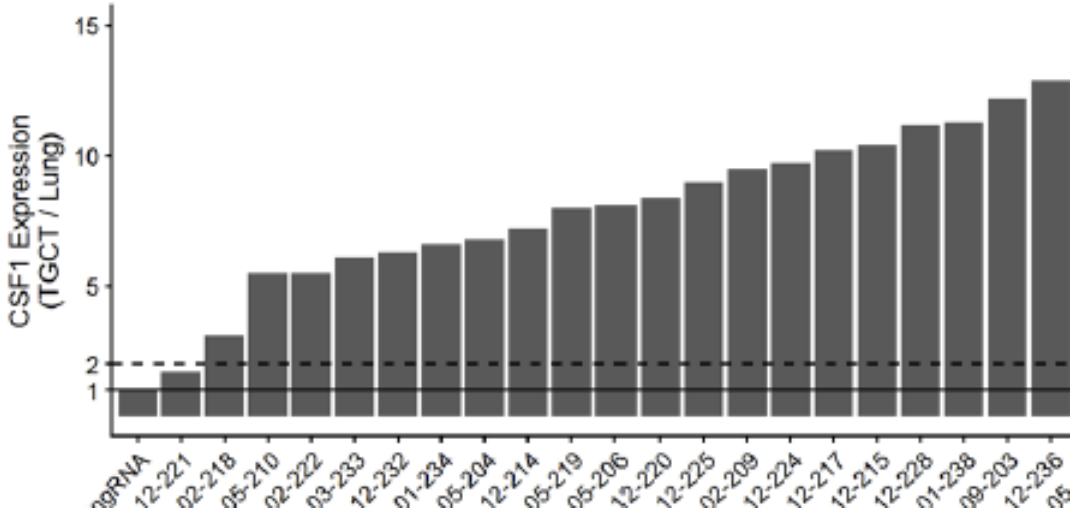
Source: Figure 14.2.16
AUC_{0-24} = area under the concentration-time curve from time zero to 24 hours; C = Cycle;
CSF1 = colony-stimulating factor-1; D = Day

Given the sensitivity of the CD14+/CD16+ ratio in monocytes to pexidartinib, relationships with PK exposures were evaluated using Run-In phase data in addition to the active treatment phase. The dataset for this analysis included 89 biomarker-PK exposure observation pairs in 36 patients, 6 of whom had data from the Run-In period. 3 of the 6 possible relationships exhibited p-values less than or equal to 0.1. However, all of the relationships were weak in both visual and statistical terms, suggesting that a plateau in the PK-PD response is achieved at very low pexidartinib doses.

CSF-1 expression and genetic alterations

Analysis and review of the sequencing data revealed two general patterns of CSF-1 rearrangement in the PVNS tissues. The most common pattern was a rearrangement near the exon8/9 junction or within exon9 (3' untranslated region; UTR) of CSF-1 which typically partnered with intergenic sequences often downstream of CSF-1 on Chromosome 1. The other common pattern was gene fusion of CSF-1 exon5/6 junction with exons of various other genes. Both patterns of CSF-1 alteration would eliminate the 3'UTR microRNA regulatory sites, suggesting a loss of negative regulation of CSF-1 gene expression. Consistent with this hypothesis, all of the PVNS tissues showed elevated CSF-1 expression relative to lung RNA control with 24 of the 25 exceeding 2-fold of lung CSF1 expression (Figure 6).

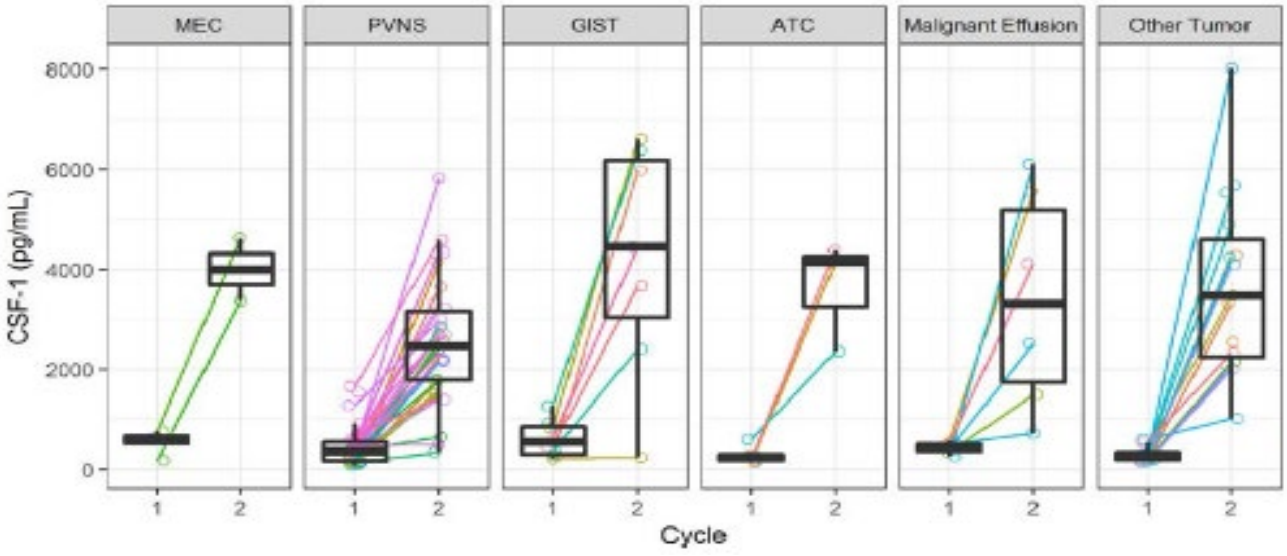
Figure 6: CSF1 expression in TGCT in relation to lung RNA control



Effects of pexidartinib (PLX3397) on CSF-1 plasma levels

Paired plasma samples for 62 patients were available for CSF-1 analysis. All cohorts showed a robust increase in plasma CSF-1 levels after 4 weeks of dosing (Figure 7).

Figure 7: Plasma CSF-1 levels at baseline and cycle 2 day 1



Study PLX108-01 Extension phase: At the RP2D dose of 1000 mg/day, 6 extension cohorts, including pigmented villonodular synovitis (PVNS), were enrolled and followed for safety and tumour response as assessed by CT scan every 8 weeks. In the PVNS extension study, there were 30 patients with paired plasma samples taken at pre-dose on study days Cycle 1 Day 1 and Cycle 2 Day 1 (Table 6).

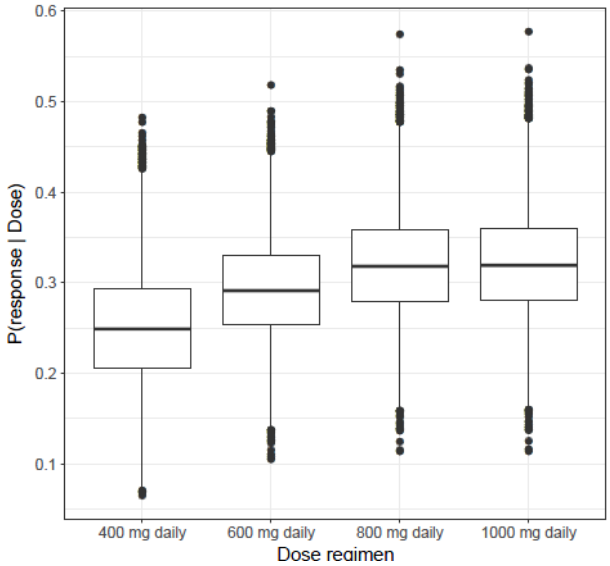
Table 6: Summary of plasma CSF-1 increase from baseline to cycle 2 day 1

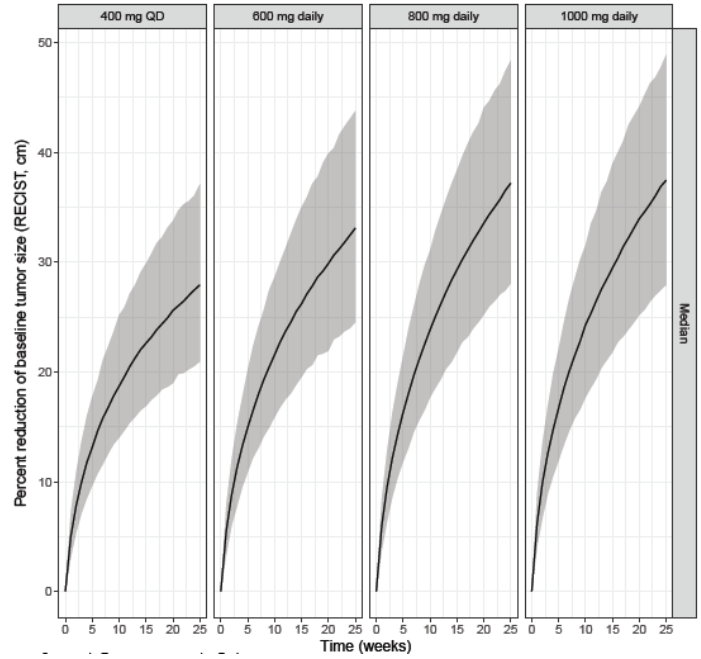
Cohort	Number of Subjects Analyzed	% Increase from Baseline		p-value[a]
		Median	Range	
MEC	2	1174.5	510–1839	0.5
PVNS	30	556	6–3147	1.9×10^{-9}
GIST	7	623	7–2104	0.016
ATC	4	2507.5	296–6031	0.125
Malignant Effusion	6	630	43–2216	0.031
Other Tumor	13	1321	69–2487	0.0002

[a] Wilcoxon Test.

Exposure-response analysis for pexidartinib was also performed. Simulations with tumour size models were done up to Week 25. Exposure-response analysis demonstrated an exposure (AUCdavg)-dependent increase in ORR by RECIST at Week 25. The relationship showed little difference in the exposure range of the 2 dose regimens tested in the Phase 3 study (Figure 8).

Figure 8: Population simulations for RECIST-based ORR at week 25 and predicted change in tumour size (RECIST) over time following pexidartinib treatment at various dosing regimens





Over a broader dose range, the probability of overall response showed an increase from 0.25 (90% CI: 0.15, 0.36) at 400 mg once daily to 0.32 (90% CI: 0.23, 0.42) at a dose of 1000 mg/day for 14 days, followed by 800 mg/day using AUCdavg as the exposure metric. The predicted probability of response rate was similar with 800 mg/day versus starting at a dose of 1000 mg/day for 14 days followed by 800 mg/day.

Overall, clinical efficacy of pexidartinib increased with increase in exposure, reaching near maximal efficacy around 800 mg/day, as the steady state exposure at 800 mg daily dose is >2 times the estimated EC50 from the exposure-response analysis (Table 7).

Table 7: Predicted AUCdavg versus EC50 in Exposure-Response Model (ORR) in Patients with TGCT

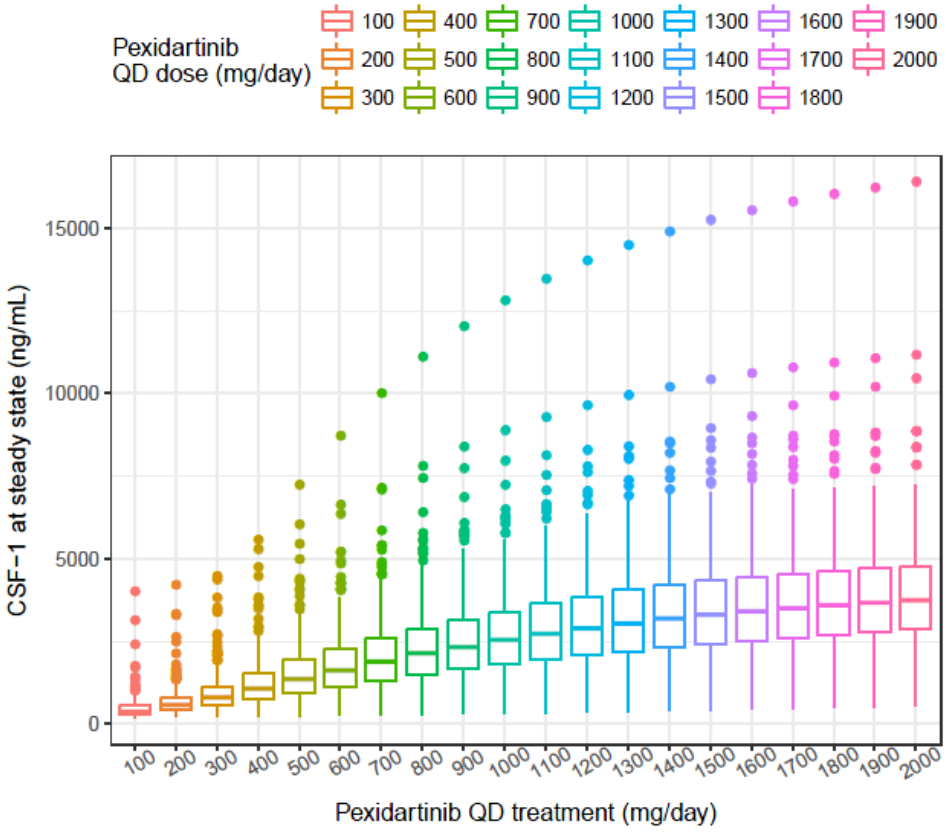
Predicted Median AUCdavg (ng.h/mL) (95% CI)	Median EC_{50} (95% CI) Based on AUCdavg (ng.h/mL) versus ORR Exposure-Response model	
	RECIST	Tumor Volume Score
144,925 (95,692, 254,929)	66,900 (4760, 911,000)	50,100 (9580, 796,000)

Abbreviations: AUCdavg = average daily area under the concentration-time curve through up to 25 weeks of dosing; AUC_{0-12} = area under the concentration-time curve from time 0 to 12 hours postdose; CI = confidence interval; EC_{50} = concentration of the drug that gives half-maximal response; h = hours; ORR = overall response rate; RECIST = Response Evaluation Criteria in Solid Tumors; TGCT = tenosynovial giant cell tumor.
Note: AUCdavg is 2 times AUC_{0-12} at steady state.

In an updated ER analysis of ORR including 113 TGCT patients from study PLX108-10, the baseline CSF-1 of responders (patients with CR or PR) was generally comparable to that of non-responders.

Pexidartinib demonstrated dose-dependent inhibition of its CSF1R target as shown by the exposure dependent increase in its PD biomarker, plasma CSF-1 concentrations. This relationship was confirmed with the direct PK/PD model of longitudinal CSF-1, which demonstrated an exposure dependent increase in plasma CSF-1 (Figure 9).

Figure 9: Simulated CSF-1 fold change from baseline at steady state by dose regimen



At 800 mg/day, the predicted steady state Cmax (8625 ng/mL) is higher than the EC50 (4430 ng/mL).

Secondary pharmacology

- Thorough QTc Study (Study PL3397-A-U125)

A double-blind, placebo- and active-controlled (open-label moxifloxacin), 3-treatment crossover study to determine the effect of pexidartinib on QTc interval in healthy subjects. Treatment groups: A, Pexidartinib 1800 mg (9 × 200 mg); B, Placebo 1800 mg (9 × 200 mg); C, Moxifloxacin 400 mg (1 × 400 mg). Thirty-six healthy subjects were enrolled in the study and all completed the study. They were randomized to 1 of the following sequences: ABC, ACB, BAC, BCA, CAB, CBA. There was a washout of at least 10 days between treatments.

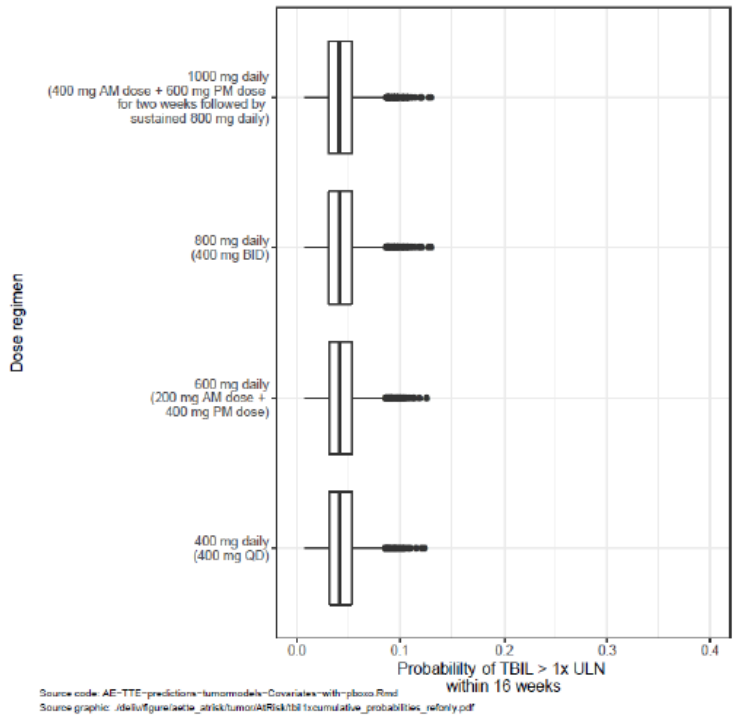
Administration of a supratherapeutic dose of pexidartinib did not prolong the QTc interval in a clinically relevant way (i.e., not more than 10 ms) and was well-tolerated in healthy subjects. No deaths or SAEs occurred. No TEAEs reported resulted in subjects discontinuing from the study. All Grade 2 and Grade 3 TEAEs reported were unrelated to the study drug. No ECG abnormalities identified in any subject were considered clinically significant by the Investigator. No vital sign or ECG findings were considered clinically relevant by the Investigator.

Dose-effect relationship

- Pexidartinib-related hepatotoxicity

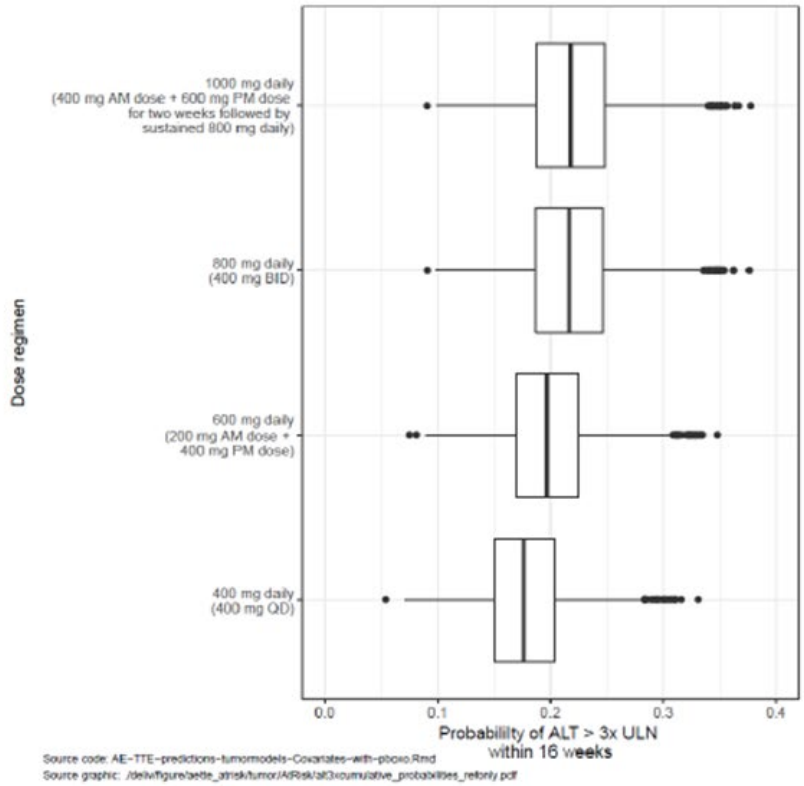
An exposure-response (ER) analysis was submitted to evaluate the relationship of pexidartinib dose to hepatic adverse reactions. The analysis showed no apparent relationship of exposure with TBIL. There was no apparent difference in probability of TBIL elevations at projected doses of 400 mg/day and 600 mg/day compared to 800 mg/day and 1000 mg/day (Figure 10).

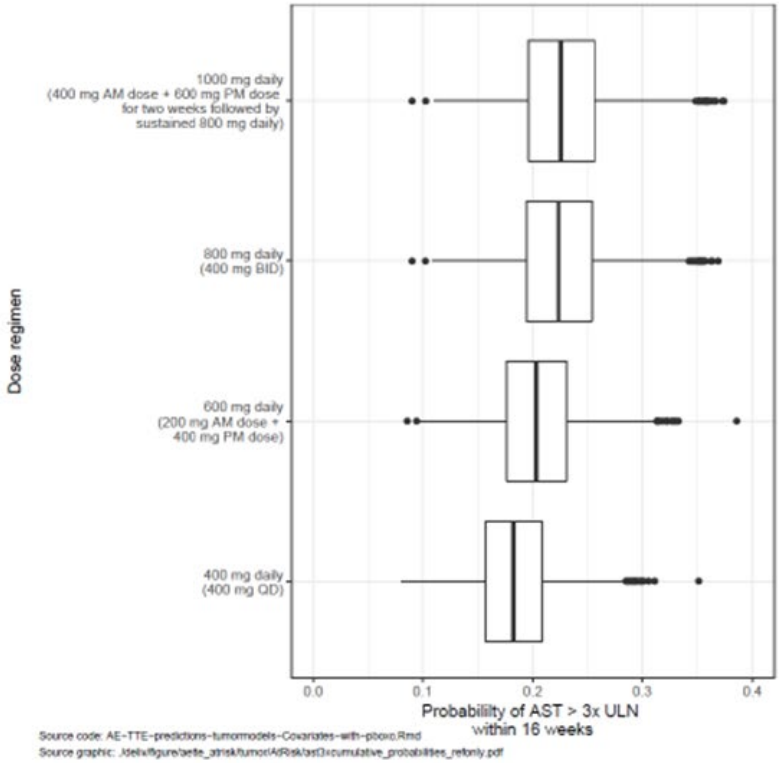
Figure 10: Predicted probability of TBIL >ULN within 16 weeks at different doses of pexidartinib



An analysis was also performed to evaluate the relationship of pexidartinib dose to hepatic enzyme elevations. This analysis showed that subjects with higher pexidartinib exposure tended to have a higher incidence and rate of ALT and AST laboratory abnormalities across the dose range of 400 mg/day to 1000 mg/day. The predicted incidence of ALT increases within 16 weeks of the start of dosing was nearly identical for the 1000 mg/day for 2 weeks followed by 800 mg/day relative to the 800 mg/day continuous dose regimen (Figure 11). For ALT and AST AEs, the incidence was predicted to be lower for the 600 mg/day and 400 mg/day regimens. These results show a clear exposure-response relationship of pexidartinib and liver enzyme abnormalities. This effect is dose-dependent, usually persists with continued treatment, and resolves upon treatment interruption. Hepatic enzyme increases in the absence of bilirubinaemia were generally low grade, asymptomatic and reversible on treatment.

Figure 11: Predicted probability of ALT >3 x ULN and AST >3 x ULN within 16 weeks at different doses of pexidartinib





Using the final ER models with Cavg as the exposure parameter and ALT >3×ULN and AST >3×ULN as the response parameters, population simulations were performed and the incidences within 16 weeks were compared by sex and BW. The incidence of ALT >3×ULN was at least 10% higher in female than in male patients of similar BW (Table 8 and Figure 12). A similar trend was observed for AST >3×ULN (Table 9 and Figure 13).

Table 8: Predicted ALT >3xULN by sex and BW

Gender	Body weight (kg)	Pr(ALT 3xULN)*
Female	[43,60]	0.328 (0.132-0.616)
Female	(60,72]	0.342 (0.173-0.573)
Female	(72,84]	0.329 (0.209-0.535)
Female	(84,118]	0.268 (0.0669-0.746)
Male	[63,78.8]	0.205 (0.0546-0.358)
Male	(78.8,90.2]	0.147 (0.106-0.366)
Male	(90.2,98.6]	0.153 (0.101-0.489)
Male	(98.6,154]	0.182 (0.101-0.41)

Body weight categories were defined by weight quartiles in female and male
* median and 90% credible interval.

Figure 12: Predicted ALT >3xULN by sex and BW

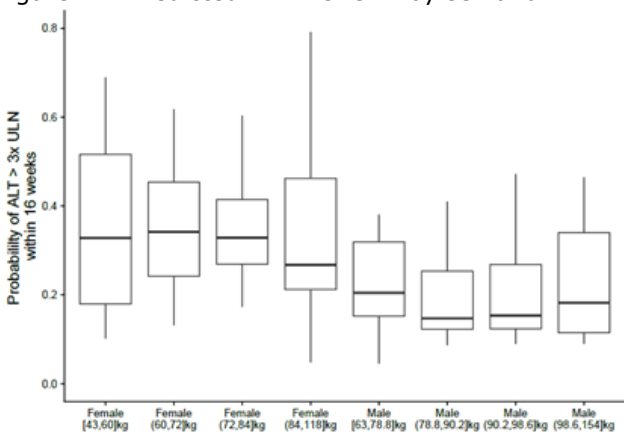
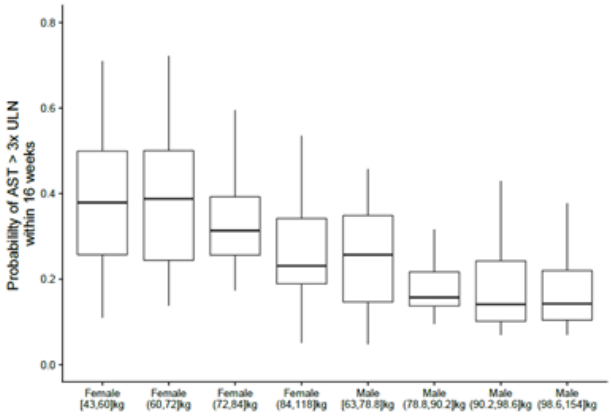


Table 9: Predicted AST >3xULN by sex and BW

Gender	Body weight (kg)	Pr(AST 3xULN)*
Female	[43,60]	0.379 (0.153-0.631)
Female	(60,72]	0.388 (0.196-0.645)
Female	(72,84]	0.313 (0.203-0.581)
Female	(84,118]	0.231 (0.072-0.621)
Male	[63,78.8]	0.257 (0.06-0.436)
Male	(78.8,90.2]	0.157 (0.118-0.306)
Male	(90.2,98.6]	0.141 (0.0802-0.514)
Male	(98.6,154]	0.143 (0.0851-0.342)

Body weight categories were defined by weight quartiles in female and mal
* median and 90% credible interval.

Figure 13: Predicted AST >3xULN by sex and BW



Based on exploratory graphical analysis, higher pexidartinib and ZAAD average concentration during the first two weeks of dosing were associated with faster onset and higher incidence of elevated ALT (3- and 5-fold ULN) and AST (3- and 5-fold ULN) but not TBIL (above ULN and 2-fold baseline). Due to the high correlations between average pexidartinib and ZAAD-1006a concentrations, the models were not able to identify whether pexidartinib or ZAAD exposure drives the risk of AEs.

Further ER analyses were submitted as basis for new sex- and body weight-based dosing recommendations to reduce pexidartinib exposure and hereby the ALT/AST-elevation risk. Based on the new modelling (Table 10 and Figure 14), a dose reduction by 200 mg/day is generally proposed for females and an additional reduction by 200 mg/day in low weight female and male patients.

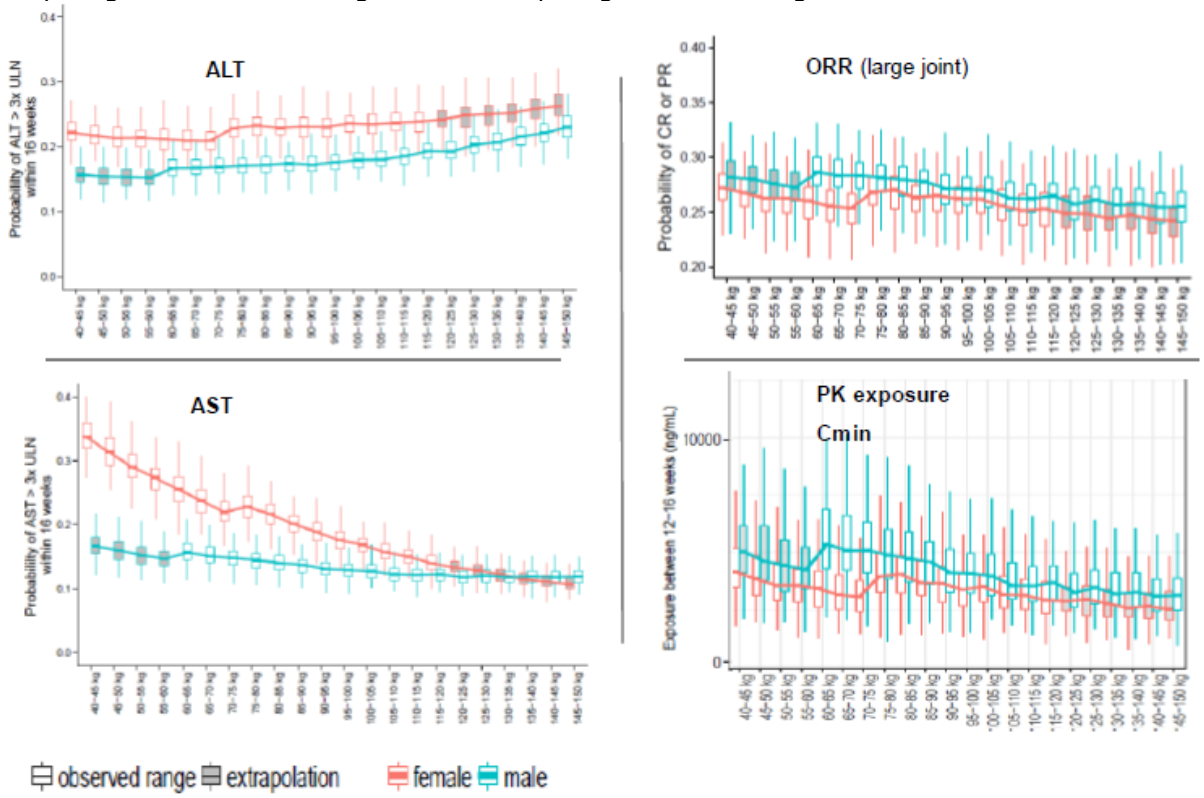
Table 10: Predicted probability (Pr, mean and 90% credible interval) of event (risk of ALT/AST >3 x ULN or ORR), by sex and body weight when dosed using sex- and body weight-based dosing

Sex	Dose (mg/day)	Pr ALT >3 × ULN	Pr AST >3 × ULN	Pr ORR (large joint)
Female <75 kg	400	0.214 (0.183 – 0.252)	0.274 (0.205 – 0.362)	0.262 (0.228 – 0.295)
Female ≥ 75 kg	600	0.240 (0.203 – 0.284)	0.152 (0.102 – 0.234)	0.255 (0.217 - 0.288)
Male < 60 kg	600	0.155 (0.130 – 0.183)	0.157 (0.127 – 0.191)	0.277 (0.241 – 0.308)
Male ≥ 60 kg	800	0.185 (0.151 – 0.238)	0.129 (0.104 – 0.167)	0.269 (0.232 – 0.303)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BW = body weight; ORR = overall response rate; Pr = predicted probability; ULN = upper limit of normal

Note: Results from large joint reported here. As ORR for small and large joints are proportional, ORR of either of them can be utilized for data presentation.

Figure 14: Predicted probability of event (risk of ALT/AST >3 x ULN or ORR) and median cmin, by sex and body weight when dosed using sex- and body weight-based dosing



ALT = alanine aminotransferase; AST = aspartate aminotransferase; BW = body weight; Cmin = minimum plasma concentration; CR = complete response; ORR = overall response rate; PK = pharmacokinetic; PR = partial response; ULN = upper limit of normal

Note: Females: 400 mg/day for BW <75 kg; 600 mg/day for BW ≥75 kg

Note: Males: 600 mg/day for BW <60 kg; 800 mg/day for BW ≥60 kg

Note: Results from large joints reported here. Predicted ORR for small joints presented in A4-Q17.

Additional ER analyses assessed whether circulating CSF-1 level was a potential prognostic or predictive factor for safety:

- The risk of ALT and AST AEs (>3xULN, >5xULN) increased when baseline CSF-1 decreased from 450 ng/mL (75th percentile) to 220 ng/mL (25th percentile).
- The incidence of cognitive disorder was estimated to be slightly higher in TGCT subjects than non-TGCT subjects. Higher baseline CSF-1 was estimated to be associated with a slightly increased risk of cognitive disorder.

2.4.4. Discussion on clinical pharmacology

- Pharmacokinetics

The pharmacology dataset contains data from 16 clinical studies, of which 2 were performed in patients, and from 3 PopPK models, which is comprehensive and, overall, allowed for detailed assessment. Various capsule formulations have been utilized during clinical development, and all relevant PK results are available from the proposed commercial formulation (J-3397-AF optimized) or its bioequivalent pre-optimized formulation.

The free base pexidartinib (MW 417.81 g/mol) is poorly soluble at physiological pH but shows a high permeability. The fact that increase of gastric pH by esomeprazole reduces its exposure to about 50% and a low-fat or high-fat meal increase exposure to 160% or 200%, respectively, are corroborating this. In view of the twice-daily administration and considering the dose adjustment recommendations for strong CYP3A4 inhibitors, explicit recommendations with regard to food were reflected in the proposed SmPC; accordingly, the recommendation is to take pexidartinib in fasted state only (i.e., at least 1 hour before or 2 hours after a meal, at approximately the same times of the day and approximately 12 hours apart).

In vitro studies with human hepatocytes revealed a complete (100%) metabolism of pexidartinib by CYP3A4 and 3A5, and to lesser extends by CYP2D6 (65%) and 2C8, 2C9, and 2C19 (27%) into 12 different radioactive metabolites. By UGT1A4, pexidartinib was *N*-glucuronized (25%) to its main metabolite ZAAD-1006a. The applicant acknowledged that in human also an N-dealkylation reaction occurs resulting in M1 and a trifluoromethyl-pyridine derivative (M12), and proposed that its formation is 1:1 proportional with M1 which is found with 5.4% in urine, so that its (M12) impact on efficacy and safety would be low. However, it was not unequivocally shown that M12 is clinically irrelevant; the applicant therefore has to further analyse M12 levels in the ongoing clinical study PL3397-A-U129.

Pop PK modelling and inter-occasion variability data together with a consistency of T1/2 with observed accumulation, did not indicate time-dependency for the PK of pexidartinib.

A reason for the high inter-occasion variability in absorption (absorption rate constant KA and bioavailability F1) may be the intake of food (and the type of food) as well as the physiological day to day variations within individual patient.

The overall PK behaviour of the major metabolite ZAAD-1006a was similar to that of parent drug pexidartinib, with a comparably long t1/2 and an >4.5-fold accumulation with multiple dosing. Though inactive at the target structures at usual exposures, it was evaluated regarding exposure-safety relationship. No other identified and/or detected metabolites were pharmacologically characterised.

Female patients had ~15% lower clearance and 15-20% higher AUC and Cmax than males for parent and metabolite. This is considered one reason for the trend that females suffered from more severe and more serious AEs than males, especially hepatotoxicity (see below).

In the dedicated RI study upon haemodialysis the exposure of pexidartinib was similar in patients and healthy subjects, indicating that pexidartinib was adequately dialyzed/removed from the blood, due to its MW <500kDa. In contrast, for the glucuronide metabolite ZAAD-1006a, which is excreted via urine only, there was an up to 200-fold high plasma accumulation, even higher than after CYP3A4 inhibition. This is due to the fact that this molecule is too large to be sufficiently removed by HD, which is less effective for molecules of 500-2000kDa. Data from ESRD subjects were not included in the popPK analysis.

Based on the submitted simulations, dose reductions to 600 mg per day (200 mg in the morning and 400 mg in the evening) for RI patients were acceptable.

Pexidartinib PK was less affected by mild or moderate HI; however, CIs widths extended far beyond the 80-125% limits so that an effect of HI on the PK of pexidartinib cannot be ruled out. A dose adjustment for patients with mild to moderate hepatic impairment on the basis of PK alone is however not required. The effect of severe hepatic impairment on pexidartinib PK was not evaluated.

Based on safety findings, pexidartinib is contraindicated in patients with hepatic impairment, that is, with persistent elevations of transaminases or bilirubin above 1 x the upper limit of normal or with active liver or biliary tract disease.

- Modelling

Population PK modelling gave estimations of pexidartinib Vc at 98L and Vp at 116L, consistent with the results from the studies. These values indicate good tissue penetration. Pexidartinib is highly protein bound (>99%) in human plasma.

A population pharmacokinetic model for ZAAD-1006a was developed using data from 40 volunteers with different degrees of renal impairment. Results are that patients with renal impairment (CrCl < 90 mL/min) are expected to have an about 1.5- to 3-fold increase in exposure (AUC) compared to patients with normal renal function. Dose adjustments are required in patients with renal impairment.

In addition, high RSE for creatinine clearance on pexidartinib CL (RSE = 116%) was reported. This was similarly high for ZAAD-1006a. The Applicant provided updated PK models using pooled dataset including renal impaired patients and a detailed discussion. Pooling the data broadens the range of the CrCL, but the relative contribution of renal function-impaired patients compared to patients with normal renal function is low, which is a limitation of this approach. Overall results from the updated model, using a pooled dataset, were similar compared to the previous model. A statement in the proposed SmPC was included reflecting the knowledge gained from the population analysis for renal impairment for pexidartinib and the metabolite, although the data from renally impaired patients are limited.

A PopPK model to assess the effect of race on pexidartinib pharmacokinetics showed race was a significant covariate, but the effect on exposure was limited. There were limited data in Asian subjects (6%); therefore, these results should be interpreted with caution.

With respect to body weight, exposure was similar across the study population, so that no dose adjustment based on body weight alone is warranted. Further, the predicted effect of increasing exposure with decreasing body weight was in the range of 80%-125%, except for that at the extreme low value of 53 kg (the 5th percentile weight). Therefore, the proposed SmPC section 5.2 reads that based on a PopPK

analysis, pexidartinib pharmacokinetics is affected by body weight with an increase in exposure with lower body weight, but in most cases the increase in exposure is less than 20%.

- DDI

Non-clinical and clinical studies dedicated to investigating the potential of pexidartinib for drug-drug interaction showed that clinically relevant interactions on the level CYP and UGT enzymes and systemic gastric acid reducers can be expected. This is true for pexidartinib effects on other drugs (as a perpetrator) and effects of other drugs on pexidartinib (as a victim).

With regard to pexidartinib as a perpetrator, a multiple-dose DDI study (Study PL3397-A-U126) evaluated the effect of pexidartinib on the PK of CYP3A4 (midazolam) and CYP2C9 (tolbutamide) substrates. Based on the study results, the proposed SmPC was updated to state that co-administration of Turalio 800 mg daily decreased midazolam (CYP3A4 substrate) Cmax by 28% and AUC by 52% compared to midazolam alone and increased tolbutamide (CYP2C9 substrate) AUC by 36%.

Pexidartinib did not affect the CYP2C19 mediated metabolism of omeprazole as the MPR of 5-hydroxy omeprazole to omeprazole was similar when omeprazole was administered alone versus when co-administered with pexidartinib, can be followed. Slightly decreased AUC and Cmax of omeprazole and its metabolite when concomitantly taken with pexidartinib indicated, however, a possible interaction not related to CYP2C19. The effects were thought to be likely due to a physicochemical interaction between omeprazole and the large amount of pexidartinib and/or excipients resulting from the single-dose design employed in this study where nine capsules of pexidartinib were co-administered with omeprazole to match pexidartinib steady state Cmax and AUC in patients. This number of capsules (9 x 200 mg) is 4.5-times greater than the number administered at the highest typical dose of pexidartinib (2 x 200 mg capsules). It was concluded that pexidartinib does not inhibit CYP2C19 at clinically relevant concentrations.

Co-administration of pexidartinib resulted in a 32% increase in digoxin Cmax and a small (8% to 9%) increase in AUCs. This mild interaction would probably not be regarded of clinical significance. As argued by the Applicant, the IC50 for BCRP and P-gp was similar in the non-clinical study OPT-2015-066 (BCRP 42.6 µM and P-gp 43.4 µM), which indicates that the DDI risk for BCRP would be similar under the conditions of the provided clinical study. Non-clinical studies indicated that pexidartinib inhibited various transporter activities, e.g. of multidrug and toxic compound extrusion (MATE)1, MATE2-K, OATP1B1, OATP1B3, OATP2B1, and P-gp and, to a lesser extent, BCRP. Consequently, the results of the *in vitro* evaluations were included in the proposed SmPC, indicating possible effects on OATP1B1 (e.g. statins) and MATE (e.g. metformin) based on *in vitro* results.

Pexidartinib as a victim was investigated in three clinical studies. When co-administered with the potent inhibitor of CYP3A4 itraconazole, the pexidartinib peak (Cmax) and total exposure (AUC) increased by approximately 50% and 70%, respectively. Additionally, consistent with increased exposure of parent, co-administration of pexidartinib with itraconazole resulted in a higher exposure of the glucuronide conjugate ZAAD-1006a, as peak (Cmax) and total exposure (AUCinf) of this metabolite rose by 50% and 97%, respectively. The M/P molar ratio was increased by approximately 17% compared to pexidartinib alone. It is possible that as the CYP3A4 pathway of metabolism is inhibited, relatively more parent drug goes through the UGT-mediated metabolic pathway leading to increased formation of the glucuronide metabolite ZAAD-1006a. Co-administration of pexidartinib with strong CYP3A inhibitors should be avoided and, if strong CYP3A inhibitors need to be administered, a reduced daily pexidartinib dose of 400 mg (200 mg BID) should be considered, (see section 4.2 of the proposed SmPC). In addition, the effects of a

moderate CYP3A4 inhibitor were modelled and indicated a 65% increase of steady-state pexidartinib exposure. Therefore, a dose reduction also in combination with moderate CYP3A4 inhibitors is recommended.

Study PL3397-A-U122 evaluated the effect of probenecid, a general UGT inhibitor, on the PK of pexidartinib and its major metabolite, ZAAD-1006a. The increase of the glucuronide metabolite ZAAD-1006a during treatment with the UGT inhibitor probenecid is unexpected. It is a theoretical consideration that the increased total exposure of ZAAD-1006a when co-administered with probenecid, which is also an inhibitor of OAT, is likely due to decreased renal elimination of ZAAD-1006a via OATs in the kidney. Moderate increased levels of the metabolite ZAAD-1006a are not of concern, since ZAAD-1006a is minimally active pharmacologically and, in a monkey toxicity study was not associated with any toxicity at an exposure higher than the predicted steady state exposure in patients with TGCT. Co-administration of pexidartinib with UGT inhibitors should be avoided and if UGT inhibitors need to be administered, a reduced daily pexidartinib dose should be considered (see section 4.5 of the proposed SmPC).

Study PL3397-A-U119 documented effects of a potent CYP3A4 inducer, rifampin, on the pharmacokinetic (PK) parameters of pexidartinib and its major metabolites. Co-administration of strong CYP3A inducers with pexidartinib should be avoided as mild to moderate effects on Cmax and AUC have been shown with rifampin.

With respect to co-administration of pexidartinib with moderate CYP3A4 inducers, the efavirenz PBPK model was not sufficiently qualified for its purpose and no conclusion can be drawn. Accordingly, the use of moderate and strong CYP3A4 inducers should be avoided, as reflected in the proposed SmPC (section 4.5).

Pexidartinib is a CYP3A4 substrate and induction of this enzyme, even by mild inducers, may result in increased pexidartinib metabolism. The Applicant discussed the possibility of the metabolite M12 containing a pyridine moiety to exert toxic effects in the liver. M12 is formed by oxidation so that CYP enzymes could be involved. Oxidative N-dealkylation of pexidartinib is expected to be mediated through various CYP isozymes including CYP3A4. Since various CYP isozymes are involved, any DDIs increasing the formation of M12 could be of concern if the generated M12 could be expected to reach levels of unacceptable toxicity.

- Pharmacodynamics

The serum CSF-1 level is the most relevant PD response biomarker for pexidartinib activity in TGCT.

In the dose escalation part of study PLX108-01, CSF-1 levels increased in all patients after initiation of PLX3397 dosing in a concentration-dependent pathway inhibition. Doses of 1000 mg/d were needed for near maximal increases in CSF-1 concentrations although a significant increase could be still achieved at doses of 400 mg/day. This rise in plasma CSF-1 levels may be the result of a compensatory mechanism or a decrease in receptor mediated clearance of the cytokine.

The characterization of *CSF1* expression and genetic alterations in TGCT samples from study PLX108-01 suggests a loss of negative regulation of *CSF1* gene expression. In addition, all of the TGCT tissues showed elevated *CSF1* expression which suggests an important role for CSF1 and its receptor CSF1R in the pathogenesis of the disease. However, no correlation of anti-tumour activity with CSF-1 concentrations has been established. The relevance of CSF-1 levels as a predictive biomarker for pexidartinib efficacy remains unclear.

In contrast, exposure-safety analyses found that baseline CSF-1 levels were inversely correlated with the risk of pexidartinib AEs of ALT and AST increases above 3x/5xULN. Patients in the 4th quartile of CSF-1

levels (≥ 465ng/ml) had an about 2-fold less probability of AST/ALT elevations compared to the lowest quartile < 211ng/ml). However, based on current data no conclusions can be drawn for CSF-1 levels at baseline as a potentially prognostic tool for safety.

PopPK modelling was used to investigate exposure-response for hepatic injury of Hy's law; however, the modelling underpredicted the measured pexidartinib concentrations for some patients. Based on this, an exposure-response relationship was observed, where all 4 patients with hepatic injury (all 4 started with 1000 mg dose/day; 3 of 4 were female; weight was <69kg in 3 of 4) had C1D15 steady-state pre-dose concentrations in the upper range of observed values.

There was no difference in probability of TBIL elevations at projected doses of 400 mg/day and 600 mg/day compared to 800 mg/day and 1000 mg/day (Figure 10). This lack of dose-response relationship is possibly due to the low incidence rate for TBIL related AE. However, it may also reflect the lack of dose dependence of mixed or cholestatic hepatotoxicity.

For ALT and AST AEs, the incidence was predicted to be lower for the 600 mg/day and 400 mg/day regimens. These results show a clear exposure-response relationship of pexidartinib and liver enzyme abnormalities. This effect is dose-dependent, usually persists with continued treatment, and resolves upon treatment interruption. Hepatic enzyme increases in the absence of bilirubinaemia were generally low grade, asymptomatic and reversible on treatment.

It had already initially been modelled (report PMx-002) that the probability of certain liver enzyme increases was higher above an, arbitrarily set, average concentration (Cave) of 5000 ng/ml. Similarly, it was shown that female gender and low body weight were associated with increased exposure and lower clearance of pexidartinib. While each of these covariates on its own was not deemed clinically relevant, the relation of both as combined risk factors was further analysed and clearly indicated that females have an overall 2.2-fold increased risk for hepatotoxicities compared to males with a flat dosing of 400mg twice daily; thus, female patients would need to reduce the dose by 50% (from 800 mg/day to 400 mg/day) to have a similar risk of elevated liver enzymes compared to male patients. Predictions showed that also within the sex subgroups, the probabilities of liver enzyme increase varied in inverse correlation to weight. Simulations for AST gave predictions similar to ALT.

The relationship of dosing and ORR probability showed little difference in the exposure range of the 2 dose regimens tested in the Phase 3 study, consistent with the clinical efficacy results. At 800 mg/day, the predicted steady state Cmax (8625 ng/mL) is higher than the EC50 (4430 ng/mL) and, therefore, the response was closer to Emax at this dose. However, this result (predicted Cmax) should be viewed with caution given the high shrinkage observed on Vc/F (34%) and the trend to over-predict Cmax as shown with the predictive performance of the developed PopPK model. In addition, lower doses of pexidartinib had less effect on CSF-1, showing less effective inhibition of CSF1R.

The probability of ORR was predicted to decrease in case of (flat) dose reductions. However, TGCT is not rapidly deteriorating and thus, there is no imperative medical need to start with the highest recommended dose for best response probability, in particular in view of the risk of hepatotoxicity especially in female patients.

Exposure-safety analyses suggested that therapeutic drug monitoring (TDM) of pexidartinib trough levels was a relevant option, with a Cmin target that maximised ORR and minimised liver enzyme elevation-potential for individual dose titration, based on gender and weight. In response to a corresponding request, the applicant argued against TDM, citing too many covariates are associated with liver toxicity,

thus TDM may not decrease the risk. Indeed, fixing C_{min} would be based on assumptions at this time and not on exposure-safety data such as expected from the post-authorisation study to be conducted.

Since Cavg is predictive of both efficacy and safety endpoints, and since Cmin is correlated to Cavg with results similar to Cavg, assessing Cmin in a clinical study (such as the post-authorisation study to be conducted) will help to optimise the use of pexidartinib.

The combined sex- and body weight-based dose reductions (Table 10), together with an overall dose reduction of 200 mg/day for elderly ≥ 65 years of age, are appropriate based on current knowledge from ER models, which indicate that the probability of a tumour response would not be reduced to a relevant extent, but the probability of ALT and / or AST elevations would be reduced.

These dose recommendations and reductions have to be evaluated in a post-authorisation study in order to improve ER models and to support effective and safe dosing of pexidartinib; the protocol of the post-authorisation study to be conducted yet has to be agreed.

The thorough QTc study shows no QT prolongation at pexidartinib supratherapeutic dose. No QT prolongation adverse event was reported in the TGCT studies.

2.4.5. Conclusions on clinical pharmacology

Non-clinical and clinical studies dedicated to investigating the potential of pexidartinib for drug-drug interaction showed that clinically relevant interactions at the level of CYP and UGT enzymes and systemic gastric acid reducers can be expected, for pexidartinib effects on other drugs and effects of other drugs on pexidartinib.

Pexidartinib was specifically designed to inhibit CSF1R, the receptor for CSF-1 and IL-34. The serum CSF-1 level is the most relevant PD response biomarker for pexidartinib activity in TGCT. Doses of 1000 mg/d pexidartinib were needed for near maximal increases in CSF-1 concentrations although a significant increase could be still achieved at doses of 400 mg/day. Nevertheless, no correlation of anti-tumour activity with CSF-1 concentrations has been established.

The ER analyses underline the clinical findings that efficacy was similar with daily 800 mg and safety was better at the tested lower doses. Female gender and low body weight as well as higher age are definitive risk factors for liver damage due to high exposure/low clearance of pexidartinib. The gender- and body weight-based dose recommendations are an adequate start to treat TGCT patients in clinical practice. Since these are based on ER model estimations only, the post-authorisation study to be conducted should include PK sampling and to reported improved ER models.

In addition, frequent monitoring for signs of liver toxicity (including tests of liver enzyme levels) during the first cycles (SmPC section 4.4) is necessary to reduce the risk of hepatic damage due to high pexidartinib levels (see discussions on clinical safety for further detail).

2.5. Clinical efficacy

The efficacy of pexidartinib in the initially claimed indication is mainly supported by the results of trial 2014-000148-14 (PLX108-10), a randomised, placebo-controlled therapeutic-confirmatory trial of pexidartinib in adult patients with TGCT in whom surgical resection would have been associated with potentially worsening functional limitation or severe morbidity.

Table 5: Overview of main clinical studies in TGCT

Study ID	Design	Study Posology	Study Obj.	Subjs by arm entered/ compl.	Gender M/F Median Age	Diagnosis Incl. criteria	Primary End point
PLX108-10 Phase 3 ongoing *Pivotal study*	2-part, Double blind randomized, controlled study	1000 mg/d for 2 weeks then 800 mg/d	Efficacy, safety, PD, PK	Planned: 126 subjects; Actual: 120 subjects: 61 subjects Pexidartinib ; 59 subjects palcebo	pexidartinibM: 42.6% F: 57.4% 44.6 yrs placebo: M: 39% F: 61% 44.3 yrs	A diagnosis of TGCT where surgical resection would have been associated with potentially worsening functional limitation or severe morbidity (locally advanced disease), with morbidity having been determined consensually by qualified personnel (eg, 2 surgeons or a multi-disciplinary tumour board).	ORR (CR+PR) recist 1.1 criteria
Study PLX108-01 Ongoing Supportive study	first-in-human dose escalation study with an Extension cohort phase	Extension TGCT cohort: the RP2D dose of 1000 mg/day of pexidartinib	Efficacy, safety in TGCT, PD via plasma and urine biomarkers	39 TGCT patients	M : 17 (43.6%) F :22 (56.4%) 45.1 yrs	Histologically confirmed diagnosis of inoperable progressive or relapsing PVNS, or resectable tumour requiring mutilating surgery, as well as demonstrated progressive disease in the last 12 months.	ORR

2.5.1. Dose response study(ies)

- PLX108-01

Phase 1 Study to Assess Safety, Pharmacokinetics, and Pharmacodynamics of PLX3397 in Patients with Advanced, Incurable, Solid Tumours in which the Target Kinases Are Linked to Disease Pathophysiology.

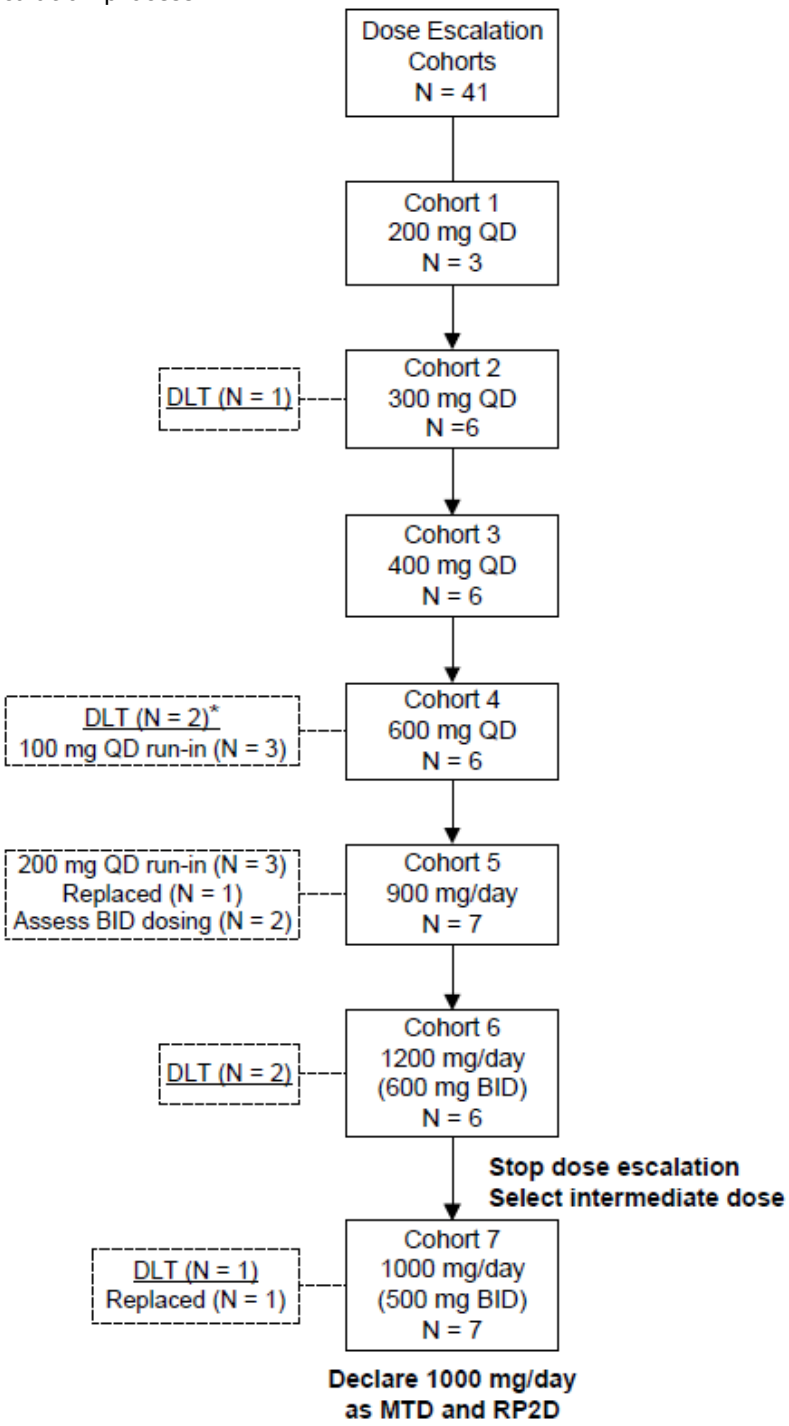
This was a first-in-human dose escalation study with an Extension cohort phase. The dose escalation phase of the study was an open-label, ascending dose study of daily oral doses of pexidartinib administered to subjects with solid tumours in order to evaluate PK and observed toxicity. Once the recommended phase 2 dose (RP2D) was reached, an additional 6 extension cohorts were enrolled (Figure 15).

- Study Initiation: Dose Escalation Phase:
- First Patient Screened: 01 October 2009
- First Patient Dosed: 08 October 2009
- Study Completion: Last Dose Escalation Patient Completed Dosing: 23 April 2012
- Last Dose Escalation Study Visit: 24 April 2012

Each patient in the dose escalation phase of the study was to receive the designated dose of pexidartinib for 4 weeks, and then was offered continued dosing with pexidartinib if it was well tolerated and in the absence of tumour progression. Forty-one patients enrolled in 7 dose escalation cohorts and received pexidartinib in dose levels ranging from 200 mg once daily to 1200 mg/day.

Forty-one patients enrolled in 7 dose escalation cohorts and received study drug, including 3, 6, 6, 6, 7, 6, and 7 patients in Cohorts 1 (200 mg once daily), 2 (300 mg once daily), 3 (400 mg once daily), 4 (600 mg once daily), 5 (900 mg/day), 6 (1200 mg/day), and 7 (1000 mg/day).

Figure 15: Dose escalation process



Source: Listing 16.2.1.1, Listing 16.2.5.11, Listing 16.2.7.20, Listing 16.2.7.21; Patient Tracker generated by Clinical Project Manager

BID = twice daily; DLT = dose limiting toxicity; MTD = maximum tolerated dose; QD = once daily; RP2D = recommended Phase 2 dose

* One patient in Cohort 4 experienced a DLT of lymphopenia that was subsequently exempted as a DLT by Amendment 4.

The RP2D was based on dose-limiting toxicities in patients with solid tumours at a basis of daily oral dosing of pexidartinib in 28-day cycles. The MTD and identified RP2D was 1000 mg/day administered as a split dose. Of note, the only DLT reported by more than 1 patient was AST increased (2 patients). These DLT of grade 3 increased AST occurred in cohort 6 (1200 mg daily split into two doses) and 7 (1000 mg daily split into two doses).

The RP2D of 1000 mg/day was further used in the TGCT cohort in the extension phase of study PLX108-01. This was supported by the TGCT PD biomarker, circulating CSF-1, for which near-maximal responses required doses of 1000 mg/d.

2.5.2. Main study(ies)

2014-000148-14 (PLX108-10): Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in adult Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumour of the Tendon Sheath (ENLIVEN)

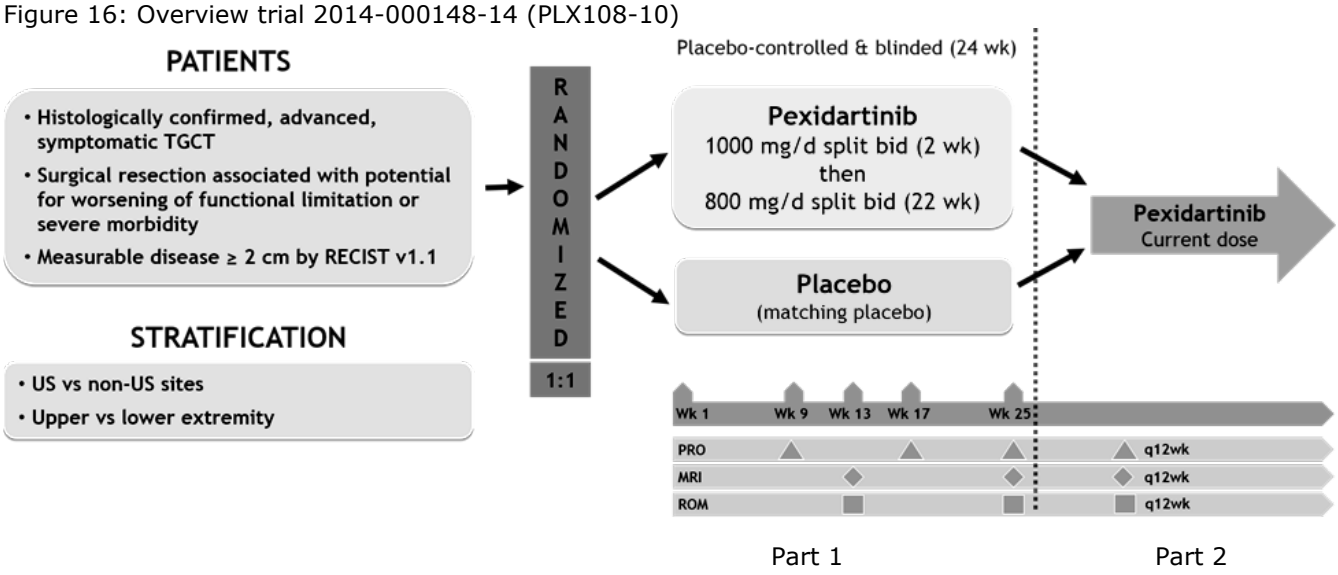
Methods

This was a 2-part, multi-centre, double-blind, randomized, placebo-controlled Phase 3 study in adult subjects with locally advanced, symptomatic TGCT for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity.

In the double-blind phase of the study (Part 1), eligible subjects were centrally randomized in a 1:1 ratio to receive either pexidartinib or placebo for 24 weeks. Subjects who completed Part 1 were eligible to advance to Part 2, a long-term treatment phase where all subjects were to be transitioned to open-label pexidartinib. The pexidartinib dosing for Part 2 was the same as the pexidartinib dose or pexidartinib-equivalent dose of placebo at the end of Part 1.

During the course of this study and in response to the emergence of 2 cases of potential cholestatic liver injury, the study Data Monitoring Committee (DMC) recommended safety measures that changed the conduct of this study to address the protection of subjects (details in section Conduct of the study).

Figure 16: Overview trial 2014-000148-14 (PLX108-10)



Study Participants

Main inclusion criteria

1. TGCT (i) histologically confirmed by a pathologist at the treating institution or a central pathologist, and (ii) where surgical resection would have been associated with potentially worsening functional limitation or severe morbidity (locally advanced disease), with morbidity determined consensually by qualified personnel (that is, by 2 surgeons or a multi-disciplinary tumour board)
2. Measurable disease as defined by RECIST 1.1 except that a minimal size of 2 cm was required
3. Symptomatic disease because of active TGCT, defined as worst pain and / or stiffness of at least 4 at any time during the week preceding the Screening Visit (on a scale of 0 to 10, with 10 "as bad as you can imagine")
4. 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 and on stable analgesic regimen (if any)
5. Women of childbearing potential must have had a negative serum pregnancy test. Males and females of childbearing potential so long as they consented to avoid getting their partner pregnant or becoming pregnant, respectively, by using a highly effective contraception method

Main exclusion criteria

1. Previous use of pexidartinib or any biologic treatment targeting CSF-1 or the CSF1R (allowing oral tyrosine kinase inhibitor not selective for CSF-1 receptor)
2. Active cancer, except for 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
3. metastatic TGCT
4. Significant concomitant arthropathy in the affected joint, serious illness, uncontrolled infection

Treatments

Pexidartinib and placebo capsules were identical in appearance to maintain the blind during Part 1.

Study drug administration began at the P1-C1D1 visit in the morning. At that visit, subjects were instructed to take 1000 mg/d pexidartinib or matching placebo; this amount was divided into a morning dose of 2 capsules and an evening dose of 3 capsules. After 2 weeks, the dose was reduced to 2 capsules in the morning and 2 capsules in the evening (800 mg/d pexidartinib or matching placebo). Subjects who had a dose reduction during the first 2 weeks continued treatment at their reduced dose.

Subjects were instructed to take pexidartinib in the fasting state.

Each dosing cycle was 28 days.

When subjects from the pexidartinib treatment group began Part 2, they took open-label pexidartinib at the same dose they were taking at the completion of Part 1, also split into a morning and an evening dose (maximum 800 mg/day). In both Parts 1 and 2, reducing or interrupting the dose for toxicity may have taken place at any time according to the study guidelines. Those unable to tolerate pexidartinib 400 mg/d or matching placebo were discontinued. Once dose reduction took place for toxicity, a dose re-escalation was generally not allowed unless approved after discussion with the sponsor's Medical Monitor or designee.

Objectives

The primary objective of this study was to compare the response rate of pexidartinib with that of placebo per RECIST 1.1 at Week 25 in subjects with symptomatic, locally advanced TGCT.

The secondary efficacy objectives were to evaluate:

- Range of motion (ROM) at Week 25
- Response based on tumour volume score (TVS) at Week 25
- Patient-reported Outcomes (PROs) at Week 25
- Duration of response

Outcomes/endpoints

The primary efficacy endpoint was the

- proportion of subjects who achieved a CR or PR at the Week 25 Visit based on blinded centrally-read MRI scans and RECIST 1.1; no confirmation on a subsequent scan was required

Secondary efficacy endpoints

- Mean change from baseline in relative ROM of the most affected joint at the Week 25 Visit. ROM was assessed by qualified, independent and blinded third-party assessors at the investigational sites, such as orthopaedic surgeon or a physical therapist, the same person evaluated patients over time, whenever possible. Raw measurements of the affected joint were performed according to a standardized method based on the American Medical Association disability criteria using a goniometer and expressed in degrees. At baseline, the plane of movement with the smallest relative value (most impaired ROM) was selected for subsequent analyses.

- Proportion of responders based on centrally evaluated MRI scans and Tumour Volume Score (TVS) at the Week 25 Visit, where TVS is semi-quantitative scale with 10% increments of the MRI-estimated volume of the maximally distended synovial cavity or tendon sheath involved by the TGCT (e.g. a TGCT that was equal in volume to that of a maximally distended synovial cavity or tendon sheath was scored 10). TVS response was assigned by central blinded reading of MRI scans based on the following criteria: CR, lesion completely gone; PR, at least 50% decrease in TVS relative to baseline; PD: at least 30% increase in TVS relative to lowest score during the trial; SD, does not meet any of the prior criteria.
- Mean change from baseline score in the PROMIS Physical Function Scale at the Week 25 Visit. From the PROMIS physical function item bank version 1.2, in total 13 items relevant to the assessment of lower and 11 items for upper limb function were selected and administered to subjects with lower and upper extremity tumours, respectively. The item sets were combined for analysis.

  Subjects were to complete the instruments (including PROMIS Physical Function Scale, Worst Stiffness NRS item, BPI Worst Pain NRS item, the PROMIS, EQ-5D-5L EuroQol 5-dimensional descriptive system, PGRC Patient Global Rating of Concept item) at screening, weeks 1, 9, 17, 25, 37, 49, and 61 prior to any invasive procedures and prior to the morning dose, using an electronic diary.
- Mean change from baseline score in the Worst Stiffness NRS item at the Week 25 Visit, based on a 1-item, self-administered questionnaire asking for the "worst" stiffness in the last 24 hours at the site of the tumour on a numeric rating scale (NRS; from 0 "no stiffness" to 10 "stiffness as bad as you can imagine").
- Proportion of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 criteria at Week 25 Visit, based on a 1-item, self-administered questionnaire asking for the "worst" pain in the last 24 hours at the site of the tumour on a numeric rating scale (from 0 "no pain" to 10 "pain as bad as you can imagine"). Responder was defined as a subject who (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use, comparing data collected during a 7-day period prior to the current visit for responder assessment with baseline values collected prior to the first dose of study drug. Subjects who did not provide data for the endpoint were assessed as to be non-responders.
- Duration of response (CR or PR) based on MRI and RECIST 1.1
- Duration of response (CR or PR) based on MRI and TVS

Sample size

For the purpose of sample size evaluation, the assumed rates of responders for the primary endpoint were 10% (placebo) and 35% (pexidartinib), respectively. Based on the use of a 2-sided, 2-sample comparison of proportions at the alpha = 0.05 level of significance by Fisher's exact test, a sample size of 126 ITT randomized subjects (63 subjects per group) would provide 90% power to detect this magnitude of difference.

Randomisation

Randomization and treatment assignments for this study were implemented through use of a customized IXRS system. The randomization ratio for Part 1 of the study was 1:1 for active (pexidartinib) versus placebo. Randomization was stratified by

- US versus non-US study sites and
- by upper extremity versus lower extremity involvement.

Blinding (masking)

Part 1 was the placebo-controlled double-blind phase of the study. An update to the conduct of the study changed the unblinding policy as a result of the DMC recommendation, which did not allow subjects on placebo in Part 1 to enter Part 2 and receive open-label pexidartinib. After completion of the end of Part 1 assessments, subjects who wished to continue onto the open-label part of this study (Part 2) were unblinded. Those on placebo were discontinued; subjects on pexidartinib in Part 1 could continue into Part 2 to continue to receive pexidartinib.

In the cases of emergency where, in the investigator's opinion, immediate unblinding of the treatment was necessary in order to evaluate further course of action, the investigator was granted the possibility to access the IXRS to initiate subject unblinding. No events of emergency unblinding occurred prior to the data cut-off date 27 March 2017.

Statistical methods

Analysis sets: The Intent-to-treat (ITT) analysis set was defined as all randomized subjects. The Per-protocol (PP) analysis set was defined as subjects in the ITT Analysis Set who did not have major eligibility/protocol violations and who were compliant with regard to study drug administration, defined as taking at least 70% of their scheduled dose of study drug, regardless of scheduled dose reduction.

The primary efficacy analysis was to be completed using the ITT analysis set. The proportions of responders in the 2 treatment groups at week 25 were to be compared using Fisher's exact test (1-sided, at the alpha = 0.025 level of significance), and this provided the statistical inferential test within the framework of prespecified hierarchical testing. As a supportive analysis, mid-p adjustment of Fisher's exact test was also to be performed. Additionally, as a sensitivity analysis, the Cochran-Mantel-Haenszel (CMH) test was to be carried out with the strata of US and non-US study sites.

Secondary efficacy analyses included the following treatment comparisons at the week 25 Visit using the ITT analysis set:

1. Mean change from Baseline in relative ROM of the most affected joint: The raw measurements for a given joint were to be normalized to a reference standard, i.e., the full ROM for the same joint, to provide a relative value. The change from Baseline in relative ROM at the Week 13 and Week 25 Visits was to be then calculated. Mixed models for repeated measurements (MMRM) were to be employed to analyse the change from Baseline, and a statistical comparison between treatment groups was to be made for the Week 25 Visit; joint type was accounted for in the model.
2. Proportion of TVS responders (CR+PR)

3. Mean change from Baseline score in the PROMIS Physical Function Scale
4. Mean change from Baseline score in the Worst Stiffness NRS item
5. Proportion of responders based on BPI Worst Pain NRS item and analgesic use (BPI-30)

The above-listed endpoints were to be analysed using a hierarchical "gatekeeping" testing procedure, in the final order set out above which was a consequence of unexpected and important study conduct issues (see section Conduct of the study).

Other secondary endpoints were to be analysed using MMRM. The dependent endpoint was the change from Baseline. Each of these models included fixed effects for treatment group, time point, treatment group-by-time interaction, stratification factor of US study sites versus non-US study sites, and the Baseline value of the corresponding endpoint as well as the Baseline-by-time interaction. An unstructured variance-covariance matrix was to be used.

Duration of response (DoR) was summarized for responders based on (i) RECIST 1.1 and (ii) TVS. Duration of response was defined from the date of the first recorded evidence of response to the first date of documented disease progression. For subjects who did not have radiologic progression, the date of the last MRI scan was the censoring date for duration. The Kaplan-Meier product limit method was used to compute the estimate and 95% CI of the median, as well as the 25^{th} and 75^{th} percentiles of the duration of response.

The analyses for the primary analysis, ROM endpoint and BPI-30 endpoint were also to be performed on the Per-Protocol analysis set as sensitivity analyses.

Results

Participant flow

Subject disposition is summarized for Part 1 and Part 2 in Table 11.

Table 11: Subject disposition

Subject Accounting	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Total (N = 120)	Screened but Not Randomized
				53
Randomized but not Dosed[a]	1	0	1	
Analysis Set				
ITT[a]	59 (100.0)	61 (100.0)	120 (100.0)	
Per-Protocol	54 (91.5)	51 (83.6)	105 (87.5)	
Safety	59 (100.0)	61 (100.0)	120 (100.0)	
Treatment Status with respect to Part 1				
Completed/Fulfilled Therapy Requirements per Protocol for Part 1	48 (81.4)	52 (85.2)	100 (83.3)	
Early Discontinuation of Study Treatment	11 (18.6)	9 (14.8)	20 (16.7)	
Primary Reason for Early Discontinuation				
Adverse Event	0	8 (13.1)	8 (6.7)	
Disease Progression	1 (1.7)	0	1 (0.8)	
Withdrawal of Consent by Subject to Continue Study[b]	6 (10.2)	1 (1.6)	7 (5.8)	
Prior to Urgent Safety Measure	1 (1.7)	0	1 (0.8)	
After Urgent Safety Measure	5 (8.5)	1 (1.6)	6 (5.0)	
Investigator Decision[b]	3 (5.1)	0	3 (2.5)	
Prior to Urgent Safety Measure	0	0	0	
After Urgent Safety Measure	3 (5.1)	0	3 (2.5)	
Protocol Violation	0	0	0	
Surgery	0	0	0	
Subject Noncompliance	1 (1.7)	0	1 (0.8)	
Termination of Study by Sponsor or IRB/IEC	0	0	0	
Death	0	0	0	
Lost to Follow-up	0	0	0	

Subject Accounting	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Total (N = 120)	Screened but Not Randomized
Enrollment by Country				
United States of America	22 (37.3)	23 (37.7)	45 (37.5)	
Italy	9 (15.3)	8 (13.1)	17 (14.2)	
Australia	7 (11.9)	5 (8.2)	12 (10.0)	
Netherlands	4 (6.8)	7 (11.5)	11 (9.2)	
Spain	3 (5.1)	5 (8.2)	8 (6.7)	
France	5 (8.5)	2 (3.3)	7 (5.8)	
Germany	2 (3.4)	4 (6.6)	6 (5.0)	
Canada	3 (5.1)	2 (3.3)	5 (4.2)	
Denmark	2 (3.4)	1 (1.6)	3 (2.5)	
Hungary	1 (1.7)	2 (3.3)	3 (2.5)	
Poland	0	2 (3.3)	2 (1.7)	
Great Britain	1 (1.7)	0	1 (0.8)	
Subjects Receiving at Least 1 Dose in Part 2	30 (50.8)	48 (78.7)	78 (65.0)	
Treatment Status for Part 2				
Completed Study	0	0	0	
Ongoing Study Treatment in Part 2 at the Time of Data Cut-off	26 (86.7)	39 (81.3)	65 (83.3)	
Early Withdrawal/Discontinuation from Study	4 (13.3)	9 (18.8)	13 (16.7)	
Primary Reason for Early Discontinuation from Study				
Adverse Event	2 (6.7)	3 (6.3)	5 (6.4)	
Disease Progression	0	0	0	
Withdrawal of Consent by Subject to Continue Study[b]	1 (3.3)	5 (10.4)	6 (7.7)	
Prior to Urgent Safety Measure	0	2 (4.2)	2 (2.6)	
After Urgent Safety Measure	1 (3.3)	3 (6.3)	4 (5.1)	
Investigator Decision[b]	0	1 (2.1)	1 (1.3)	
Prior to Urgent Safety Measure	0	0	0	
After Urgent Safety Measure	0	1 (2.1)	1 (1.3)	
Protocol Violation	0	0	0	
Surgery	0	0	0	
Subject Noncompliance	0	0	0	
Termination of Study by Sponsor or IRB/IEC	0	0	0	
Death	1 (3.3)	0	1 (1.3)	
Lost to Follow-up	0	0	0	

ICF = informed consent form; IEC = Independent Ethics Committee; IRB = Institutional Review Board; ITT = Intent to Treat; N = number; SAE = serious adverse event.

Notes: Percentages in Part 1 were based on the number of subjects in the ITT analysis set.

Percentages in Part 2 were based on the number of subjects who received at least 1 dose in Part 2.

Subjects who had signed ICF and were screened but not randomized were not included in the total number of the Randomized analysis set.

[a] Based on updated safety information including 2 SAEs in this study consistent with cholestatic liver dysfunction and in response to the emergence of these cases, the Data Monitoring Committee recommended the implementation of urgent safety measures. At that time, there was 1 subject who was randomized but who did not receive any study drug and was discontinued. This subject (Subject No. 30010002) was excluded from the ITT analysis set. Otherwise the ITT analysis set was the same as the Randomized analysis set.

[b] Resultant to the urgent safety measure, subjects who withdrew consent to continue or those who discontinued as a result of the investigator's decision were further categorized as "Prior to Urgent Safety Measure", which was before 30 Sep 2016, or "After Urgent Safety Measure", which was on or after 30 Sep 2016.

Source: Table 14.1.1

Recruitment

Conduct of the study

Subsequent to major protocol violations that were considered to affect efficacy, 16.4% of patients in the pexidartinib arm and 8.5% in the placebo arm were excluded from the PPS. No discussion of major protocol deviations was submitted by the applicant.

After 2 SAEs consistent with cholestatic liver dysfunction occurred, the study DMC was requested to review unblinded safety data related to these cases and recommended safety measures, which were implemented effective 30 September 2016:

- Enrolment was stopped. No new subjects were permitted to start study drug. Subjects in screening and randomized subjects who had not started treatment were discontinued.
- Subjects on placebo in Part 1 were no longer allowed to enter Part 2 to receive open-label pexidartinib. After completion of the end of Part 1 assessments, subjects who wished to continue onto the open-label part of this study (Part 2) were unblinded and those on placebo were discontinued; subjects on pexidartinib in Part 1 were allowed to continue into Part 2 and continued to receive pexidartinib.
- Liver function testing was intensified as follows: ALP, ALT, AST, total and direct bilirubin, and GGT should be assessed at screening, weekly during P1-C1 beginning on Day 1, weekly during P1-C2 beginning on Day 1, biweekly during P1-C3 beginning on Day 1, and on Day 1 of every cycle thereafter. ALP, ALT, AST, total and direct bilirubin, and GGT should also be assessed weekly during P2-C1 beginning on Day 1, weekly during P2-C2 beginning on Day 1, biweekly during P2-C3 beginning on Day 1, and on Day 1 of every cycle thereafter.
- Investigators and subjects were informed of the new safety information and decided whether to continue in the study. If, after consultation with the subject, it was deemed to be in their best interest to continue treatment, the subject had to be re-consented.
- By the time of the DMC recommendation, 120 of the intended 126 subject target had been randomized and treated. After database lock and unblinding, it was revealed that 30 subjects on the placebo arm had crossed over to pexidartinib in Part 2 prior to the DMC recommendation.

In May 2018, based on blinded assessments of the aggregated whole database prior to database lock and unblinding, it was found that a number of subjects were missing valid end-of-part 1 week 25 assessments for BPI NRS, PROMIS and Worst Stiffness NRS scores. One underlying issue were the above-mentioned safety measures, which had the effect that more than the expected number of enrolled subjects discontinued the study prior to week 25 assessments. Another underlying issue was missing valid PRO data due to subject noncompliance and technical problems with the electronic diary such as incorrect programming of the reporting period, device malfunction and data transmission errors. The greatest impact was on the BPI Worst Pain NRS Week 25 responder endpoint, because it had the greatest amount of missing data and it was to be evaluated using a responder analysis that included only Baseline and Week 25 results. For other secondary endpoints of ROM and PROs, the analysis and statistical inference were based on the treatment difference of central tendency, using a MMRM analysis.

To partially mitigate the statistical impact of these issues on the secondary efficacy endpoint hierarchy, the BPI-30 responder analysis was moved to the bottom of the comparative secondary endpoints from its

previous place as the first secondary endpoint. The ROM endpoint was moved to be analysed first, rather than third, in the sequential hierarchy, because it is an objective, clinically relevant endpoint with greater completeness of data. Additional analyses and sensitivity analyses were specified before unblinding and added to the SAP to assess the impact of missing data.

Baseline data

Demographics and other baseline characteristics were analysed using the ITT analysis set (Table 12).

Table 12: Demographic and Baseline Characteristics (ITT Analysis Set)

	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Total (N = 120)	All Pexidartinib Treated (N = 91)
Age (years)				
n	59	61	120	91
Mean	44.3	44.6	44.5	45.6
StdDev	13.58	13.23	13.35	13.21
Median	45.0	44.0	44.5	46.0
Minimum	18	22	18	20
Maximum	79	75	79	79
<18	0	0	0	0
18-64	56 (94.9)	57 (93.4)	113 (94.2)	85 (93.4)
18-40	19 (32.2)	24 (39.3)	43 (35.8)	31 (34.1)
41-64	37 (62.7)	33 (54.1)	70 (58.3)	54 (59.3)
65-84	3 (5.1)	4 (6.6)	7 (5.8)	6 (6.6)
65-74	0	3 (4.9)	3 (2.5)	3 (3.3)
75-84	3 (5.1)	1 (1.6)	4 (3.3)	3 (3.3)
≥85	0	0	0	0
Sex				
Male	23 (39.0)	26 (42.6)	49 (40.8)	40 (44.0)
Female	36 (61.0)	35 (57.4)	71 (59.2)	51 (56.0)
Time from Diagnosis to Informed Consent (days)				
n	59	61	120	91
Mean	1404.5	2424.7	1923.1	2082.6
StdDev	1494.34	3097.71	2487.76	2765.51
Median	903.0	1440.0	1251.0	1225.0
Minimum	17	−12	−12	−12
Maximum	8059	14884	14884	14884
PVNS/GCT-TS				
PVNS	53 (89.8)	52 (85.2)	105 (87.5)	79 (86.8)
GCT-TS	6 (10.2)	9 (14.8)	15 (12.5)	12 (13.2)
Both	0	0	0	0
Extremity Involvement				
Upper	5 (8.5)	5 (8.2)	10 (8.3)	9 (9.9)
Shoulder	1 (1.7)	1 (1.6)	2 (1.7)	2 (2.2)
Elbow	0	1 (1.6)	1 (0.8)	1 (1.1)
Wrist	2 (3.4)	2 (3.3)	4 (3.3)	3 (3.3)
Hand	0	0	0	0
Finger	1 (1.7)	0	1 (0.8)	1 (1.1)
Spine	1 (1.7)	1 (1.6)	2 (1.7)	2 (2.2)

Lower	54 (91.5)	56 (91.8)	110 (91.7)	82 (90.1)
Hip	7 (11.9)	6 (9.8)	13 (10.8)	9 (9.9)
Knee	39 (66.1)	34 (55.7)	73 (60.8)	53 (58.2)
Ankle	7 (11.9)	14 (23.0)	21 (17.5)	17 (18.7)
Foot	1 (1.7)	2 (3.3)	3 (2.5)	3 (3.3)
Toe	0	0	0	0
Other	0	0	0	0
Most Disturbing Symptom				
(non-missing n)	47	47	94	71
Pain	13 (27.7)	12 (25.5)	25 (26.6)	19 (26.8)
Stiffness	6 (12.8)	9 (19.1)	15 (16.0)	12 (16.9)
Difficulty with Everyday Activities	28 (59.6)	26 (55.3)	54 (57.4)	40 (56.3)
Missing	12	14	26	20
Global Rating of Concept				
How Much had Tumor Limited Physical Functioning				
(non-missing n)	47	47	94	71
Not at All	4 (8.5)	2 (4.3)	6 (6.4)	6 (8.5)
A Little	10 (21.3)	17 (36.2)	27 (28.7)	19 (26.8)
Somewhat	23 (48.9)	18 (38.3)	41 (43.6)	31 (43.7)
Severely	9 (19.1)	9 (19.1)	18 (19.1)	14 (19.7)
Extremely	1 (2.1)	1 (2.1)	2 (2.1)	1 (1.4)
Missing	12	14	26	20

EU = European Union; GCT-TS = giant cell tumor of the tendon sheath; ICF = informed consent form; ITT = Intent to Treat; N = number in population; n = number in calculation; PVNS = pigmented villonodular synovitis; StdDev = standard deviation; US = United States.

Notes: Denominator for percentages was n, the number of subjects with non-missing responses in the ITT analysis set, if n was displayed; otherwise N.

The Baseline value was defined as the last non-missing value before the P1-C1D1 Visit.

There were 2 subjects whose time from diagnosis of tumor to informed consent (in days) was 0 days or less. Subject No. 80020005 had their time from diagnosis to informed consent equal to 0 due to their diagnosis being documented/confirmed on the day after ICF. Subject No. 80020009 was consented, but the study site could not locate the subject's archival tumor tissue and, as such, they were rescreened with an additional biopsy.

Rescreen information was in electronic data capture; however, the original ICF date was maintained resulting in a −12-day duration.

Source: Table 14.1.2.1

A summary of prior treatments that subjects had received is presented in Table 13.

Table 13: Summary prior treatments

Table 14.1.3: Summary of Prior Treatment
ITT Analysis Set

	Randomized to Placebo (N=59)	Randomized to Pexidartinib (N=61)	Total (N=120)	All Pexidartinib Treated (N=91)
Number of Prior Biopsies, Procedures or Surgeries for PVNS/GCT-TS				
0	1 (1.7)	4 (6.6)	5 (4.2)	4 (4.4)
1	29 (49.2)	29 (47.5)	58 (48.3)	45 (49.5)
2	16 (27.1)	12 (19.7)	28 (23.3)	20 (22.0)
3	5 (8.5)	11 (18.0)	16 (13.3)	13 (14.3)
4 or Higher	8 (13.6)	5 (8.2)	13 (10.8)	9 (9.9)
Number of Surgeries for PVNS/GCT-TS Treatment				
0	28 (47.5)	29 (47.5)	57 (47.5)	45 (49.5)
1	12 (20.3)	13 (21.3)	25 (20.8)	18 (19.8)
2	12 (20.3)	7 (11.5)	19 (15.8)	13 (14.3)
3 or Higher	7 (11.9)	12 (19.7)	19 (15.8)	15 (16.5)
Number of Prior Systemic Therapies for PVNS/GCT-TS				
0	56 (94.9)	53 (86.9)	109 (90.8)	81 (89.0)
1	3 (5.1)	7 (11.5)	10 (8.3)	9 (9.9)
2	0	1 (1.6)	1 (0.8)	1 (1.1)
3 or Higher	0	0	0	0
Number of Subjects by Type of Prior Systemic Therapy [a]				
No Prior Systemic Therapy	56 (94.9)	53 (86.9)	109 (90.8)	81 (89.0)
Nilotinib	0	1 (1.6)	1 (0.8)	1 (1.1)
Imatinib	3 (5.1)	7 (11.5)	10 (8.3)	9 (9.9)
Other	0	0	0	0
Number of Courses of Radiation Treatment for PVNS/GCT-TS				
0	57 (96.6)	56 (91.8)	113 (94.2)	85 (93.4)
1	2 (3.4)	4 (6.6)	6 (5.0)	5 (5.5)
>=2	0	1 (1.6)	1 (0.8)	1 (1.1)

Numbers analysed

The numbers of subjects in each analysis set were:

- 120 subjects: ITT analysis set (100% of subjects in both the pexidartinib and placebo groups).
- 105 subjects: Per-Protocol analysis set (83.6% and 91.5% of subjects in the pexidartinib and placebo groups, respectively).
- 120 subjects: Safety analysis set (100% of subjects in both the pexidartinib and placebo groups) (identical to the ITT analysis set).
- 121 subjects: Randomized analysis set summarizes subject membership for the ITT, PP, and Safety analysis sets.

All efficacy analyses were performed on the ITT analysis set. Sensitivity analyses of the primary efficacy, ROM and response rate based on BPI-30 were performed on the Per- Protocol analysis set.

Outcomes and estimation

Primary efficacy outcome

Table 14: Primary efficacy endpoint: Proportion of subjects who achieved a CR or PR at the Week 25 Visit based on centrally-read MRI scans and based on RECIST 1.1 (data cut-off 27 March 2017)

End of Part 1 Assessment	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Difference in % (Pexidartinib – Placebo)[a]
CR			
n (%)	0 (0.0)	9 (14.8)	
95% CI	[0.00, 6.11]	[7.96, 25.72]	
PR			
n (%)	0 (0.0)	15 (24.6)	
95% CI	[0.00, 6.11]	[15.51, 36.68]	
PD			
n (%)	1 (1.7)	1 (1.6)	
95% CI	[0.30, 9.00]	[0.29, 8.72]	
NE			
n (%)	12 (20.3)	12 (19.7)	
95% CI	[12.04, 32.27]	[11.63, 31.31]	
Response (CR or PR)			
n (%)	0 (0.0)	24 (39.3)	39.34
95% CI	[0.00, 6.11]	[28.07, 51.88]	[26.52, 51.88]
Fisher's Exact Test *P*-value (1-sided)			<0.0001
Fisher's exact test with mid-p Adjustment *P*-value (1-sided)			<0.0001
CMH *P*-value Stratified by Region (US, non-US) (1-sided)			<0.0001

CI = confidence interval; CR = complete response; ITT = Intent to Treat; N = number; NE = not evaluable; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

Notes: Denominator for percentages was the number of subjects in the ITT analysis set.
End of Part 1 responder was determined based on centrally read MRI in Part 1 and RECIST 1.1. Please refer to Table 2.1 of the protocol for further detailed definitions of response.
Subjects who do not have an end of Part 1 response assessment for any reason or whose Week 25 assessment was after the first dose in the open-label extension or outside of the visit window of ±14 days were assessed as a non-responder.
All *P*-value tests for a treatment difference in response (CR+PR) rates, with 1-sided *P*-value testing for superiority in pexidartinib group. If a 1-sided test was used for inference, the significance level of 0.025 was applied.
The CIs for proportions within treatment groups were 2-sided and calculated using the Wilson method.
[a] 95% CI using the Newcombe method.

Source: Table 14.2.1.1

Supportive analyses of primary efficacy outcome response rate

The response rate based on RECIST 1.1 for the ITT Analysis Set, but excluding subjects in the placebo group who discontinued after urgent safety measures, was supportive for the primary analysis and statistically significant by the 1-sided Fisher's exact test (p <0.001) in favour of pexidartinib by a difference of 39.4 percentage points (95% CI: 26.2, 51.9).

The response rate based on RECIST 1.1 for the ITT Analysis Set, but excluding subjects who discontinued after urgent safety measures, was statistically significant (p <0.001, 1-sided Fisher's exact test) in favour of pexidartinib by a difference of 40.0 percentage points (95% CI: 26.7, 52.6)

Secondary efficacy outcomes

Mean change from Baseline in relative ROM of the most affected joint at week 25

Table 15: Secondary efficacy endpoint: Mean change from baseline in ROM (ITT Analysis Set) (data cut-off 27 March 2017)

Visit	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Difference in Mean (Pexidartinib – Placebo)
Baseline			
n	58	61	
Mean (SE)	62.9 (2.86)	62.5 (3.18)	
Change from Baseline – Week 25			
n	43	45	
LS Mean (SE)	6.20 (2.374)	15.07 (2.086)	8.87 (3.033)
95% CI	(1.49, 10.91)	(10.93, 19.22)	(2.85, 14.90)
P-value for Treatment Comparison at Week 25			0.0043

CI = confidence interval; ITT = Intent to Treat; LS = least squares; N = number; ROM = range of motion; SE = standard error.

Notes: The baseline value was defined as the last non-missing value before initial administration of study drug in Part 1.

At baseline, the plane of movement with the smallest (worst) relative value (expressed in % when normalized with the reference standard) was identified, and this plane was used for evaluating the relative ROM subsequently. In the event of ties of more than 1 planes at baseline, the average of relative ROM values for all such planes was calculated for each post-baseline ROM assessment.

Subject assessments falling outside of the visit window were excluded from the change from baseline analysis and by visit summaries. Subject assessments that occurred after first dose in Part 2 were excluded from the analysis of Part 1 results.

All *P*-values were 2-sided. If *P*-value was used for inference, a 2-sided alpha of 0.05 applied. The inference was on Treatment Comparison at Week 25.

Source: Table 14.2.2.1

Proportion of TVS responders (CR+PR) at week 25

Table 16: Secondary efficacy endpoint: TVS response rate (ITT Analysis Set) (data cut-off 27 March 2017)

End of Part 1 Assessment	Randomized to Placebo	Randomized to Pexidartinib	Difference in % (Pexidartinib – Placebo)[a]
CR			
n (%)	0 (0.0)	3 (4.9)	
95% CI	[0.00, 6.11]	[1.69, 13.49]	
PR			
n (%)	0 (0.0)	31 (50.8)	
95% CI	[0.00, 6.11]	[38.60, 62.94]	
PD			
n (%)	2 (3.4)	1 (1.6)	
95% CI	[0.93, 11.54]	[0.29, 8.72]	
NE			
n (%)	12 (20.3)	12 (19.7)	
95% CI	[12.04, 32.27]	[11.63, 31.31]	
Response (CR or PR)			
n (%)	0 (0.0)	34 (55.7)	55.7
95% CI	[0.00, 6.11]	[43.30, 67.49]	[41.88, 67.49]
Fisher's Exact Test *P*-value (1-sided)			<0.0001
Fisher's exact test with mid-p Adjustment *P*-value (1-sided)			<0.0001
CMH *P*-value Stratified by Region (US, non-US) (1-sided)			<0.0001

CI = confidence interval; CR = complete response; ITT = Intent to Treat; PD = progressive disease; PR = partial response; N = number; NE = not evaluable; TVS = Tumor Volume Score.

Notes: Denominator for percentages was the number of subjects in the ITT Analysis Set.

End of Part 1 responder was defined as those who achieve a TVS response of CR or PR at the Week 25 Visit based on a centrally read MRI scan.

Subjects who did not have a Week 25 response assessment for any reason or whose Week 25 assessment was after the first dose in the open-label extension or outside of the visit window of ± 14 days were assessed as a non-responder.

All *P*-values tested for a treatment difference in response rates, with 1-sided *P*-value testing for superiority in Pexidartinib group. If a 1-sided test was used for inference, a 1-sided alpha of 0.025 was applied. The CIs for proportions within treatment groups were 2-sided, and calculated using the Wilson method.

* 95% confidence interval using the Newcombe method.

Source: Table 14.2.3

Mean change from Baseline score in the PROMIS Physical Function Scale at week 25

Table 17: Secondary efficacy endpoint: mean change from baseline in PROMIS Physical Function Score at week 25 (ITT Analysis Set) (data cut-off 27 March 2017)

Visit	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Difference in Mean (Pexidartinib – Placebo)
Baseline			
n	57	60	
Mean (SE)	38.9 (0.81)	37.5 (0.64)	
Change from Baseline – Week 25			
n	31	38	
LS Mean (SE)	-0.89 (1.038)	4.06 (1.132)	4.95 (1.557)
95% CI	(-2.95, 1.16)	(1.82, 6.30)	(1.87, 8.03)
P-value for Treatment Comparison at Week 25			0.0019

CI = confidence interval; ITT = Intent to Treat; LS = least squares; N = number; PROMIS = Patient-reported Outcomes Measurement Information System; SE = standard error.
Notes: The baseline value was defined as the last non-missing value before initial administration of study drug in Part 1.
Subject assessments that fell outside of the visit window were excluded from the change from baseline analysis and by visit summaries. Subject assessments that occurred after first dose in Part 2 were excluded from the analysis of Part 1 results.
All *P*-values were 2-sided. If *P*-value was used for inference, a 2-sided alpha of 0.05 was applied. The inference was on Treatment Comparison at Week 25.
Source: Table 14.2.4

Mean change from Baseline score in the Worst Stiffness NRS item at week 25

Table 18: Secondary efficacy endpoint: Mean change from baseline in worst stiffness NRS at week 25 (ITT analysis set) (data cut-off 27 March 2017)

Visit	Randomized to Placebo (N=59)	Randomized to Pexidartinib (N=61)	Difference in Mean (Pexidartinib - Placebo)
Baseline			
n	58	59	
Mean (SE)	5.9 (0.25)	5.6 (0.22)	
Change from Baseline - Week 25			
n	35	33	
LS Mean (SE)	-0.28 (0.292)	-2.45 (0.293)	-2.17 (0.407)
95% CI	(-0.86, 0.30)	(-3.03, -1.87)	(-2.97, -1.36)
P-value for Treatment Comparison at Week 25			<0.0001
P-value for Treatment			<0.0001
P-value for Time Point (Visit)			0.6873
P-value for Treatment by Visit Interaction			0.0015
P-value for Region (U.S., non-U.S.)			0.3009

Notes: Worst Stiffness NRS at baseline and a post-treatment visit is the average over a 7-day period prior to the clinic visit.
Subject assessments falling outside of the visit window will be excluded from the change from baseline analysis and by visit summaries.
Subject assessments occurring after first dose in Part 2 will be excluded from the analysis of Part 1 results.
All p-values are 2-sided. If p-value is used for inference, a 2-sided alpha of 0.05 will apply. The inference is on Treatment Comparison at Week 25.
Mixed Model Repeated Measures (MMRM) include fixed effects for treatment group, time point (visit), treatment group-by-time interaction, stratification factor of U.S. sites versus non-U.S. sites, baseline value as well as the baseline-by-time interaction as explanatory variables. P-values for model terms, such as treatment, time point and treatment by visit interaction, are shown for information only.

Proportion of responders based on BPI Worst Pain NRS item and analgesic use (BPI-30)

Only 33 (54.1%) and 35 (59.3%) subjects in the pexidartinib and placebo groups, respectively, had valid mean BPI Worst Pain NRS at Baseline and Week 25. The proportion of responders based on BPI-30 at the Week 25 Visit is presented in Table 19.

Table 19: Secondary efficacy endpoint: BPI-30 response rate (ITT Analysis Set) (data cut-off 27 March 2017)

Week 25 Assessment	Randomized to Placebo (N = 59)	Randomized to Pexidartinib (N = 61)	Difference in % (Pexidartinib – Placebo)[a]
Number of Subjects with Valid Mean BPI Worst Pain NRS at Baseline and Week 25	35 (59.3)	33 (54.1)	
Number of Subjects with Decrease of At Least 30% in the Mean BPI Worst Pain NRS Item	9 (15.3)	19 (31.1)	
Number of Subjects Without a 30% or Greater Increase in Narcotic Analgesic Data[b, c]	35 (59.3)	35 (57.4)	
Number of Subjects with both Valid Mean BPI Worst Pain NRS at Baseline and Week 25 and Sufficient Narcotic Analgesic Data for Assessment	35 (59.3)	33 (54.1)	
Response			
n (%)	9 (15.3)	19 (31.1)	15.9
95% CI	[8.24, 26.52]	[20.94, 43.59]	[0.69, 30.18]
Fisher's Exact Test *P*-value (1-sided)			0.0320
Fisher's exact test with mid-p Adjustment *P*-value (1-sided)			0.0215

BPI = Brief Pain Inventory; CI = confidence interval; ITT = Intent to Treat; N = number; NRS = Numeric Rating Scale.
Notes: Denominator for percentages was the number of subjects in the ITT Analysis Set.
A responder was defined as a subject who, at Week 25 (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item, and (ii) did not experience a 30% or greater increase in narcotic analgesic use, comparing data collected over a 7-day period prior to the study site visit for responder assessment with baseline values collected 7 days prior to the initial administration of study drug in Part 1.
Subjects who did not provide sufficient data for the endpoint determination (either BPI-30 or narcotic analgesic data) were assessed as non-responders.
All *P*-values tested for a treatment difference in response rates, with 1-sided *P*-value testing for superiority in Pexidartinib group. If a 1-sided test was used for inference, a 1-sided alpha of 0.025 was applied. The CIs for proportions within treatment groups were 2-sided and calculated using the Wilson method.

[a] 95% confidence interval using the Newcombe method.
[b] Sufficient narcotic analgesic data were defined as a minimum of 4 out of 7 days of valid recorded data, which included recording of no narcotic analgesic use for a day. That was, if the subject made it to Week 25 and there was no recording of narcotic analgesic use in the week prior, a weekly average of 0 mg was used and considered to be sufficient narcotic analgesic data.
[c] Subjects with 0 narcotic analgesic usage at both Baseline and Week 25 were assessed as without 30% or greater increase.

Source: Table 14.2.6.1

Duration of response based on RECIST 1.1

At the time of the 31 January 2018 data cut-off, disease progression had occurred in only 1 subject, and duration was censored for the remainder (Table 20); neither the median nor the quartiles of duration of response could be estimated.

Table 20: Secondary efficacy endpoint: duration of response by RECIST (data cut-off 27 March 2017)

Table 14.2.18.1.1_A: Exploratory Analysis: Duration of Response Based on RECIST 1.1 - SLD
ITT Analysis Set

	Randomized to Placebo (Part 1 Only) (N=59)	Randomized to Pexidartinib (Parts 1 and 2) (N=61)	Cross-over Pexidartinib (Part 2 Only) (N=30)	All Pexidartinib Treated (N=91)
Duration of Response (Months)				
Number of responses (CR or PR)	0	33	16	49
Median		----	----	----
95% CI for Median		[----; ----]	[----; ----]	[----; ----]
25% and 75%-ile		[----; ----]	[----; ----]	[----; ----]
Range		0.03+;24.87+	3.12+;23.06+	0.03+;24.87+

Notes: Only subjects with the best overall response of CR or PR are summarized.
Duration of response is defined as the time from first recorded response of CR or PR in the study period noted for each treatment group to first documentation of subsequent disease progression.
Subjects who are Randomized to Placebo are right-censored at the end of Part 1. In Part 2, the reference visit for RECIST 1.1 evaluation is the last assessment prior to first dose of active treatment (P2-C1D1) for the cross-over Pexidartinib group.
In the case of no radiographic progression, subjects are right-censored at the date of their last MRI scan.
Median, 95% CI for median, and percentiles for duration of response and 95% CI for proportion are estimated based on Kaplan-Meier methodology.
Minimum and maximum include the censored observations, where "+" indicates a censored value.

The mean ± 1 standard deviation of the duration of response by RECIST 1.1 for subjects who achieved a best overall response of CR or PR was 13.5 ± 6.0 months at the time of the 31 January 2018 data cut-off.

Responders maintaining a response at Week 48 in overlapping patient groups:

- All pexidartinib group: the proportion of responders maintaining a response was 0.97 (95% CI: 0.81, 1.00): 24 subjects remained responders at Week 48 and 1 subject had disease progression (24 subjects were censored).
- Crossover pexidartinib group (Part 2 only): the proportion of responders maintaining a response was 1.00 (95% CI: -, -): 9 subjects remained responders at Week 48 and no subjects had disease progression (7 subjects were censored).
- Pexidartinib group (Part 1 and Part 2): the proportion of responders maintaining a response was 0.95 (95% CI: 0.69, 0.99): 15 subjects remained responders at Week 48 and 1 subject had disease progression (17 subjects were censored).

Results for duration of response based on TVS are not included in this report.

Ancillary analyses

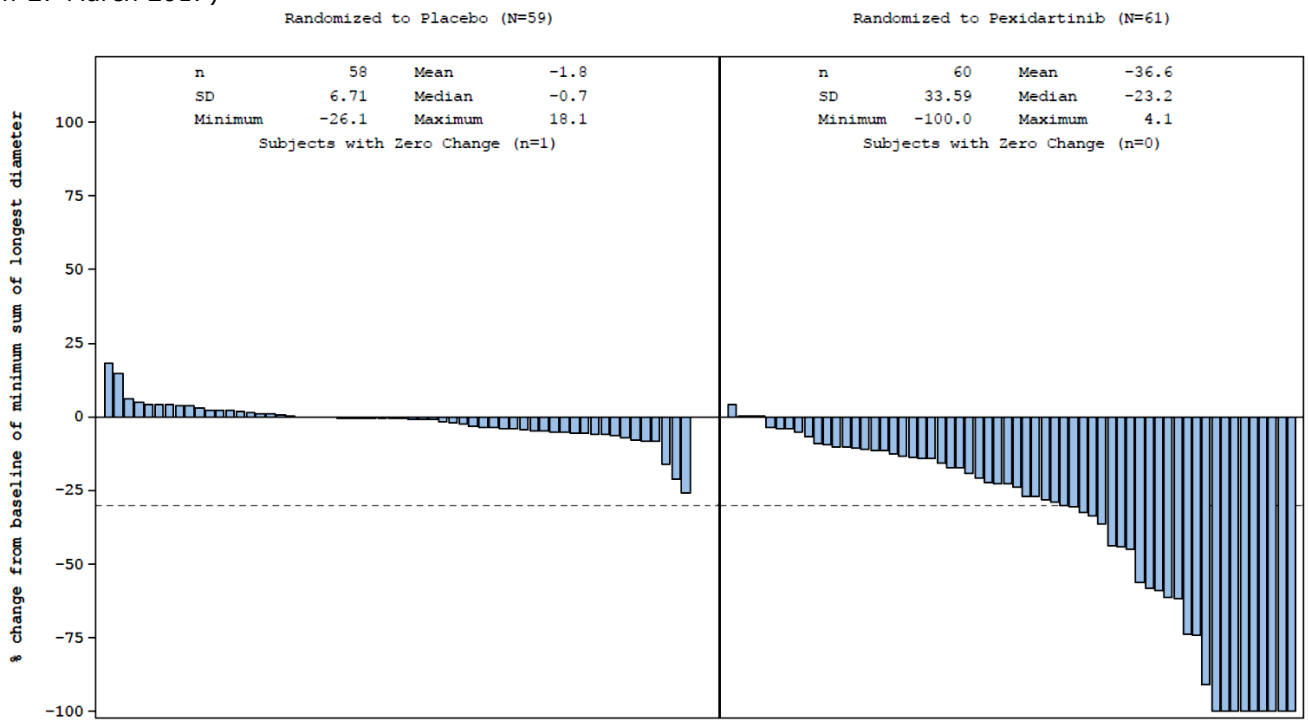
- Objective response by RECIST 1.1 by subgroups

Table 21: Objective response (CR+PR) rates (ORR) by subgroups for Part 1 based on RECIST 1.1 assessment for pexidartinib group (the objective response rate was 0 for the placebo arm in all subgroups) (data cut-off 27 March 2017)

Disease location	**$N_{Pexidartinib}$ / $N_{Placebo}$**	**ORR % (95% CI)**
- Large joint (knee, shoulder, elbow or hip)	42/47	35.7% (20.9, 50.8)
- Small joint (joints other than shoulder, elbow, hip or knee)	19/12	47.4% (15.9, 68.3)
- Knee	34/39	41.2% (23.9, 57.8)
Type of disease		
- GCT-TS (i.e., localized TGCT)	9/6	55.6% (7.0, 81.1)
- PVNS (i.e., diffuse TGCT)	52/53	36.5% (23.0, 50.1)
Tumour extremity location		
- Lower extremity	56/54	37.5% (24.2, 50.6)
- Upper extremity	5/5	60.0% (3.0, 88.2)
Geographic location		
- US	23/22	43.5% (20.3, 63.2)
- Non-US	38/37	36.8% (20.4, 52.7)
- EU only	31/27	35.5% (16.5, 53.1)
Age		
- <50 years old		41.0 pp (24.5, 56.6)
- 50 to 65 years old		44.4 pp (17.3, 66.3)
Sex		
- Male		38.5 pp (17.0, 57.5)
- Female		40.0 pp (22.6, 56.4)

- Response based on RECIST 1.1 at 25 weeks

Figure 17: Waterfall plot of the sum of the longest TGCT diameters for part 1 (ITT analysis set) (data cut-off 27 March 2017)



ITT = Intent to Treat; N = number in population; n = number in calculation; StdDev = standard deviation.
Source: Figure 14.2.10.6.2

- BPI Worst Pain NRS item and analgesic use (BPI-30)

Table 22: Sensitivity analysis of BPI response rate by non-responder status at week 25 (using adjusted rule to calculate weekly average), ITT analysis set (data cut-off 27 March 2017)

Week 25 Assessment	Randomized to Placebo (N=59)	Randomized to Pexidartinib (N=61)	Difference in % (Pexidartinib - Placebo) [a]
Number of Subjects with Valid Mean BPI Worst Pain NRS at Baseline and Week 25	37 (62.7)	40 (65.6)	
Number of Subjects Without a 30% or Greater Increase in Narcotic Analgesic Data [c]	37 (62.7)	41 (67.2)	
Number of Subjects with both Valid Mean BPI Worst Pain NRS at Baseline and Week 25 and Sufficient Narcotic Analgesic Data for Assessment	37 (62.7)	40 (65.6)	
BPI-30			
Number of subjects with Decrease of At Least 30% in the Mean BPI Worst Pain NRS Item	10 (16.9)	23 (37.7)	
Non-response			
Verified	27 (45.8)	18 (29.5)	
Unknown	22 (37.3)	21 (34.4)	
Response			
n (%)	10 (16.9)	22 (36.1)	19.1
95% CI	[9.48, 28.46]	[25.17, 48.61]	[3.27, 38.72]

Notes: Denominator for percentages is the number of subjects in the ITT Analysis Set.

A responder is defined as a subject who (i) experienced a decrease of at least 30%, 50% or 2 points (for BPI-30, BPI-50, BPI-2p respectively) in the mean BPI Worst Pain NRS item, and (ii) did not experience a 30% or greater increase in narcotic analgesic use, comparing data collected during a 7-day period prior to the current visit for responder assessment with baseline values collected 7 days prior to the P1-C1D1 visit.

This sensitivity analysis allows the average BPI to be calculated if at least 2 out of 7 entries were completed.

Subjects who do not provide sufficient data for the endpoint determination (either BPI or narcotic analgesic data) will be considered to be non-responders. All p-values test for a treatment difference in response rates, with 1-sided p-value testing for superiority in PLX3397 group. If 1-sided test is used for inference, a 1-sided alpha of 0.025 will apply. CIs for proportions within treatment groups are 2-sided, and calculated using the Wilson method.

[a] 95% confidence interval using Newcombe method.

[b] Sufficient narcotic analgesic data is defined as a minimum of 2 out of 7 days of valid recorded data, which includes recording of no narcotic analgesic use for a day.

[c] Subjects with 0 narcotic analgesic usage at both Baseline and Week 25 are counted toward without 30% or greater increase.

Source: adam.ADQS; adam.ADSL; Listing 16.2.6.2.1

Updated efficacy results with a data cut-off of 31 January 2018 and a median duration of follow up of 20 months (range, 16 to 31 months) are presented in the following two sections.

Best overall tumour response

Table 23: Best overall response based on RECIST and TVS of centrally reviewed MRI while on treatment for the pexidartinib treatment groups (data cut-off 31 January 2018)

RECIST 1.1 - SLD Best Overall Response	Randomized to Pexidartinib (Parts 1 and 2) (N = 61)	Cross-over Pexidartinib (Part 2 Only) (N = 30)	All Pexidartinib Treated (N = 91)
RECIST 1.1 - SLD Best Overall Response (CR or PR)			
n (%)	32 (52.5)	16 (53.3)	48 (52.7)
95% CI	[40.16, 64.47]	[36.14, 69.77]	[42.59, 62.68]
TVS Response Best Overall Response (CR or PR)			
n (%)	39 (63.9)	20 (66.7)	59 (64.8)
95% CI	[51.39, 74.83]	[48.78, 80.77]	[54.61, 73.86]
Modified RECIST 1.1 - SSD Best Overall Response (CR or PR)			
n (%)	43 (70.5)	22 (73.3)	65 (71.4)
95% CI	[58.11, 80.44]	[55.55, 85.82]	[61.43, 79.69]

CI = confidence interval; CR = complete response; PR = partial response; ITT = intent-to-treat; NE = not evaluable; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors, version 1.1; SD = stable disease; SLD = Sum of the Longest Diameters; SSD = Sum of Short axis dimensions; TVS = Tumor Volume Score.

Notes: Denominator for percentages is the number of subjects in the ITT Analysis Set
The best overall response on treatment is determined from responses recorded between the first dose and last dose date. For subjects randomized to Placebo the best overall response on treatment is determined separately within each part of the study.
If SD is believed to be the best overall response, the date of the first SD must be a minimum of 22 weeks since first dose of treatment, shorter-duration SD will not be considered for the best overall response on treatment and hence set to NE.
To see the best overall response determined from all available tumor assessments from first dose of treatment, please see Table 14.2.8.2_A.

- Function and symptom variables

Updated results in terms of ROM, PROMIS, Worst Stiffness NRS and Worst Pain NRS as related to secondary efficacy endpoints are summarised in Table 24.

Table 24: Change from baseline in function and symptom variables (ITT analysis set) (data cut-off 31 January 2018)

Visit	Pexidartinib (Parts 1 and 2) (N = 61)	Cross-over Pexidartinib (Part 2 Only) (N = 30)	All Pexidartinib Treated (N = 91)
ROM			
Baseline			
N	61	30	91
Mean (StdDev)	62.5 (24.83)	66.5 (22.86)	63.8 (24.15)
CFB - Week 25/End of Part 1			
N	45	24	69
Mean (StdDev)	15.6 (14.92)	13.1 (12.88)	14.8 (14.20)
95% CI	[11.15; 20.12]	[7.70; 18.57]	[11.35; 18.18]
CFB - Week 49			
N	33	22	55
Mean (StdDev)	14.4 (19.54)	12.0 (13.41)	13.4 (17.25)
95% CI	[7.43; 21.29]	[6.09; 17.99]	[8.77; 18.09]
PROMIS Physical Function			
Baseline			
N	60	30	90
Mean (StdDev)	37.5 (4.92)	38.7 (6.87)	37.9 (5.64)
CFB - Week 25/End of Part 1			
N	38	16	54
Mean (StdDev)	3.6 (4.93)	4.9 (6.32)	4.0 (5.36)
95% CI	[1.95; 5.19]	[1.52; 8.26]	[2.50; 5.42]
CFB - Week 49			
N	25	14	39
Mean (StdDev)	4.7 (4.36)	7.6 (6.25)	5.8 (5.23)
95% CI	[2.95; 6.54]	[4.03; 11.25]	[4.09; 7.48]

Visit	Pexidartinib (Parts 1 and 2) (N = 61)	Cross-over Pexidartinib (Part 2 Only) (N = 30)	All Pexidartinib Treated (N = 91)
Worst Stiffness NRS			
Baseline			
N	59	26	85
Mean (StdDev)	5.6 (1.72)	5.7 (2.31)	5.6 (1.91)
CFB - Week 25/End of Part 1			
N	33	18	51
Mean (StdDev)	−2.7 (2.15)	−3.0 (3.11)	−2.8 (2.50)
95% CI	[−3.43; −1.91]	[−4.54; −1.45]	[−3.49; −2.08]
CFB - Week 49			
N	22	10	32
Mean (StdDev)	−3.5 (1.92)	−2.2 (2.75)	−3.1 (2.25)
95% CI	[−4.33; −2.62]	[−4.18; −0.24]	[−3.89; −2.27]
Worst Pain NRS			
Baseline			
N	59	26	85
Mean (StdDev)	5.6 (1.58)	5.2 (2.45)	5.5 (1.88)
CFB - Week 25/End of Part 1			
N	33	18	51
Mean (StdDev)	−2.7 (2.19)	−2.6 (3.05)	−2.7 (2.50)
95% CI	[−3.51; −1.95]	[−4.09; −1.05]	[−3.38; −1.97]
CFB - Week 49			
N	22	10	32
Mean (StdDev)	−3.3 (1.67)	−2.8 (3.39)	−3.2 (2.30)
95% CI	[−4.08; −2.60]	[−5.23; −0.39]	[−4.00; −2.34]

CFB = change from baseline; CI = confidence interval; PROMIS = Patient reported Outcomes Measurement Information System; ITT = intent-to-treat; NRS = Numeric Rating Scale; StdDev = standard deviation.
Notes: For subjects randomized to pexidartinib, baseline is defined relative to the initial pre-dose visit in Part 1; for cross-over subjects, baseline is defined as the Week 25/End of Part 1 visit; and for all

- Relation of TGCT best overall response with function and symptom variables

Table 25: Changes in secondary endpoint outcomes by primary endpoint (RECIST tumour response) at week 25 in the pexidartinib arm (N = 59) for trial 2014-000148-14 (PLX108-10) (data cut-off 27 March 2017)

Week 25 endpoints		**CR (n=9)**	**PR (n=15)**	**SD (n=24)**	**PD (n=1)**	**NE (n=12)**
ROM (change from baseline)	n mean (95% CI)	8 20 (7.1, 33)	13 17 (9.5, 25)	22 13 (5.7, 20)	1 23 (NA)	1 9.3 (NA)
PROMIS (change from baseline)	n mean (95% CI)	8 6.5 (2.9, 10)	10 2.8 (-0.67, 6.3)	18 2.9 (0.28, 5.5)	0	2 1.9 (-24, 27)
BPI-30 Pain (response)	n (%)	5 (56)	6 (40)	6 (25)	0	2 (17)

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 26: Summary of efficacy for trial 2014-000148-14 (PLX108-10)

Title: A Double-blind, Randomized, Placebo-controlled Phase 3 Study of Orally Administered PLX3397 in Subjects with Pigmented Villonodular Synovitis or Giant Cell Tumour of the Tendon Sheath			
Study	Study PLX108-10 (ENLIVEN)		
Design	2-part, multi-centre, double-blind, randomized, placebo-controlled Phase 3 study		
	Duration of part 1: Duration of part 2:		25 weeks 24 weeks (Part 2 continued until all subjects had either reached at least the Week 49 Visit or withdrew from the trial). Subjects who completed Part 2 were allowed to continue pexidartinib treatment for longer efficacy
Hypothesis	Superiority		
Treatments groups	Pexidartinib		Part 1: 1000mg/d split into two doses (2 weeks) then 800 mg/d split into two doses (22 week), N=61 Part 2: same as the
	Placebo		Matching placebo same number of capsules as for pexidartinib for parts 1 and 2
Endpoints and definitions	Primary endpoint	ORR	Objective response rate (CR+PR) based on RECIST 1.1 (blinded central image review; no confirmation)

	Secondary endpoint	ROM	Mean change from baseline in ROM of the affected joint, relative to a reference standard for the same joint,
	Secondary endpoint	TVS response	Proportion of responders (CR+PR) based on Tumour volume scope in centrally
	Secondary endpoint	PROMIS	Mean change from baseline score in the PROMIS Physical Function Scale at week 25
	Secondary endpoint	Worst stiffness NRS	Mean change from baseline score in the Worst Stiffness numerical rating scale (NRS) item at week 25 visit
	Secondary endpoint	BPI-30	Proportion of responders based on the BPI Worst Pain NRS item and analgesic use by BPI-30 criteria at week 25
	Secondary endpoint	Duration of response	Duration of response (CR or PR) based on MRI and RECIST
Database lock	27 March 2017		
Results and Analysis			
Analysis description	Primary analysis		
Analysis population and time point description	Intent to treat defined as all randomized patients (N=120) as randomised. After DMC recommendations, the 121st randomized subject was subsequently discontinued from the study and was not included in the ITT analysis.		
Descriptive statistics and estimate variability	Treatment group	Pexidartinib	Placebo
	Number of subjects	61	59
	CR n (%)	9 (14.8)	0 (0)
	95% CI	7.96-25.72	0-6.11
	PR n (%)	15 (24.6)	0 (0)
	95% CI	15.51-36.68	0-6.11
	ORR n (%) 95% CI	24 (39.3) 28.07-51.88	0 (0) 0-6.11
	ROM (LS mean change from baseline in % normal reference for corresponding joint and plane of motion) (95% CI)	15.1% (10.9-19.2)	6.2% (1.5-10.9)
	TVS Response (95% CI)	55.7% (43.3-67.5)	0% (0-6.1)
	PROMIS (LS mean change from baseline) (95% CI)	4.1 (1.8-6.3)	-0.9 (-3.0-1.2)
	Worst Stiffness NRS (LS mean change from baseline; NRS 0 (normal) – 10) (95% CI)	-2.5 (-3.0, -1.9)	-0.3 (-0.9, 0.3)

	BPI-30 (pain response, ≥30% improvement from baseline without increased analgesic use) (95% CI)	31.1% (20.9-43.6)	15.3% (8.2-26.5)
Effect estimate per comparison	Primary endpoint ORR	Comparison groups	Pexidartinib-placebo
		Difference in %	39.34
		95% CI	26.52-51.88
		P-value (1-sided)	<0.001
	Secondary endpoint ROM	Comparison groups	Pexidartinib-placebo
		Difference in mean	8.9 pp
		95% CI	1.6-14.8
		P-value (2-sided)	0.0043
	Secondary endpoint TVS Response	Comparison groups	Pexidartinib-placebo
		Difference in %	55.7 pp
		95% CI	41.9-67.5
		P-value (1-sided)	<0.001
	Secondary endpoint PROMIS	Comparison groups	Pexidartinib-placebo
		Difference in mean	5.0
		95% CI	1.9-8.0
		P-value (2-sided)	0.0019
	Secondary endpoint worst stiffness NRS	Comparison groups	Pexidartinib-placebo
		Difference in mean	-2.2
		95% CI	3.0-1.4
		P-value (2-sided)	<0.001
	Secondary endpoint BPI-30	Comparison groups	Pexidartinib-placebo
		Difference in %	15.9
		95% CI	0.7-30.2
		P-value (2-sided)	0.052

Analysis performed across trials (pooled analyses and meta-analysis)

Analyses of pooled PLX108-01 and PLX108-10 overall response data

Demographic and baseline characteristics of subjects in studies PLX108-10 and PLX108-01 were similar. A small percentage of subjects received prior treatment with imatinib (1.1%) and nilotinib (9.9%) in Study PLX108-01 and imatinib (8.3%) and nilotinib (0.8%) in Study PLX108-10. In the TGCT cohort of Study PLX108-01, 31 subjects (79.5%) had undergone previous surgery, while 43 subjects (47.3%) in Study PLX108-10 had received prior surgery. Tumour response for this analysis followed the definition used in study PLX108-10, which did not require response confirmation; as a result, the number of responders for study PLX108-01 has 2 more PRs.

At the data cut-off of 31 May 2019, in the pooled analysis across the 130 TGCT patients treated with pexidartinib in study PLX108-10 (n=91) and the TGCT cohort of the phase 1 study PLX108-01 (n=39), the median duration of treatment was 19 months. 54 (42%) subjects remained on pexidartinib treatment and 5 (4%) discontinued pexidartinib treatment due to disease progression as assessed by the investigator. At

the data cut-off of 31 May 2019 (Table 27), the best objective response (BOR) rate was 60% (95% CI 51-70) among pexidartinib-treated subjects (N=91). A median duration of response based on RECIST had not been reached at the data cut-off of 31 May 2019, at which time the median follow-up from first dose was 36 months (range 31-47 months).

Table 27: Pooled analysis PLX108-10 (n=91) and TGCT cohort in PLX108-01 (data cut-off 31 May 2019)

Endpoint	Pooled Pexidartinib Treated TGCT Population (N=130)
RECIST Best Overall Response, n (%)	
CR	34 (26)
PR	44 (34)
SD	26 (20)
PD	1 (0.8)
NE	25 (19)
Response Rate (CR or PR) [95% CI]	**78 (60) [51, 68]**
RECIST Duration of Response, (mo)	
Median (95% CI)	**Not reached (34, —)**
Range	**0+, 70+**
TVS Best Overall Response, n (%)	
CR	14 (11)
PR	70 (54)
SD	22 (17)
PD	0
NE	24 (19)
Response Rate (CR or PR) [95% CI]	**84 (65) [56, 72]**
TVS Duration of Response, (mo)	
Median (95% CI)	**47 (47, —)**
Range	**0+, 70+**

Response rate is calculated using as the denominator of all patients treated with pexidartinib (N=130), regardless of whether the patient had no baseline or post-baseline tumor assessments.

Clinical studies in special populations

PK Trials	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
2014-000148-14 (PLX108-10)	5/84 (6.0%)	1/84 (1.2%)	0

Supportive study(ies)

Study PLX108-01 (TGCT extension cohort)

This was a first-in-human dose escalation study with an extension cohort phase. The dose escalation phase of the study was an open-label, ascending dose study of daily oral doses of pexidartinib administered to subjects with solid tumours in order to evaluate PK and observed toxicity. In Part 2, the recommended Phase 2 dose of 1000 mg/day was used in 6 extension cohorts. The TGCT cohort included subjects for which they must have had a histologically confirmed diagnosis of inoperable progressive or relapsing TGCT or resectable tumour requiring mutilating surgery as well as demonstrated progressive disease in the last 12 months. The TGCT cohort was enlarged to include a total of 39 subjects.

Subjects were enrolled and followed for safety and tumour response, assessed by radiographic scan every 8 weeks. Subjects were to remain on treatment until tumour progression, as long as there were no unacceptable toxicities.

At the time of the data cut-off (3 March 2017), 17 of the 39 TGCT subjects initially enrolled with TGCT had been on pexidartinib treatment for approximately 2 to 4 years and 15 subjects were still receiving pexidartinib treatment with continuing collection of safety and efficacy data. The most common reasons for study discontinuation were AEs (30.8%), disease progression (10.3%), and noncompliance (10.3%). Subjects were 43.6% male, 84.6% white, and 89.7% not Hispanic or Latino, with a mean age of 45.1 years.

In the TGCT cohort, 37 of 39 subjects (94.4%) were included in the Efficacy Evaluable population. Based upon investigator assessment, a PR or CR as best response was reported in 23 (62.2%) subjects (PR in 21 subjects [56.8%] and CR in 2 subjects [5.4%]), for an ORR of 62.2% (95% CI: 42.1 - 75.2%). Similar efficacy results were observed based upon central MRI review. The median progression-free survival (PFS) for the TGCT subjects was not reached at the time of the data cut-off. Median duration of response was about 33.6 months. Patient-reported outcomes data was only available for 21 TGCT subjects. In these 21 subjects, the mean pain level improved by Day 15, and this improvement was generally sustained for the duration of treatment.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy of pexidartinib as monotherapy is based on one single randomised placebo-controlled, double-blind pivotal trial (PLX108-10). The CHMP scientific advice accepted a placebo-controlled design study add-on to best supportive care. The proposed fixed duration of 24 weeks for the placebo-controlled part 1 was accepted as well.

Patients in the control arm could cross-over to the active treatment after six months under placebo. The cross-over, by confounding median- and long-term outcomes, restricts the comparative analysis to short-term period only.

Subjects could undergo surgical resection of their tumour after the completion of Part 1. Details of the surgery and its outcome were collected. However, the study was not designed to evaluate pexidartinib in the neo-adjuvant setting.

Overall, the study design was adequate to investigate the short-term benefits for the functional and symptomatic aspects of the disease.

The inclusion and exclusion criteria were considered adequate as per the scientific advice. They led to enrol a heterogeneous patient population with symptomatic TGCT (subtypes, location of the disease, progression, extension of disease). Symptomatic TGCT was defined as per worst pain and/or worst stiffness scale at least 4 at any time during the week preceding the screening visit. The Applicant did not specify for how long these symptoms should have minimally lasted (minimum required time since onset). Reasons why surgical resection was not a suitable treatment option for patients included in the trial and why postsurgical morbidity risk was not centrally assessed and it is unclear how far these criteria had been standardized across the study population; inter-rater agreement on post-surgery morbidity risk has not been presented.

Currently, for patients with a diffuse TGCT when total resection is not feasible or would induce severe morbidity, treatment options comprise subtotal resection with adjuvant therapy or exclusive therapy for the inoperable cases. Adjuvant therapy include radiation therapy and targeted therapies (NCCN guidelines version 1.2019 included off-label use of imatinib). Moderate dose external beam radiation therapy (EBR) offers a high chance of local control (75-98%) with avoiding long term radiation therapy induced toxicity.

TGCT is a rare pathology affecting young and middle-aged subjects with no specific comorbidities and with a slightly higher prevalence among females. Overall, patients included in the trial are considered representative of the target population. The majority of patients had a diagnosis of diffuse TGCT known as PVNS (87.5%). This is considered consistent with the target population of the treatment; PVNS involve more surgical difficulties to be completely resected which may lead to significant postsurgical morbidities. Lower extremity was the most affected extremity (n = 110, 91.7%), and the knee was the most commonly involved joint (n = 73, 60.8%). The distributions of the demographic characteristics and baseline disease characteristics between subjects receiving pexidartinib or placebo were generally similar. The most notable difference is a longer time since diagnosis in the experimental arm. This could constitute a prognostic marker (more indolent disease, or more advanced stage). Subjects in pexidartinib arm had their bone erosion score and cartilage loss score worse than subjects in placebo arm.

The prior treatments reflect the current practice in treatment of TGCT patients. However, almost 50% of patients enrolled have never had TGCT surgery before inclusion. This is not typical of severe PVNS, since in the clinic most patients with a PVNS that are 'inoperable or for whom surgical resection would have been associated with severe morbidity' have had multiple surgeries in the past.

The pexidartinib starting dose (1000 mg/d split into two doses) in the pivotal study was based mainly on the maximum tolerated dose (MTD) in study PLX108-01. This was also supported by the PD biomarker, circulating CSF-1, for which near maximal response required doses of 1000 mg/d. The correlation of anti-tumour activity with CSF-1 concentrations has not been established. This dose selection strategy resulted in a rather high dose with regard to safety because approximately 50% of patients in the TGCT cohort required dose reductions to 800 mg/d or less within the first 2 cycles. Therefore, and based on only purely clinical empirical observations, a reduced maintenance dose of 800 mg/d of pexidartinib, beginning after 2 weeks of treatment with 1000 mg/d, was implemented in the confirmatory trial (each split into two doses).

There are no validated global response criteria for TGCT. The CHMP scientific advice had considered the value of Objective Response Rate (ORR based on centrally read MRI scans and RECIST 1.1 criteria) as a primary endpoint an item of discussion and that ORR would need to be supported with PRO data and durability of the objective response.

ROM (which assessed functionality of the most affected joint) and symptomatic endpoints encompassing PROs of pain, stiffness and physical function were secondary endpoints. The assessment of these endpoints in the setting of TGCT disease is then pivotal as they provide direct evidence from the patient perspective for the meaningfulness of changes observed in tumour size. The CHMP scientific advice had recommended that durable symptomatic response and surgery could be used to define success as co-primary endpoint to ORR. The Applicant adopted the hierarchical testing sequence including as primary endpoint ORR measured by RECIST 1.1 and as first secondary endpoint the key PRO outcome measure (BPI worst pain NRS).

In September 2016, in response to the emergence of the 2 cases of potential cholestatic liver injury, the study DMC recommended safety measures that changed the conduct of this study to address the protection of subjects. Enrolment was stopped and subjects on placebo in Part 1 were no longer allowed to enter Part 2 to receive open-label pexidartinib. As a consequence, the primary analysis at the data cut-off 27 March 2017 is limited to 61 patients on active treatment and 59 on placebo (120 of initially planned sample size of 126 subjects). 30 patients were switched from placebo to pexidartinib prior to the amendment, resulting in only 91 patients with at least some data on treatment with pexidartinib. In addition, more than the expected number of enrolled subjects discontinued the study prior to the end of Part 1 assessments. A total of 100 (83.3%) subjects completed Part 1 of the study with similar rates for early discontinuation between the 2 treatments groups (11 subjects [18.6%] in placebo group versus 9 subjects [14.8%] in pexidartinib group). Adverse events in 8 (13.1%) subjects were the most common reason for study discontinuation for the pexidartinib group. Withdrawal of consent by 6 (10.2%) subjects was the most common reason for discontinuation for the placebo group. After the urgent safety measures (USM), a greater number of discontinuations (withdrawal of consent or investigator decision) was observed in the placebo arm (9 subjects) compared to pexidartinib arm (1 subject) despite the blinding of the study.

Moreover, the protocol (Version 8.0) was amended to revise the sequential-analysis hierarchy of certain efficacy endpoints. Before the amendment of the SAP and the protocol, the hierarchical testing sequence included as primary endpoint ORR and as first secondary endpoint BPI worst pain NRS as it is the most relevant clinical endpoint to patients and physicians. During the study, as a consequence to the substantial amount of missing data, the secondary endpoints hierarchy was re-ordered; BPI-30 switched to the last place in the hierarchical testing. Eventually, results for BPI-30 were the only results in the hierarchically tested efficacy endpoints that did not reach statistical significance.

Three GCP inspections were conducted in January and March 2019 in the USA, the Netherlands and Italy. No significant findings of GCP non-compliance have been identified, and no sites were closed for non-compliance reasons.

Efficacy data and additional analyses

The ITT population related to the originally claimed indication was limited to 120 subjects. The number of patients with major protocol violations that were considered to potentially affect efficacy in the pexidartinib arm seems relatively high (see Conduct of the study).

The study met its primary efficacy endpoint as a statistically significant effect on ORR between pexidartinib and placebo group was demonstrated, favouring pexidartinib with a difference of 39.3 percentage points (95% CI: 26.5-51.8, 1-sided P <0.0001). There were 9 out of 61 patients with a complete response (CR) in the pexidartinib arm, where no patient in the placebo arm had an objective response (PR or CR). Of the

59 patients in the placebo group, one patient (2%) had progression of disease and all others had stable disease. In general, subgroup analyses for ORR showed a consistent effect over most subgroups.

The ROM endpoint is an objective measure of joint function, which in concept relates to the ability to perform activities of daily life. The LS mean change from Baseline at Week 25 in relative ROM scores favoured pexidartinib achieving statistical significance (P = 0.004, 2-sided) by a difference of 8.9 ± 3.0 percentage points (95% CI: 2.9, 14.9) relative to normal joint function. However, the clinical interpretability of this endpoint is difficult. Data were missing for a considerable proportion of subjects in the two arms (27%). The correlation of ROM with the PROMIS endpoint was weak (r = 0.31).

The LS mean change from Baseline at Week 25 in PROMIS physical function selected item set scores was higher in favour of pexidartinib by a difference of 4.95 ± 1.6 percentage points (95% CI: 1.9, 8.0) (p=0.0019, 2-sided). However, assessment data at week 25 were lacking for a significant number of patients (37% in the pexidartinib arm and 48% in the placebo arm). Interpretability of results is thus limited by the large amount of missing data which causes bias in the estimation of both between- and within-group effects.

The LS mean change from Baseline at Week 25 in Worst Stiffness NRS was better in the pexidartinib group compared with the placebo group with statistically significant results (P <0.001, 2-sided) in favour of pexidartinib by a difference of -2.2 ± 0.4 percentage points (95% CI: -3.0, -1.4). The individual improvement of stiffness ranged from little to moderately improved. However, the substantial proportion of missing values at week 25 (40% in the placebo arm and 46% in the pexidartinib arm) hamper the interpretation of these results. In addition, there was no standardization of anti-inflammatory / anti-rheumatic and analgesic dosing during the part 1 of the study.

The response rate for Part 1 at the Week 25 Visit based on BPI-30 was higher in the pexidartinib group compared with the placebo group by a difference of 15.9 percentage points (95% CI: 0.7, 30.2); however, results were not statistically significant (P = 0.032; 1-sided exact test). Data were missing for a considerable proportion of subjects in the pexidartinib arm (46%) and the placebo arm (40%). Analgesics other than narcotics (such as non-steroidal anti-inflammatory drugs) were not considered for determination of BPI-30.

LOCF analysis were performed based on last available part 1 BPI-30 assessment and results favoured pexidartinib by a difference of 25.6 percentage points (95% CI: 13.8, 49.5) (1-sided p<0.0008). This method was also performed for additional sensitivity analyses of the mean change from baseline for ROM, PROMIS and worst stiffness. As data at week 25 may not be missing completely at random, this imputation method may lead to biased conclusions especially since the proportion of missing data is high.

Longer-term efficacy data

At a data cut-off point of 31 May 2019, the BOR rate according to RECIST 1.1 increased with continuation of pexidartinib treatment to 62.3% (95% CI 49.7-73.4%) among the 61 subjects randomized to pexidartinib and treated in both part 1 and 2 (N = 61) and to 60% (95% CI 42.3-75.4%) among the patients (N = 30) who were on placebo on part 1 and crossed over to pexidartinib in part 2.

There is a lack of evidence for long-term clinical benefit with pexidartinib. The results on joint function and symptoms at week 49 (beyond week 25) are limited to a small number of patients, absent a control group. Further support or evidence for the long-term benefit with pexidartinib treatment is needed.

A median duration of response based on RECIST had still not been reached as of the 31 May 2019 data cut-off, at which time the median follow-up from first dose was 36 months.

Recommendations for the dosing regimen

A comparison of results between the pexidartinib cohort in part 1 (n = 61; 1000 mg/d for 2 weeks followed by 800 mg/d) and the cross-over cohort in part 2 (n=30; 800 mg/d pexidartinib) showed at 25 weeks of pexidartinib comparable activity (objective response) and function and symptom changes, with a less unfavourable safety/tolerability profile in the cross-over cohort (no cholestatic liver injury, fewer patients with liver enzyme abnormalities or hepatic TEAEs). However, this comparison is not robust because it was not randomized and involved a small comparison group; moreover, increased selection bias is likely since only about half of the patients on placebo crossed over.

Revised age, gender- and body weight-based dosing without an initial period at higher dose might be an adequate regimen to start to treat TGCT patients in clinical practice (Table 28 and section 4.2 in the SmPC). Projected probabilities for liver enzyme elevations and for tumour shrinkage with this dosing regimen are in Table 10. Dose modifications for adverse reactions are in Table 41.

The optimal dosing for pexidartinib in the target population is still insufficiently established; accordingly, further dose-finding efforts or trials are recommended to provide information on an effective dose with a better safety profile, while taking into consideration the serious risk of hepatotoxicity as well as PK and clinical data from the post-authorisation study to be conducted to substantiate the above-mentioned dosing regimen.

Table 28: Recommendation for revised dosing regimen for pexidartinib

Age	**Gender**	**Weight**	**Dose (mg/day)**
< 65 yrs	Female	< 75 kg	400
< 65 yrs	Female	>= 75 kg	600 (200 mg in the morning, 600 mg in the evening)
< 65 yrs	Male	< 60 kg	600 (200 mg in the morning, 600 mg in the evening)
< 65 yrs	Male	>= 60 kg	800
>= 65 yrs	Female	< 75 kg	200
>= 65 yrs	Female	>= 75 kg	400
>= 65 yrs	Male	< 60 kg	400
>= 65 yrs	Male	>= 60 kg	600(200 mg in the morning, 600 mg in the evening)

Efficacy in population corresponding to the restricted indication

Subsequent to the efficacy and safety concerns, the applicant proposed a restricted indication to include a TGCT population with undisputable unmet medical need and for whom for benefits relative to the risk of hepatotoxicity from pexidartinib would be favourable, as follows: "Turalio is indicated as monotherapy for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability."

According to the applicant, this restricted indication corresponds to in total 20 pexidartininib-treated patients in the main clinical trial: 14 subjects randomized to pexidartinib and 6 subjects who crossed over from placebo to pexidartinib. The TGCT was located in the knee for 9 of these 20 subjects. The subjects were identified as follows:

- The TGCT was severe, defined as mean patient-reported brief pain inventory (BPI) 7 of 10 or higher, mean patient-reported worst stiffness 7 of 10 or higher, or use of narcotic analgesics, and
- The TGCT was not suitable for surgery, defined as expected post-operative morbidity evaluated as severe, or operative risk due to other medical conditions was high.

In these 20 subjects, the best overall response (BOR) was 55% ORR, and to explore the clinical effects of this ORR, ROM was assessed in a case-by-case approach. Since 2 subjects of the restricted indication population were not adequately evaluable, only 18 patients were assessed case-by-case. Among these 18 patients assessed, 4 patients had a probably clinically relevant improvement based on a responder analysis (more than 15 percentage points improvement in relative ROM at the latest evaluable ROM assessment, patient-level data not shown), one concerning the knee, two the ankle and one the hip.

In 9 of the 20 subjects, ROM measurements related to the knee; among these 9 subjects, 6 had a ROM measurement at week 25 and 8 had a ROM measurement at the visit when the post-baseline sum of the longest diameters of the TGCT had the lowest value. The knee ROM change from baseline was only 3.4% (mean; SEM 3.4) and 4.6% (4.7) at these times, respectively, corresponding to an absolute increase of only 5° and 7° in the range of motion of the knee (normal: about 150°).

The change in ROM was highly variable in the same subject at different time-points, even when the longest tumour diameter or TVS was stable, which raises concerns regarding the validity of this parameter for supporting clinical benefit of tumour shrinkage. Two patients with TGCT complete response (RECIST v1.1) had no change in ROM.

Taken together, the activity data in patients corresponding to the restricted target population provide a low level of evidence for a clinically relevant benefit in terms of improvement in joint function.

Additional expert consultation

The Scientific Advisory Group (SAG) in Oncology was consulted during this procedure and gave the following answers. The proposed indication discussed by the SAG was, "Treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), which is associated with severe morbidity or functional limitations, and which is not amenable to improvement with surgery". CHMP questions with SAG answers:

"1. The activity of Turalio on tenosynovial giant cell tumours (TGCT) is established in the pivotal trial on the basis of an objective response rate (ORR) of 39% (95%CI: 27-52%).

(a) Could the experts define the different clinical situations where TGCT shrinkage is of interest to patients? If yes, which clinical parameter would establish the clinical relevance of benefit in such situations?

TGCT shrinkage and disappearance of the disease is a general objective of treatment. However, the clinical importance of shrinkage depends on the different clinical situations, in particular the residual functionality of the joint as well as the association with symptoms due to the size and location of the disease. In some cases, the shrinkage has an undisputable effect in restoring function, decreasing symptoms, and improving

aesthetic outcome. The association between shrinkage and symptom improvement was observed to a reasonable extent with Turalio, looking at correlations with physical functioning, range of motion, pain, and stiffness, despite the limitations due to missing data.

Tumour shrinkage is relevant when surgery is not the preferred option and when the size and location of the disease are associated with important symptoms. Surgery may not be the preferred option when complete resection is unachievable or when it is associated with important morbidity.

The choice between surgery and other therapies is complex and there is a risk that less efficacious and less safe treatments are chosen instead of surgery. The decision of when to start surgical or other treatment is also complex. Thus, the clinical decisions should take place with an expert multi-disciplinary team taking patient preferences into account ensuring patients have full information about benefits, harms, and uncertainties associated with the different options.

(b) Is TGCT shrinkage as observed in the pivotal trial well correlated with an improvement or less worsening of disability?

The assessment of correlations is difficult due to missing data on many endpoints and substantial variability. However, in general, a reasonable association was observed in the pexidartinib arm between shrinkage and increased ROM, decreased pain, decreased stiffness, and increased physical functioning, corroborating that tumour shrinkage is associated with some degree of clinical benefit.

(c) What are clinical situations where primary or secondary TGCT surgery, respectively, cannot be performed, and how frequent are these situations?

In principle, surgery, can almost always be performed or attempted but in a number of situations this may be futile or result in high morbidity and loss of function, e.g., amputation. In about 50% percent of patients, the disease will recur after initial surgery. Following second surgery, again the disease will recur in about 80% of patients and often further surgery might not be the preferred option. Thus about 40% of initially diagnosed patients may be in a situation where TGCT surgery might not be a good further treatment option.

(d) In which respect could Turalio have a place in therapy, taking into account also anti-cancer medicines used in clinical practice to treat patients with TGCT?

Turalio could have a clear place in therapy after recurrence when the aim is long term pain control and improvement in physical functioning, in situations where further surgery may be futile (e.g., quick relapse; multiple surgeries) or complete resection unachievable, or in any situation when surgery could result in high morbidity and important loss of function.

Currently, it is not known if Turalio can be used to delay or avoid primary surgery. There is a potential risk that off-label use prior to primary surgery could lead to worse outcomes. Based on the available data, Turalio should not be used with a neoadjuvant intent when radical surgery is considered feasible. Upon approval, there will be a need to monitor which patients are treated and that unintended "stage" shift (increasingly, surgery not preferred) is minimised.

There are no other established anti-cancer medicines used in clinical practice. There is very little off-label use of other therapies, but these are no evidence-based. Radiotherapy (RT) has been used specially in inoperable tumours. However, RT has heavy caveats as TGCT is a benign tumour and often affects young patients.

Pexidartinib is better than what is used off label and clearly can have a place in therapy.

2. Does the anti-tumour activity and the clinical effects observed in the pivotal trial indicate that treatment with Turalio would provide clinically relevant benefit in patients, in the proposed indication or in an alternative indication considered of interest by the experts?

Turalio has shown to provide a clinically relevant benefit in the proposed indication based on the very durable responses in a high proportion of patients and the reasonable correlation with clinically relevant outcomes such as pain, range of motion, and physical functioning. The effect seemed to be particularly impressive / noted in earlier stages and in smaller TGCTs, although on the basis of exploratory analyses.

Proposed Indication by the Applicant at the time of the meeting: "Turalio is indicated as monotherapy for the treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT), which is associated with severe morbidity or functional limitations, usually in the recurrent setting, and with no expectation that surgery will stabilize or improve the patient's condition."

Concerning the proposed therapeutic indication above, there are some aspects that could be improved, namely:

- Avoid the term "usually" in the indication. This should be changed to recurrent disease or when radical surgery is not feasible or indicated.
- Although the timing of treatment start remains a matter to be further investigated, use should be limited to patients with clinically relevant physical function deterioration, noting that neither symptomatic / asymptomatic nor morbidity severity can be well defined.

3. Is the safety and toxicity profile of Turalio sufficiently predictable and manageable for using Turalio in the clinic, in certain patients? Consider in particular the risk for severe liver injury.

The toxicity profile of Turalio is mostly predictable and manageable. The severe liver injury is unpredictable and is the main concern. A balance of benefits-and risks has to be done at individual level considering the available therapeutic options and symptoms. In many situations, patients will consider that the benefit-risk balance is positive, but the risks have to be clearly explained, monitoring (e.g., circulating liver enzymes) is particularly frequent in the first months and patients are trained to be aware of symptoms. Treatments should only be given in expert centres, in a multidisciplinary setting, by professionals experienced with targeted therapies.

Recommended further investigations:

- There is a need to further minimise the risks for severe liver injury to occur. Further research should be conducted post-approval aiming to identify risk factors.
- There are also concerns about the incidence of severe liver injury in the real-world and this should be monitored.
- Dosing seems far from optimal dosing and it should be investigated if dosing could be further optimized (based on biological criteria and not on MTD) and individualised. Also, are treatment holidays possible?
- Lastly, there is a need to clarify the molecular biology regarding the presence of CSF1 gene fusions and the level of CSF1 expression for all patients, to explore if patient subgroups with better/worse response to treatment with Turalio can be identified."

The CHMP noted that the risk of hepatic toxicity of pexidartinib will remain unpredictable and that the effectiveness of the risk minimisation measure is uncertain, even when pexidartinib treatments should only

be given in expert centres, in a multidisciplinary setting, by professionals experienced with targeted therapies, as expressed by the SAG.

2.5.4. Conclusions on the clinical efficacy

The design of the pivotal trial is acceptable with the provision that the primary endpoint (objective tumour response: CR and PR) would need to be supported with PRO data.

Pexidartinib monotherapy has shown a statistically significant effect in terms of tumour response according to RECIST criteria with a difference in ORR of 39.3 % (95% CI: 28.07-51.88) compared to placebo at week 25 in the controlled part of the study. This clearly indicates activity in terms of tumour shrinkage.

Despite favourable trends, the effects on clinical endpoints (ROM, PROMIS, stiffness, pain / BPI-30) are difficult to interpret due to many missing observations, in particular for the effect on pain in the absence of statistical significance.

In addition, the maintenance and the persistence of effects in the long term after treatment discontinuation is not well documented.

A PASS is proposed to collect real-world data regarding pexidartinib Pk, safety and activity for up to 7 years and to specially evaluate the risk mitigation processes to manage the high risk of potentially fatal hepatotoxicity.

2.6. Clinical safety

The safety profile of pexidartinib for the proposed indication is primarily based on safety data from the phase 3 Study 2014-000148-14 / PLX108-10 (ENLIVEN) and from the TGCT expansion cohort in the Phase 1 Study PLX108-01 (TGCT population) and supported by safety data from 6 pexidartinib monotherapy studies in cancer patients (Non-TGCT monotherapy population).

TGCT population

The safety data were pooled for integrated safety analysis (ISS). For the TGCT studies PLX108-10 and PLX108-01, the data cut-off was in 27 March 2017 and 03 March 2017, respectively. At the time of the data cut-off of March 2017 for the primary study analyses, 65 and 15 TGCT subjects were continuing on pexidartinib in studies PLX108-10 and PLX108-01, respectively. Both studies have updated safety results with a data cut-off of 31 January 2018 that are presented side-by-side with March 2017 data cut-off for each study. Updated safety data were presented in response documents with data cut-off of 31 May 2019.

Table 29: Summary groups of pooled analyses for TGCT population

Treatment code	Description
A	Randomized to Placebo in PLX108-10 (Part 1 data only, N=59)
B	Randomized to Pexidartinib in PLX108-10 (Part 1 data only, N=61; dose: 1000 mg/day [split dose] × 2 weeks, then 400 mg BID)

C	Randomized to Pexidartinib in PLX108-10 (Part 1 and 2 data, N=61; same subjects as Group B but here also including their results after the Part 1 randomized comparison period)
D	Crossover in PLX108-10 (Part 2 with open label Pexidartinib data only, N=30, dose 400 mg BID)
E	TGCT cohort in PLX108-01 study (N=39, dose: 1000 mg/day [split dose] with an earlier pexidartinib formulation)
F	All pexidartinib Treated (Total of group C, D, and E, N=130)

The group D from TGCT population corresponds to the claimed posology in this application (800 mg/day).

Non-TGCT monotherapy population

Of the 6 pexidartinib monotherapy studies in cancer patients, 5 were pooled for analysis (PLX108-01, PLX108-03, PLX108-04, PLX108-06, and PL3397-A-A103). Safety data from the acute myeloid leukaemia (AML) study, PLX108-05, is also presented in the ISS, but separately because the AML population has many unique disease-related AEs, and because doses of pexidartinib administered were much higher (800 mg/day to 5000 mg/day).

Table 30: Non-TGCT Monotherapy Population by Summary Group

Treatment code	**Description**
A	Pexidartinib 200 mg/day to 600 mg/day: Non-TGCT solid tumours treated with pexidartinib 200 mg/day to 600 mg/day (N=24): - PLX108-01 non-TGCT solid tumours (n=21) - PL3397-A-A103 non-TGCT solid tumours (n=3)
B	Pexidartinib 900 mg/day to 1200 mg/day: - Non-TGCT solid tumours treated with pexidartinib 900 mg/day to 1200 mg/day (N=144) - PLX108-01 non-TGCT solid tumours (n=72) - PLX108-03 Hodgkin's lymphoma (n=20, 900 mg/day dose) - PLX108-04 glioblastoma multiforme (n=38, 1000 mg/day dose) - PLX108-06 castrate-resistant prostate cancer (n=6, 1000 mg/day dose) - PL3397-A-A103 (Taiwan) (n=8, 1000 mg/day dose only)
C	Total non-TGCT: Total non-TGCT solid tumours treated at any pexidartinib dose (N=168), comprised combined data from Summary Group A (Pexidartinib 200 mg/day to 600 mg/day) and Summary Group B (Pexidartinib 900 mg/day to 1200 mg/day) above
D	AML: PLX108-05 (N=90, 800 mg/day to 5000 mg/day)

Additional supportive safety data were submitted from other clinical studies that were not part of the integrated analysis, including combination therapy in cancer, clinical pharmacology studies, ongoing study results, and investigator-initiated studies.

Patient exposure

Across these studies, 630 subjects with cancer or TGCT received pexidartinib and were assessed for safety and efficacy in 13 sponsored clinical studies, 2 of which were focused in TGCT. Other pexidartinib studies such as clinical pharmacology studies and investigator-initiated studies included 476 subjects treated.

In TGCT population, treatment with pexidartinib was ongoing in 80 of the 130 (61.5%) subjects at the time of the March 2017 data cut-off for the primary analyses of each study.

- Drug exposure

Dose exposure and dose intensity are heterogeneous among the TGCT groups, which lead to limitations for comparison among the groups.

As of 31 March 2017, the median duration of exposure to pexidartinib was 43 weeks (range: 2 weeks to 211 weeks): 37.9 weeks in Study PLX108-10 and 73.0 weeks in Study PLX108-01. The median total number of doses taken per subject was 321.5 (range: 14 to 1156). The median dose intensity of all Pexidartinib-treated subjects was 3704.3 mg per week (range: 75 to 6232 mg/week).

In the TGCT group D at the intended dosage of 800 mg/day, the median study drug exposure is 31.8 weeks for 30 subjects and median dose intensity was 4114.2 mg per week (range: 1675 to 5594 mg/week).

As of 31 January 2018, 48 and 13 subjects are continuing on pexidartinib treatment in Studies PLX108-10 and PLX108-01, respectively, with median exposure durations of 71 weeks and 73 weeks, respectively.

Overall, the median study drug exposure is higher in TGCT group compared to Non-TGCT and AML groups (43 weeks in TGCT group vs 7.9 weeks in Non-TGCT and 6.3 weeks in AML). The maximum exposition is TGCT group is 211 weeks at March 2017 cut-off date.

Among the TGCT population, the median study drug exposure was higher in Phase 1 PLX108-01 study (73 weeks) compared to subjects in Phase 3 PLX108-10 study (24 weeks for group B, 43.1 weeks for group C and 21.8 weeks for group D). In non-TGCT solid tumour population, the median study drug exposure was similar for the 2 dosage groups (7.9 weeks).

In contrast, the median total number of doses per subject taking into account the missed and reduced doses was much lower in Phase 1 PLX108-01 study (38.0 doses/subject) compared to Phase 3 Study (285.0 doses/subjects in group B, 460.0 doses/subject in group C and 307.5 doses/subject in group D).

The median dose intensity was lower in Phase 1 PLX108-01 study (476.2 mg/week) compared to subjects in Phase 3 study PLX108-10 (5050.0 mg/week for group B, 4592.8 mg/week in group C and 4114.2 mg/week in group D).

- Subject disposition (data cut-off 31 March 2017)

In TGCT population, it is noted that 46 (35.4%) subjects had an early treatment discontinuation of which 25 (19.2%) was due to an adverse event.

In the controlled part of study PLX108-10, 11 (18.6%) subjects in placebo arm and 9 (14.8%) subjects in pexidartinib arm had an early discontinuation of treatment. The higher number of subjects who discontinued treatment in placebo arm compared to pexidartinib arm is due to the withdrawal of consent by subject and investigator decision.

In the non-TGCT solid tumour subjects treated at any dose of pexidartinib (200 mg/day to 600 mg/day or 900 mg/day to 1200 mg/day), all (100%) subjects discontinued study treatment.

The primary reason for discontinuation of pexidartinib was progressive disease (67.9%, 114 subjects), followed by withdrawal by subject (9.5%, 16 subjects), AEs (7.1%, 12 subjects), and other (7.1%, 12 subjects).

- Demographic and other characteristics of study population

Pexidartinib-treated TGCT subjects had a median age of 45.0 years and were mostly female (56.2%) and white (88.5%). Demography of the study population in general revealed that almost all patients (N=115/130; 88.5%) were Caucasians and males were slightly underrepresented [Male: 57/130 (43.8); Female]. 92.6% of the included trial population was younger than 65 years and 64.6 below the age of 50 years. Comparing the demographic characteristics of the included study population with literature data (e.g. Ehrenstein et al, 2017) it is confirmed that the trial population adequately reflects the applied target population.

Of all the subjects randomized to a treatment group in the pivotal study PLX108-10, 47.5% of subjects had not had a prior surgery for TGCT, 87.5% were diagnosed with diffuse TGCT, and 60.7% and 62.7% had no expected probability of a complete resection from surgery (pexidartinib and placebo groups, respectively). For most of the subjects, the lower extremity was involved, and the main localisation was the knee.

In TGCT cohort in study PLX108-01, all the subjects had PVNS, mainly localized in the knee (21/39 subjects).

- Updated data (DCO 31 May 2019)

An updated data cut with follow-up through 31 May 2019 provides an additional 16 months of follow-up past the MAA data cut-off of January 2018 and 26 months of follow-up past the original ISS data cut-off of March 2017. This data set includes all TGCT subjects who have been treated with pexidartinib, a total of 140, from the following studies: PLX108-01 (n=39), PLX108-10 (n=91), PL3397-A-A103 (n=1), PL3397-A-U126 (n=9).

Table 31: Summary of updated pexidartinib exposure in the TGCT population

	TGCT Population March 2017 (N=130)1	**TGCT Population May 2019 (N=140)2**
Study Drug Exposure (week)		
Mean (SD)	53 (42)	102 (78)
Median	43	74
Min, Max	2, 211	2, 328

Study Drug Exposure by Time Period, n (%)		
< 1 Day	0	0
2 Days to 4 Weeks	3 (2.3)	4 (2.9)
Over 4 to 8 Weeks	7 (5.4)	7 (5.0)
Over 8 to 12 Weeks	2 (1.5)	3 (2.1)
Over 12 to 16 Weeks	3 (2.3)	3 (2.1)
Over 16 to 20 Weeks	3 (2.3)	3 (2.1)
Over 20 to 24 Weeks	3 (2.3)	3 (2.1)
Over 24 to 36 Weeks	30 (23)	6 (4.3)
Over 36 to 48 Weeks	25 (19)	19 (14)
Over 48 to 72 Weeks	28 (22)	18 (13)
Over 72 to 96 Weeks	9 (7)	9 (6.4)
Over 96 Weeks	17 (13)	65 (46)

[1]Includes subjects from PLX108-10 (n=91) and PLX108-01 (n=39). [2]Includes subjects from PLX108-10 (n=91), PLX108-01 (n=39), PL3397-A-U126 (n=1), and PL3397-A-A103 (n=1).

Adverse events

- Overview of TEAEs

In TGCT population (DLP March 2017), the majority of subjects experienced at least 1 or more treatment-emergent adverse events (TEAEs) (99.2%. 129 subjects), most of which were treatment-related (97.7%, 127 subjects).

Table 32: Overall summary of TEAEs in TGCT population, Safety Analysis Set (data cut-off date March 2017)

	PLX108-10 Px				PLX108-01 Px	ALL Px
Category	PBO Part 1 A (N=59) n (%)	Px Part 1 B (N=61) n (%)	Px Part 1-Part 2 C (N=61) n (%)	Px Part 2 XO D (N=30) n (%)	E (N=39) n (%)	F (N=130) n (%)
Subjects with any TEAEs	55 (93.2)	60 (98.4)	60 (98.4)	30 (100.0)	39 (100.0)	129 (99.2)
Subjects with any Treatment-Related TEAEs[a]	38 (64.4)	59 (96.7)	59 (96.7)	29 (96.7)	39 (100.0)	127 (97.7)
Subjects with CTCAE Grade 3, 4, or 5 TEAEs	7 (11.9)	27 (44.3)	31 (50.8)	8 (26.7)	17 (43.6)	56 (43.1)
Subjects with Treatment-Related CTCAE Grade 3, 4, or 5 TEAEs	2 (3.4)	23 (37.7)	27 (44.3)	6 (20.0)	14 (35.9)	47 (36.2)
Subjects with CTCAE Grade 5 TEAEs	0	0	0	1 (3.3)	0	1 (0.8)
Subjects with Treatment-Related CTCAE Grade 5 TEAEs	0	0	0	0	0	0
Subjects with any Treatment Emergent SAEs	1 (1.7)	8 (13.1)	9 (14.8)	3 (10.0)	4 (10.3)	16 (12.3)
Subjects with any Treatment-Related Serious TEAEs	0	6 (9.8)	7 (11.5)	1 (3.3)	1 (2.6)	9 (6.9)
Subjects with TEAEs Leading to:						
Discontinuation	0	8 (13.1)	11 (18.0)	3 (10.0)	12 (30.8)	26 (20.0)
Dose reduction/interruption	6 (10.2)	23 (37.7)	28 (45.9)	11 (36.7)	31 (79.5)	70 (53.8)
Subjects with any TEAEs of Special Interest	9 (15.3)	36 (59.0)	39 (63.9)	14 (46.7)	21 (53.8)	74 (56.9)
Cognitive Disorder	3 (5.1)	3 (4.9)	3 (4.9)	3 (10.0)	15 (38.5)	21 (16.2)
Hepatic Disorder	3 (5.1)	29 (47.5)	33 (54.1)	9 (30.0)	8 (20.5)	50 (38.5)
Myelosuppression	2 (3.4)	11 (18.0)	14 (23.0)	8 (26.7)	4 (10.3)	26 (20.0)
Cardiac Function	2 (3.4)	0	0	0	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; PBO = placebo; Px = pexidartinib; SAEs = serious adverse events; TEAEs = treatment-emergent adverse events; TGCT = tenosynovial giant cell tumor; XO = crossover.

Note: A = Randomized to placebo in PLX108-10 (Part 1 data),
B = Randomized to pexidartinib in PLX108-10 (Part 1 data),
C = Randomized to pexidartinib in PLX108-10 (Part 1 and 2 data),
D = Crossover in PLX108-10 (Part 2 with open label pexidartinib data),
E = TGCT cohort in PLX108-01 study,
F = All pexidartinib treated subjects in Study PLX108-01 and PLX108-10 (Group C + Group D + Group E).

% = (n/N)x100.
a Treatment-related TEAE is defined by the investigator to be related, possibly, or probably related to study drug or TEAEs with a missing causality.
For each row category, a subject with 2 or more adverse events in that category is counted only once.
Adverse events were graded using CTCAE version 4.03. Source: ISS Table 14.2.1.1 (TGCT Population)

- TEAEs listings

The most frequently reported SOCs were skin and subcutaneous tissue disorders (90.0%), general disorders and administration site conditions (73.1%), GI disorders (70.0%), and nervous system disorders (65.4%).

The frequency of TEAEs was similar between the crossover cohort compared with the pexidartinib randomized cohort and the Study PLX108-01 cohort, but less cases of fatigue and nausea were reported in the crossover group.

Table 33: Number (%) of Subjects Reporting Common (≥5%) TEAEs by PT and by Decreasing Frequency in TGCT population, Safety Analysis Set (data cut-off date March 2017)

	PLX108-10 Px				PLX108-01 Px	ALL Px
Preferred Term	PBO Part 1 A (N=59) n (%)	Px Part 1 B (N=61) n (%)	Px Part 1-Part 2 C (N=61) n (%)	Px Part 2 XO D (N=30) n (%)	E (N=39) n (%)	F (N=130) n (%)
Subjects with any TEAEs	55 (93.2)	60 (98.4)	60 (98.4)	30 (100.0)	39 (100.0)	129 (99.2)
Hair colour changes	2 (3.4)	41 (67.2)	43 (70.5)	25 (83.3)	28 (71.8)	96 (73.8)
Fatigue	21 (35.6)	33 (54.1)	34 (55.7)	5 (16.7)	35 (89.7)	74 (56.9)
Nausea	24 (40.7)	23 (37.7)	24 (39.3)	6 (20.0)	25 (64.1)	55 (42.3)
Arthralgia	15 (25.4)	14 (23.0)	17 (27.9)	6 (20.0)	21 (53.8)	44 (33.8)
AST increased	0	24 (39.3)	27 (44.3)	5 (16.7)	6 (15.4)	38 (29.2)
Diarrhoea	15 (25.4)	12 (19.7)	16 (26.2)	8 (26.7)	14 (35.9)	38 (29.2)
Dysgeusia	1 (1.7)	15 (24.6)	16 (26.2)	7 (23.3)	14 (35.9)	37 (28.5)
Pruritus	2 (3.4)	10 (16.4)	12 (19.7)	8 (26.7)	14 (35.9)	34 (26.2)
ALT increased	1 (1.7)	17 (27.9)	19 (31.1)	7 (23.3)	7 (17.9)	33 (25.4)
Periorbital oedema	1 (1.7)	11 (18.0)	14 (23.0)	3 (10.0)	15 (38.5)	32 (24.6)
Headache	11 (18.6)	11 (18.0)	13 (21.3)	5 (16.7)	13 (33.3)	31 (23.8)
Rash	2 (3.4)	8 (13.1)	13 (21.3)	6 (20.0)	12 (30.8)	31 (23.8)
Vomiting	3 (5.1)	12 (19.7)	13 (21.3)	2 (6.7)	11 (28.2)	26 (20.0)
Hypertension	6 (10.2)	9 (14.8)	12 (19.7)	6 (20.0)	6 (15.4)	24 (18.5)
Oedema peripheral	2 (3.4)	8 (13.1)	8 (13.1)	5 (16.7)	11 (28.2)	24 (18.5)
Decreased appetite	6 (10.2)	10 (16.4)	11 (18.0)	3 (10.0)	9 (23.1)	23 (17.7)
Dizziness	9 (15.3)	6 (9.8)	8 (13.1)	4 (13.3)	10 (25.6)	22 (16.9)
Constipation	3 (5.1)	7 (11.5)	7 (11.5)	3 (10.0)	10 (25.6)	20 (15.4)
Face oedema	1 (1.7)	8 (13.1)	8 (13.1)	6 (20.0)	6 (15.4)	20 (15.4)
Pain in extremity	4 (6.8)	4 (6.6)	6 (9.8)	3 (10.0)	10 (25.6)	19 (14.6)
Rash maculo-papular	1 (1.7)	6 (9.8)	9 (14.8)	2 (6.7)	8 (20.5)	19 (14.6)
Abdominal pain	6 (10.2)	10 (16.4)	13 (21.3)	1 (3.3)	2 (5.1)	16 (12.3)
Dry mouth	2 (3.4)	6 (9.8)	7 (11.5)	4 (13.3)	4 (10.3)	15 (11.5)
Blood ALP increased	0	9 (14.8)	9 (14.8)	1 (3.3)	4 (10.3)	14 (10.8)
Erythema	0	1 (1.6)	2 (3.3)	5 (16.7)	7 (17.9)	14 (10.8)
Cough	3 (5.1)	3 (4.9)	4 (6.6)	2 (6.7)	7 (17.9)	13 (10.0)
Hypophosphataemia	1 (1.7)	3 (4.9)	3 (4.9)	1 (3.3)	9 (23.1)	13 (10.0)
Asthenia	3 (5.1)	6 (9.8)	7 (11.5)	5 (16.7)	0	12 (9.2)
Anaemia	1 (1.7)	3 (4.9)	5 (8.2)	1 (3.3)	5 (12.8)	11 (8.5)
Dry skin	2 (3.4)	2 (3.3)	4 (6.6)	2 (6.7)	5 (12.8)	11 (8.5)
Hypercholesterolaemia	0	5 (8.2)	7 (11.5)	2 (6.7)	2 (5.1)	11 (8.5)
Upper respiratory tract infection	0	1 (1.6)	5 (8.2)	0	6 (15.4)	11 (8.5)
Blood LDH increased	0	7 (11.5)	7 (11.5)	3 (10.0)	0	10 (7.7)
Insomnia	2 (3.4)	3 (4.9)	3 (4.9)	2 (6.7)	5 (12.8)	10 (7.7)
Stomatitis	1 (1.7)	4 (6.6)	4 (6.6)	3 (10.0)	3 (7.7)	10 (7.7)
Vision blurred	0	3 (4.9)	3 (4.9)	1 (3.3)	6 (15.4)	10 (7.7)
WBC count decreased	1 (1.7)	3 (4.9)	6 (9.8)	1 (3.3)	3 (7.7)	10 (7.7)
Cognitive disorder	0	2 (3.3)	2 (3.3)	0	7 (17.9)	9 (6.9)
Nasopharyngitis	3 (5.1)	4 (6.6)	5 (8.2)	1 (3.3)	3 (7.7)	9 (6.9)
Skin hypopigmentation	0	2 (3.3)	3 (4.9)	0	6 (15.4)	9 (6.9)
Back pain	0	3 (4.9)	4 (6.6)	0	4 (10.3)	8 (6.2)
Influenza like illness	0	3 (4.9)	4 (6.6)	0	4 (10.3)	8 (6.2)
Paraesthesia	1 (1.7)	1 (1.6)	5 (8.2)	0	3 (7.7)	8 (6.2)
Pyrexia	1 (1.7)	4 (6.6)	4 (6.6)	2 (6.7)	2 (5.1)	8 (6.2)
Weight increased	0	2 (3.3)	2 (3.3)	1 (3.3)	5 (12.8)	8 (6.2)
Alopecia	0	3 (4.9)	3 (4.9)	1 (3.3)	3 (7.7)	7 (5.4)
Dyspepsia	2 (3.4)	1 (1.6)	2 (3.3)	0	5 (12.8)	7 (5.4)
Lacrimation increased	0	3 (4.9)	3 (4.9)	1 (3.3)	3 (7.7)	7 (5.4)
Memory impairment	1 (1.7)	0	0	3 (10.0)	4 (10.3)	7 (5.4)
Nasal congestion	0	1 (1.6)	1 (1.6)	1 (3.3)	5 (12.8)	7 (5.4)
Neuropathy peripheral	0	3 (4.9)	3 (4.9)	0	4 (10.3)	7 (5.4)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; MedDRA = Medical Dictionary for Regulatory Activities; PBO = placebo; PT = preferred term; Px = pexidartinib; SOC = system organ class; TEAEs = treatment-emergent adverse events; TGCT = tenosynovial giant cell tumor; WBC = white blood cell; XO = crossover.

Note: A = Randomized to placebo in PLX108-10 (Part 1 data), B = Randomized to pexidartinib in PLX108-10 (Part 1 data),
C = Randomized to pexidartinib in PLX108-10 (Part 1 and 2 data),
D = Crossover in PLX108-10 (Part 2 with open label pexidartinib data),
E = TGCT cohort in PLX108-01 study,
F = All pexidartinib treated subjects in Study PLX108-01 and PLX108-10 (Group C + Group D + Group E).

% = (n/N)x100.
A subject with more than 1 TEAE in the same SOC (or with the same PT) is counted only once for that SOC (or PT). Table is sorted by decreasing frequency of Summary Group F.
Adverse event terms were coded using MedDRA version 17.1.

Source: ISS Table 14.2.1.7 (TGCT Population)

- CTCAE Grade ≥3 TEAEs

Among the 130 TGCT subjects treated with pexidartinib, 56 (43.1%) subjects had CTCAE Grade ≥3 TEAEs, of which 7 (5.4%) subjects had CTCAE Grade 4 events and 1 subject had a CTCAE Grade 5 event in group

D. The CTCAE Grade ≥3 TEAEs were higher in the randomized pexidartinib cohort (44.3%) compared with the placebo group (11.9%).

In Part 1 of Study PLX108-10, the reported TEAEs of CTCAE Grade 3 or higher in the pexidartinib group (reported in more than one subject) included AST increased (6 [9.8%] subjects, all CTCAE Grade 3); ALT increased (1 [1.6%] subject CTCAE Grade 4, and 5 [8.2%] subjects CTCAE Grade 3); blood ALP increased (4 [6.6%] subjects, all CTCAE Grade 3); vascular disorder, hypertension (3 [4.9] subjects each, all CTCAE Grade 3); arthralgia, GGT, and liver function test abnormal (2 [3.3%] subjects each, all CTCAE Grade 3).

In subjects from placebo arm who crossed-over to pexidartinib 800 mg/day in study PLX108-10, 8 (26.7%) subjects had CTCAE Grade ≥3 TEAEs of which one CTCAE Grade 5 event (cardiac arrest, which was reported as unrelated).

- TEAEs by time period

The numbers of new reported TEAEs by PT and time to onset of TEAEs in the pooled analyses of all pexidartinib-treated subjects (group C + group D + group E) and for placebo group in study PLX108-10 have been submitted in the dossier. For most TEAEs in pexidartinib subjects, the rate of events was greatest in the first 12 weeks of pexidartinib treatment

- Updated Data, cut-off date 31 January 2018

The safety-related results from the original March 2017 data cut-off and the 31 January 2018 data cut-off are presented side by side (Table 34). As of 31 Jan 2018, 48 and 13 subjects are continuing on pexidartinib treatment in Studies PLX108-10 and PLX108-01, respectively, with maximum durations of treatment of 131 weeks and 259 weeks, respectively.

Table 34: Summary Table of Updated adverse events through 31 Jan 2018 for TGCT Subjects Treated With Pexidartinib in Study PLX108-10 and Study PLX108-01 (Safety Analyses Set)

	PLX108-10		PLX108-01	
	Main CSR (27 Mar 2017) n (%)	CSR Addendum (31 Jan 2018) n (%)	Main CSR (03 Mar 2017) n (%)	CSR Addendum (31 Jan 2018) n (%)
Adverse Events				
Subjects with any TEAE	90 (98.9)	91 (100.0)	39 (100.0)	39 (100.0)
Subjects with TEAE Grade ≥3	39 (42.9)	43 (47.3)	17 (43.6)	17 (43.6)
Subjects with Treatment-related TEAE Grade ≥3	33 (36.3)	35 (38.5)	14 (35.9)	14 (35.9)
Subjects with TEAE Grade 5	1 (1.1)	1 (1.1)	0	0
Subjects with Treatment-related TEAE Grade 5	0	0	0	0
Subjects with SAE	12 (13.2)	14 (15.4)	5 (12.8)	5 (12.8)
Subjects with Treatment-related SAE	8 (8.8)	9 (9.9)	2 (5.1)	2 (5.1)
Subjects with TEAEs Leading to Discontinuation	14 (15.4)	17 (18.7)	12 (30.8)	13 (33.3)
Subjects with TEAEs Leading to Dose Reduction/Interruption	39 (42.9)	54 (59.3)	31 (79.5)	32 (82.1)
Subjects with Special Interest TEAEs	65 (71.4)	67 (73.6)	29 (74.4)	31 (79.5)
Cognitive Disorder	6 (6.6)	8 (8.8)	16 (41.0)	16 (41.0)
Hepatic disorder	42 (46.2)	42 (46.2)	8 (20.5)	8 (20.5)
Myelosuppression	25 (27.5)	27 (29.7)	7 (17.9)	10 (25.6)
Cardiac Function	24 (26.4)	27 (29.7)	16 (41.0)	18 (46.2)
Most frequent TEAE Preferred Term				
Hair colour changes	68 (74.7)	70 (76.9)	28 (71.8)	28 (71.8)
Fatigue	39 (42.9)	42 (46.2)	35 (89.7)	36 (92.3)
Aspartate aminotransferase increased	32 (35.2)	32 (35.2)	6 (15.4)	7 (17.9)
Nausea	30 (33.0)	33 (36.3)	25 (64.1)	26 (66.7)
Diarrhoea	24 (26.4)	25 (27.5)	14 (35.9)	14 (35.9)
Arthralgia	23 (25.3)	26 (28.6)	21 (53.8)	24 (61.5)
Dysgeusia	23 (25.3)	24 (26.4)	14 (35.9)	14 (35.9)
Pruritus	20 (22.0)	16 (17.6)	14 (35.9)	14 (35.9)
Rash	19 (20.9)	24 (26.4)	12 (30.8)	12 (30.8)
Periorbital oedema	17 (18.7)	19 (20.9)	15 (38.5)	15 (38.5)

Abbreviations: AST = aspartate aminotransferase; CSR = clinical study report; Jan = January; Mar = March; max = maximum; min = minimum; SAE = serious adverse event; SD = standard deviation; TEAE=treatment-emergent adverse event; TGCT = tenosynovial giant cell tumor.

Note: % = (n/N)x100.

[a] In PLX108-10, 4 subjects (Subject Nos. 14010001, 80020005, 80020006, and 80020010) completed Part 1 treatment but did not enter the Part 2 open-label period.

- Adverse drug reactions

Based primarily upon on the frequency of TEAEs with pexidartinib compared to placebo in Part 1 of Study PLX108-10 as well as considerations of expectedness based upon pexidartinib's mechanisms of action as an inhibitor of CSF1R, KIT and FLT3-ITD, adverse drug reactions and clinical groupings of similar preferred terms were defined by the applicant.

Table 35: Adverse Drug Reactions with all TEAEs (any grade) and Grade ≥3 (safety analysis set)

		PLX108-10[a] placebo (N=59)		**PLX108-10[a] pexidartinib (N=61)**		**PLX108-10[b] all pexidartinib (N=91)**	
Clinical Grouping	Preferred Term	Any e n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
Hepatobiliary Disorders							
Hepatotoxicity		0 (0.0)	0 (0.0)	2 (3.3)	2 (3.3)	3 (3.3)	2 (2.2)
	Cholangitis	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
	Hepatocellular injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
	Hepatotoxicity	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.1)	1 (1.1)
	Liver disorder	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.1)	1 (1.1)
Metabolism and Nutrition Disorders							
Decreased appetite	Decreased appetite	6 (10.2)	0 (0.0)	10 (16.4)	0 (0.0)	14 (15.4)	0 (0.0)
Nervous System Disorders							
Dysgeusia		1 (1.7)	0 (0.0)	16 (26.2)	0 (0.0)	25 (27.5)	0 (0.0)
	Dysgeusia	1 (1.7)	0 (0.0)	15 (24.6)	0 (0.0)	24 (26.4)	0 (0.0)
	Ageusia	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
Headache		11 (18.6)	0 (0.0)	12 (19.7)	1 (1.6)	21 (23.1)	2 (2.2)
	Headache	11 (18.6)	0 (0.0)	11 (18.0)	0 (0.0)	20 (22.0)	1 (1.1)
	Head discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
	Migraine	0 (0.0)	0 (0.0)	1 (1.6)	1 (1.6)	1 (1.1)	1 (1.1)
Neuropathy		3 (5.1)	0 (0.0)	6 (9.8)	0 (0.0)	14 (15.4)	0 (0.0)
	Neuropathy peripheral	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)	4 (4.4)	0 (0.0)
	Peripheral sensory neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
	Paraesthesia	1 (1.7)	0 (0.0)	1 (1.6)	0 (0.0)	8 (8.8)	0 (0.0)
	Hypoaesthesia	2 (3.4)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
	Dyseasthesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
	Burning sensation	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
Cognitive Disorder		3 (5.1)	0 (0.0)	3 (4.9)	0 (0.0)	8 (8.8)	0 (0.0)
	Memory impairment	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	4 (4.4)	0 (0.0)
	Amnesia	1 (1.7)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
	Cognitive disorder	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (2.2)	0 (0.0)
	Attention deficit/ hyperactivity disorder	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
	Disturbance in attention	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders							
Nausea	Nausea	24 (40.7)	0 (0.0)	23 (37.7)	0 (0.0)	33 (36.3)	0 (0.0)
Vomiting	Vomiting	3 (5.1)	0 (0.0)	12 (19.7)	1 (1.6)	16 (17.6)	1 (1.1)

Constipation	Constipation	3 (5.1)	0 (0.0)	7 (11.5)	0 (0.0)	12 (13.2)	0 (0.0)
Dry mouth	Dry mouth	2 (3.4)	0 (0.0)	6 (9.8)	0 (0.0)	12 (13.2)	0 (0.0)
Abdominal pain		10 (16.9)	0 (0.0)	10 (16.4)	0 (0.0)	18 (19.8)	0 (0.0)
	Abdominal pain	6 (10.2)	0 (0.0)	10 (16.4)	0 (0.0)	15 (16.5)	0 (0.0)
	Abdominal pain upper	4 (6.8)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)
	Abdominal discomfort	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
	Abdominal pain lower	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.2)	0 (0.0)
Stomatitis		3 (5.1)	0 (0.0)	5 (8.2)	0 (0.0)	10 (11.0)	0 (0.0)
	Stomatitis	1 (1.7)	0 (0.0)	4 (6.6)	0 (0.0)	8 (8.8)	0 (0.0)
	Mouth ulceration	2 (3.4)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
Skin and Subcutaneous Tissue Disorders							
Hair color changes	Hair color changes	2 (3.4)	0 (0.0)	41 (67.2)	0 (0.0)	70 (76.9)	0 (0.0)
Pruritus		2 (3.4)	0 (0.0)	11 (18.0)	0 (0.0)	24 (26.4)	1 (1.1)
	Pruritus	2 (3.4)	0 (0.0)	10 (16.4)	0 (0.0)	16 (17.6)	1 (1.1)
	Pruritus generalized	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	8 (8.8)	0 (0.0)
Rash		4 (6.8)	0 (0.0)	17 (27.9)	1 (1.6)	41 (45.1)	3 (3.3)
	Dermatitis acneiform	0	0	1 (1.6)	0	3 (3.3)	0
	Dermatitis allergic	0	0	1 (1.6)	0	1 (1.1)	0
	Rash	2 (3.4)	0 (0.0)	8 (13.1)	1 (1.6)	24 (26.4)	1 (1.1)
	Rash maculo- papular	1 (1.7)	0 (0.0)	6 (9.8)	0 (0.0)	12 (13.2)	1 (1.1)
	Rash papular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	1 (1.1)
	Rash pruritic	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	3 (3.3)	0 (0.0)
	Urticaria	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (2.2)	0 (0.0)
	Erythema	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	8 (8.8)	0 (0.0)
Alopecia	Alopecia	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)	5 (5.5)	0 (0.0)
Skin color changes		0 (0.0)	0 (0.0)	5 (8.2)	0 (0.0)	11 (12.1)	0 (0.0)
	Skin hypopigmentation	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	5 (5.5)	0 (0.0)
	Skin depigmentation	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
	Skin discoloration	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
	Skin hyperpigmentation	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	2 (2.2)	0 (0.0)
General Disorders							
Asthenic Conditions		24 (40.7)	0 (0.0)	39 (63.9)	0 (0.0)	57 (62.6)	0 (0.0)
	Fatigue	21 (35.6)	0 (0.0)	33 (54.1)	0 (0.0)	42 (46.2)	0 (0.0)
	Asthenia	3 (5.1)	0 (0.0)	6 (9.8)	0 (0.0)	13 (14.3)	0 (0.0)
	Malaise	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	3 (3.3)	0 (0.0)
Peripheral oedema		4 (6.8)	0 (0.0)	12 (19.7)	0 (0.0)	25 (27.5)	2 (2.2)
	Face oedema	1 (1.7)	0 (0.0)	8 (13.1)	0 (0.0)	15 (16.5)	2 (2.2)
	Localised oedema	1 (1.7)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
	Oedema peripheral	2 (3.4)	0 (0.0)	8 (13.1)	0 (0.0)	16 (17.6)	0 (0.0)
	Peripheral swelling	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Pyrexia	Pyrexia	1 (1.7)	0 (0.0)	4 (6.6)	0 (0.0)	9 (9.9)	0 (0.0)
Eye Disorders							
Eye oedema		3 (5.1)	0 (0.0)	18 (29.5)	1 (1.6)	30 (33.0)	1 (1.1)
	Periorbital oedema	1 (1.7)	0 (0.0)	11 (18.0)	1 (1.6)	19 (20.9)	1 (1.1)
	Eye oedema	2 (3.4)	0 (0.0)	6 (9.8)	0 (0.0)	6 (6.6)	0 (0.0)
	Eyelid oedema	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	6 (6.6)	0 (0.0)
	Papilloedema	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
Vision changes		1 (1.7)	0 (0.0)	5 (8.2)	0 (0.0)	10 (11.0)	0 (0.0)

Clinical Grouping	Preferred Term	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)
	Vision blurred	0 (0.0)	0 (0.0)	3 (4.9)	0 (0.0)	6 (6.6)	0 (0.0)
	Photophobia	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	4 (4.4)	0 (0.0)
	Diplopia	0 (0.0)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.1)	0 (0.0)
	Visual acuity reduced	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Visual impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)
Vascular Disorders							
Hypertension	Hypertension	6 (10.0)	0 (0.0)	9 (14.8)	3 (4.9)	21 (23.1)	5 (5.5)

a randomized Part 1 of the study PLX108-10
b all pexidartinib-treated subjects in study PLX108-10 (including 30 subjects who crossed over to pexidartinib at the end of part 1, based upon the 31 Jan 2018 data cut-off)

Adverse events of special interest

- Hepatic adverse events

Hepatotoxicity is the most pronounced and relevant acute safety risk identified currently for pexidartinib. An overall summary of hepatic TEAEs across the safety population is presented below.

Table 36: Side-by-Side Summary of Hepatic TEAEs by Worst Grade for TGCT, Non- TGCT Solid Tumour, and AML Populations (Safety Analysis Set)

Preferred Term/ CTCAE Grade	TGCT (N=130) n (%)	Non-TGCT[a] (N=168) n (%)	AML (N=90) n (%)
Subjects with any TEAEs of Special Interest for Hepatic Disorder	50 (38.5)	32 (19.0)	34 (37.8)
Grade 5	0	0	0
4	3 (2.3)	2 (1.2)	2 (2.2)
3	17 (13.1)	18 (10.7)	9 (10.0)
2	9 (6.9)	5 (3.0)	10 (11.1)
1	21 (16.2)	7 (4.2)	13 (14.4)
≥ 3	20 (15.4)	20 (11.9)	11 (12.2)
Missing	0	0	0

Abbreviations: AML = acute myeloid leukemia; CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse events; TGCT = tenosynovial giant cell tumor.
[a] Non-TGCT solid tumors.
Source: ISS Table 14.2.1.3.1s

The most frequently reported hepatic TEAEs in TGCT pexidartinib-treated subjects were AST increased (38 [29.2%] subjects in which 10 [7.7%] grade 3 and more) and ALT increased (33 [25.4%] subjects in which 12 [9.2%] grade 3 and more). Other TEAEs reported in more than one subject were Blood bilirubin increased, transaminases, GGT increased, and liver function test abnormal (3 [2.3%] subjects, all of them were Grade 3 and more).

A total of 25 (14.9%) subjects experienced treatment-related hepatic TEAEs, of which 16 (9.5%) subjects experienced treatment-related hepatic TEAEs of CTCAE Grade ≥3.

Overall, among the 50 TGCT pexidartinib-treated subjects with a hepatic TEAE, 9 (6.9%) subjects treated by pexidartinib had an hepatic TEAE leading to dose discontinuation, and 19 (14.6%) subjects treated by pexidartinib had an hepatic TEAE leading to dose reduction or interruption. The majority of these discontinuation and dose reduction/interruption due to hepatic TEAE occurred in pexidartinib arm Part 1 and pexidartinib Part 1-Part 2 of Study PLX108-10.

In Study PLX108-10, AEs that were considered to be hepatotoxicity included cholangitis, hepatocellular injury, hepatotoxicity, and liver disorder. Cholestatic liver injury defined by increases in AST and ALT ≥3 × ULN with TBIL and ALP ≥2 × ULN occurred in 3 of 61 (4.9%) TGCT patients randomized to pexidartinib and did not occur in the cohort of subjects who started pexidartinib at the 800 mg/day dose (Table 37). In addition, liver enzyme abnormalities were also lower in a non-randomized comparison of the crossover cohort to subjects treated with pexidartinib with a starting dose of 1000 mg/day.

Table 37: Frequency of Hepatic Test Abnormalities Among Subject Cohorts in Study PLX108-10

Hepatic Test Abnormality	Placebo (Part 1 Only) (N=59)	Pexidartinib (Part 1 Only) (N=61)	Crossover to Pexidartinib (N=30)
AST or ALT ≥3 × ULN	0	20 (32.8)	4 (13.3)
AST or ALT ≥5 × ULN	0	12 (19.7)	2 (6.7)
ALP ≥2.5 × ULN	1 (1.7)	5 (8.2)	0
TBIL ≥2 × ULN	0	3 (4.9)	0
Concurrent AST or ALT ≥3 × ULN and TBIL ≥2 × ULN	0	3[a] (4.9)	0

A dose-exposure analysis has been performed to evaluate the relationship of pexidartinib and AST and ALT increases and with TBIL increases. This analysis showed no apparent relationship of exposure with TBIL and a clear exposure-response relationship of pexidartinib and liver enzyme abnormalities. The effect of hepatic enzyme elevations is dose dependent, usually persists with continued treatment, and resolves upon treatment interruption. There was no difference in probability of TBIL elevations at projected doses of 400 mg/day and 600 mg/day compared to 800 mg/day and 1000 mg/day.

All liver injury cases in the development program of pexidartinib began within the first 8 weeks. All cases of hepatotoxicity in Study PLX108-10 resolved upon treatment discontinuation with a duration of hyperbilirubinaemia of 1 to 7 months. However, 2 cases across the clinical program were not reversible: one death of a subject with vaginal melanoma in a context of cholestatic liver injury and one case of cholestatic hepatotoxicity leading to liver transplant.

In clinical trials of pexidartinib, patients with elevations of serum transaminases or bilirubin, or active liver or biliary tract disease are excluded. In addition, weekly monitoring of liver tests was implemented with strict dose interruption, dose reduction, and dose discontinuation criteria.

Updated safety data Jan 2018 DLP in the TGCT cohort of Study PLX108-01 and in Study PLX108-10 did not reveal any new cases of mixed or cholestatic hepatotoxicity. It is noted that there were no new inclusion

or crossover in both studies between March 2017 DLP and Jan 2018 DLP and the hepatotoxicity occurred in the first 8 weeks of treatment in the clinical development.

- Cognitive disorders

Pexidartinib crosses the blood-brain barrier and neurotoxicity was relatively high in all animal species investigated. Thus, the neurobehavioral effects observed in animals are likely a consequence of distribution into CNS tissues over the blood:brain barrier.

In TGCT population, 21 (16.2%) subjects treated with pexidartinib reported cognitive disorder, memory impairment, or similar AEs. None of them was CTCAE Grade ≥3.

Frequency of reported cognitive disorders was higher in the Phase 1 study than in the Phase 3 study, where there was no difference between the pexidartinib and placebo treatments, with 3 (5%) in each treatment arm. There were 15 (38.5%) subjects from the Phase 1 Study PLX108-01 that had a TEAE of special interest for cognitive disorder, of which 14 (35,9%) were treatment-related. In part 1 of phase 3 study, 3 (4.9%) subjects in pexidartinib arm and 3 (5.1%) subjects in placebo arm reported cognitive disorder. It is noted that the subjects from the TGCT group from Phase I study were exposed to the highest pexidartinib dose among the TGCT population (1000 mg/day) and the longest exposure to the drug (median exposure: 73 weeks; median exposure for all the pexidartinib treated TGCT population: 43.0 weeks). The reasons for this significant difference between the phase 1 and the phase 3 trial needs further clarification. (OC)

These events led to pexidartinib discontinuation in 4 subjects (3 subjects with cognitive disorders and 1 subject with disturbance in attention). The TEAEs that resulted in discontinuation (cognitive disorders and disturbance in attention) resolved upon discontinuation of study treatment.

- Cardiac disorders

Within the AML monotherapy study, there were 2 cardiac events: congestive heart failure in 1 subject and a decrease in ejection fraction (without symptoms) in another subject (both of whom had previously received anthracyclines). For this reason, heart failure had been considered an AE of special interest.

Safety pharmacology revealed that pexidartinib is a strong inhibition of cardiac potassium and calcium channels by pexidartinib; however, the effects obviously cancelled out each other so that ECG was not affected. Inflammatory infiltrates in the heart and vasculitis was also observed in non-clinical trials indicating potential cardiovascular adverse effect during treatment with pexidartinib.

There were no cardiac failure or related events among the 130 TGCT subjects or the 168 non-TGCT solid tumour subject treated with pexidartinib. Two (3.4%) subjects in the Part 1 placebo group experienced cardiac function TEAEs of CTCAE Grade 1 (cardiac hypertrophy and ejection fraction decreased in 1 [1.7%] subject each). Of these, the event of ejection fraction decreased was treatment-related. In Study PLX108-10 Part1 placebo-Part 2 Pexidartinib, there was 1 (0.8%) death due to cardiac arrest, which was unrelated to study treatment.

Nine subjects in the AML population had cardiac events of CTCAE Grades 1 to 4. This analysis did not include events of cardiac arrest. A CTCAE Grade 5 cardiac arrest reported as unrelated to pexidartinib treatment occurred in 1 subject, in whom the event was attributed to underlying cardiovascular medical history.

A thorough QTc prolongation study in healthy subjects demonstrated that a single 1800 mg dose of pexidartinib did not cause large mean increases (i.e., >10 milliseconds [ms]) in the QTc interval.

- Myelosuppression

In TGCT population, 26 (20.0%) subjects experienced a myelosuppression TEAE, and almost all of them were treatment-related (23 (17.7%) subjects). CTCAE Grade ≥3 myelosuppression TEAEs were reported in 4 (3.1%) subjects: neutropenia (2 subjects [1.5%]) and neutrophil count decreased (1 [0.8%]), all of which were treatment-related; and 1 (0.8%) subject experienced lymphocyte count decreased, which was not treatment-related.

In the controlled part of Study PLX108-10, myelosuppression TEAEs were highly reported in pexidartinib arm compared to in placebo arm, 11 (18.0%) and 2 (3.4%) subjects respectively.

In Part 1 of Study PLX108-10, 8 (13.1%) subjects had treatment-related myelosuppression TEAEs in pexidartinib arm vs 1 (1.7%) subject in placebo arm.

During Part 2, a total of 8 (26.7%) crossover subjects experienced a myelosuppression TEAE, all of which were treatment-related. No additional subjects in the crossover pexidartinib group had a CTCAE Grade ≥3 myelosuppression TEAE. A CTCAE Grade 1 anaemia was reported in 1 (3.3%) subject in the crossover group.

Serious adverse event/deaths/other significant events

- Deaths

In the pooled TGCT population, one death due to cardiac arrest was reported in the pivotal study PLX108-10 and it was considered unrelated to pexidartinib.

In the non-TGCT solid tumour population, 18 (10.7%) deaths were reported. Most of them were related to progressive disease (14 [8.3%] subjects). Of all the deaths reported, 16 (11.1%) occurred in the pooled pexidartinib 900 mg/day to 1200 mg/day dose group and 2 (8.3%) occurred in the pooled pexidartinib 200 mg/day to 600 mg/day dose group.

One (0.6%) death was related to AEs and 3 (1.8%) deaths related to "other". Nevertheless, according to the overall summary of TEAEs for non-TGCT monotherapy population, a total of 3 subjects had a CTCAE Grade 5 TEAEs, all occurring in the dosage group 900-1200 mg/day. The applicant should clarify the number of deaths that occurred due to AE. (OC)

In the non-TGCT AML population, 77 (85.6%) deaths were reported, most of them due to progressive disease (65.6%). Among all deaths, 12 (13.3%) deaths occurred related to AEs. Among them, one death due to cytokine release syndrome was considered probably treatment-related by the applicant. This subject was exposed to high dose of pexidartinib (3000 mg/day), the death occurred at Day 31 and pexidartinib last dose was taken on Day 27.

In addition to TGCT and non-TGCT pooled population, one death occurred in a context of cholestatic liver disease in Study PLX108-13 and is further detailed in section 4.4 AESI, Hepatic AE.

- Serious adverse events

In TGCT population, 16 (12.3%) subjects treated to pexidartinib had a treatment-emergent SAEs. The most frequently reported SOC were Investigations (3.1%), Hepatobiliary disorders (2.3%) and Neoplasms benign, malignant and unspecified (2.3%).

A total of 9 (6.9%) subjects in TGCT population had treatment-related SAEs. Most of them were hepatic TEAEs (6 cases): 2 cases of liver function test abnormal, one case of hepatic enzyme abnormal, one case of transaminase increased, one case of hepatotoxicity and one case of liver disorder. The others treatment-related serious TEAEs reported with pexidartinib were 2 cases of skin and subcutaneous tissue disorders, one case of hyponatremia and one case of adenosquamous carcinoma.

In part 1 of study PLX108-10, 1.7% treatment-emergent SAEs were reported in placebo arm vs 13.1% in pexidartinib arm. Among the 30 subjects that crossover in part 2, 3 (10%) presented treatment-emergent SAEs.

Laboratory findings

In general laboratory abnormalities (such as the results of hematologic and liver test during the trials) have been already discussed in the section on adverse events of special interest above, but details below in the following Table 38.

Table 38: Reported worsened laboratory values through week 25 in part 1 of study PLX108 10a

Total Worsened	**Grade 1 n (%)**	**Grade 2 n (%)**	**Grade 3 n (%)**	**Grade 4 n (%)**
Liver test values				
Increased ALT				
Pexidartinib	19 (31)	8 (13)	10 (16)	2 (3)
Placebo	13 (22)	0	0	0
Increased AST				
Pexidartinib	37 (61)	9 (15)	7 (12)	0
Placebo	9 (15)	0	0	0
Increased ALP				
Pexidartinib	19 (31)	2 (3)	3 (5)	0
Placebo	1 (2)	0	0	0
Blood bilirubin increase				
Pexidartinib	2 (3)	2 (3)	1 (2)	1 (2)
Placebo	0	0	0	0
Haematology values				
Haemoglobin Decreased				
Pexidartinib	13 (21)	5 (8)	0	0
Placebo	7 (12)	0	1 (2)	0
Lymphocyte count decrease				
Pexidartinib	13 (21)	9 (15)	1 (2)	0
Placebo	1 (2)	1 (2)	0	0
Neutrophil count decrease				
Pexidartinib	16 (26)	9 (15)	2 (3)	0
Placebo	4 (7)	1 (2)	0	0
Platelet count decrease				
Pexidartinib	19 (15)	0	0	0
Placebo	3 (5)	0	0	0
White blood cell count decrease				
Pexidartinib	20 (33)	13 (21)	0	0
Placebo	3 (5)	0	0	0

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase;
a Highest grade at any time for patients on pexidartinib (N=61) or placebo (N=59).
Source: Module 2.7.4, Appendix Table 5.2

This illustrates haematotoxicity observed during exposure with pexidartinib can be classified as mild, but again, this reflects only the consequences during exposure of in mean 47 weeks.

Safety in special populations

- Age groups

In the TGCT population treated with pexidartinib (N=130), the number of subjects >65 years of age (n=8) was small and subjects were predominantly white (n=115). Therefore, results are described for the <50-year age group (n=84), 50- to 65-year age group (n=38), females (n=73), and males (n=57).

Table 39: TGCT population: Summary of reported TEAEs by age subgroup (SAS)

MedDRA Terms	**Age <50 (N=84) N (%)**	**Age 50-65 (N=38) N (%)**	**Age 65+ (N=8) N (%)**
Total AEs	83 (98.8)	38 (100)	8 (100)
Serious AEs – Total	4 (4.8)	8 (21.1)	4 (50.0)
- Fatal	0	0	1 (12.5)
- Hospitalization/prolong existing hospitalization	Not mentioned	Not mentioned	Not mentioned
- Life-threatening	Not mentioned	Not mentioned	Not mentioned
- Disability/incapacity	Not mentioned	Not mentioned	Not mentioned
- Other (medically significant)	Not mentioned	Not mentioned	Not mentioned
AE leading to discontinuation	15 (17.9)	7 (18.4)	3 (37.5)
AE leading to dose reduction/interruption	40 (47.6)	25 (65.8)	5 (62.5)
Skin and subcutaneous disorders	76 (90.5)	35 (92.1%)	6 (75.0)
Nervous system disorders	54 (64.3)	26 (68.4)	5 (62.5)
General disorders and administration site conditions	62 (73.8)	28 (73.7)	5 (62.5)
Gastrointestinal disorders	63 (75.0)	24 (63.2)	4 (50.0)
Musculoskeletal and connective tissue disorders	50 (59.5)	22 (57.9)	2 (25.0)
AST increased	22 (26.2)	13 (34.2)	3 (37.5)
ALT increased	19 (22.6)	12 (31.6)	3 (37.5)
Hepatobiliary disorders	Not mentioned	2 (5.3)	2 (25.0)
Blood and lymphatic system disorders	21 (25.0)	6 (15.8)	1 (12.5)
Metabolism and nutrition disorders	37 (44.0)	18 (47.4)	5 (62.5)
Eye disorders	38 (45.2)	16 (42.1)	2 (25.0)
Infections and infestations	35 (41.7)	11 (28.9)	1 (12.5)

- Pregnancy / Fertility

Two subjects became pregnant during pexidartinib treatment; both were TGCT subjects in study PLX108-10:

- One PLX108-10 Subject became pregnant during the study (Randomization Treatment Regimen: Double blind: Part 1: Pexidartinib / Open label Part 2: Pexidartinib). Treatment with study drug was interrupted after a positive pregnancy test and resumed after elective termination of the pregnancy 10 days later. A narrative for this subject is provided in CSR PLX108-10.
- Another subject, aged 42 years, became pregnant while on pexidartinib (Randomization Treatment Regimen: Double blind Part 1: Placebo / Open label Part 2: Pexidartinib). At the time when pregnancy was diagnosed, the subject's estimated gestational age was reported as 4 weeks. The pregnancy ended in spontaneous abortion 61 days later. The investigator considered spontaneous abortion as related to pexidartinib.

There are no data on the effect of pexidartinib on human fertility.

Immunological events

No information regarding immunological events was submitted.

Safety related to drug-drug interactions and other interactions

See section 2.4.3.

Discontinuation due to adverse events

Overall, most of the TEAEs leading to discontinuation, dose reduction or interruption were ALT or AST increased.

- Discontinuation due to TEAE

Overall, TEAEs leading to discontinuation occurred in similar frequency among the pexidartinib-treated subjects: 26 (20%) subjects in TGCT population (of which 23 [17.7%] treatment-related), 24 (14.3%) subjects in Non-TGCT (solid tumour) population and 18 (20%) subjects in AML population.

In the controlled part of the pivotal study PLX108-10, 8 (13.1%) subjects had a TEAE leading to discontinuation in pexidartinib arm mainly due to ALT and AST increased (3 [4.9%] subjects each) whereas none occurred in placebo arm. Among the subjects that crossed-over in Part 2 study PLX108-10 at pexidartinib 800mg/day, 3 (10.0%) subjects discontinued the treatment due to TEAEs

Overall, discontinuation due to TEAE were highly reported in subjects in TGCT cohort of Phase 1 PLX108-01 compared to subjects in Phase 3 PLX108-10, 13.1% and 30.8% respectively, taking into account the higher starting dose of pexidartinib in Phase 1 PLX108-01 (1000 mg/day) compared to dosage in Study PLX108-10 (Part 1: 1000 mg/d for 2 weeks then 800 mg/day for 22 weeks; Part 2: 800 mg/day) and the higher study drug exposure in Phase 1 study.

Regarding updated safety data of TGCT population, TEAEs leading to discontinuation were reported in similar frequency at 27 March 2017 data cut-off and 31 January 2018 cut-off in study PLX108-10 (14 [15.4%] and 17 [18.7%] subjects respectively) and in study PLX108-01 (12 [30.8%] and 13 [33.3%] subjects respectively).

- Dose reduction/interruption due to TEAE

Overall, TEAEs leading to dose reduction or interruption occurred in 70 (53%) subjects in TGCT population, 56 (33.3%) subjects in Non-TGCT (solid tumour) population and 41 (45.6%) subjects in AML population.

In the controlled part of the pivotal study, the TEAEs leading to dose reduction/interruption occurred more frequently in pexidartinib arm (23 [37.7%] subjects) compared to placebo arm (6 [10.2%] subjects). Among the subjects that crossed-over in Part 2 study PLX108-10 at pexidartinib 800mg/day, 11 (36.7%) subjects experienced TEAEs leading to dose reduction or interruption. Dose reduction/interruption due to TEAE were highly reported in subjects in TGCT cohort of Phase 1 PLX108-01, i.e. 31 (79.6%) subjects.

TEAEs leading to dose reduction/interruption were reported in similar frequency at 27 Mar 2017 data cut-off and 31 January 2018 cut-off in study PLX108-01 whereas an increase of frequency of TEAEs leading to dose reduction/interruption was noted for study PLX108-10: 39 (42.9%) subjects at March 2017 data cut-off vs 54 (59.3%) subjects at the January 2018 data cut-off.

In the clinical program, dose modifications were defined to manage adverse reactions. The dose reduction levels are based upon the 200 mg capsule size and clinical experience that shows that this extent of reduction, i.e., 200 mg/day, meaningfully improves tolerance in many subjects.

The proposed dose reductions and modifications for adverse reactions are presented below.

Table 40: Dose reductions

Dose Level	Total Daily Dose	Dose
Starting dose	800 mg	400 mg (2 × 200 mg capsules) BID
First dose reduction	600 mg	200 mg capsule (1 × 200 mg capsule) in the morning and 400 mg (2 × 200 mg capsules) in the evening
Second dose reduction	400 mg	200 mg BID (1 × 200 mg capsule)

Abbreviation: BID = twice daily.

Table 41: Dose modifications for adverse reactions

Adverse reactions	Severity	Required modification
ALT/AST* (see section 4.4)	> 3-5 × ULN	- Interrupt treatment and monitor liver tests weekly until recovery to ≤ 3 × ULN. - Restart on resolution to ≤ 3 × ULN and reduce dose by one 200 mg hard capsule as indicated in Table 1.
	> 5-20 × ULN	- Interrupt treatment and monitor liver tests twice weekly until ≤ 3 × ULN. - Restart on resolution to ≤ 3 × ULN and reduce dose by one 200 mg hard capsule as indicated in Table 1. - If not improved to ≤ 3 × ULN in 4 weeks, permanently discontinue treatment.
	> 20 × ULN	- Permanently discontinue treatment. - Monitor liver tests twice weekly until ≤ 5 × ULN, then weekly until ≤ 3 × ULN.

Any ALT or AST > ULN with bilirubin increase**, or worsened ALP* with bilirubin increase** (see section 4.4).		- Interrupt treatment and re-test within one week. - Permanently discontinue treatment if bilirubin does not return to < ULN. Monitor liver tests until resolution. - Restart treatment at reduced dose by one 200 mg hard capsule as indicated in Table 1, if alternate cause for bilirubin increase is confirmed and bilirubin returns to < ULN.
Adverse reactions or other laboratory abnormalities	Severe or intolerable	- Dose interruption, reduction or discontinuation may be required. - Upon improvement or resolution, restart Turalio at a reduced dose, by one 200 mg hard capsule as indicated in Table 1.

* ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal; ALP = alkaline phosphatase

Post marketing experience

Turalio is authorised in the US since 2 August 2019. As of 31 December 2019, 67 patients were enrolled in the US Risk Evaluation and Mitigation Strategy (REMS) program and have been prescribed TURALIO (pexidartinib). Of these, 2 hepatic reactions meeting the criteria for hepatic event reporting (1 case of aminotransferase [AT] >3 × ULN and TBIL >2 × ULN, and 1 case of AT >10 × ULN) were received and are briefly described below:

Case report meeting criteria: AST or ALT > 3 × ULN and TB >2 × ULN: A 32-year-old female with villonodular synovitis (pigmented) was reported to have a serious events of elevated liver enzymes (with increases of GGT, ALP, TBIL/DBL, ALT, and AST), and non-serious events of nausea, vomiting, and fatigue during therapy with Turalio 400 mg bid. The patient's lab test results were noted to be elevated 22 days after the start of Turalio therapy with the following results: ALT 9.3 × ULN, AST 4.4 × ULN, DBL 12.5 × ULN, TBIL 3.3 × ULN, ALP 1.9 × ULN, GGT 8.9 × ULN, and International Normalized Ratio (INR) and albumin were within normal limits. Treatment with Turalio has been permanently discontinued and the patient was treated with ursodiol and prednisone. On follow-up, all liver test values were reported to be improving about 2 weeks later but not back to baseline. The outcome of the liver enzyme elevations was reported as recovering.

Case report meeting criteria: ALT or AST >10 × ULN: A 78-year-old female with non-resectable diffuse pigmented villonodular synovitis and history of gallstones and bile duct occlusion was reported to have a serious event of liver toxicity with ALT, AST, ALP, and GGT increases during therapy with TURALIO 400 mg bid. About 5 weeks after the start of Turalio, patient's lab test results were elevated with the following maximum elevations: ALT 10.9 × ULN, AST 9.4 × ULN, ALP 5.4 × ULN, GGT 18.0 × ULN, and TBIL, albumin, and INR within normal limits. No other events were reported. Therapy with pexidartinib was withdrawn and the outcomes of all events were reported as "not recovered" on follow-up 1 week after the event.

Follow-up on these patients' clinical status and liver testing is ongoing.

As of 22 May 2020, the US post-marketing data reported 6 cases of serious hepatotoxicity among 125 registered TGCT patients in the REMS program treated with pexidartinib:

- 5 patients: AT > 3 x ULN + TBL > 2 x ULN (3 with AT > 10 x ULN)
- 1 patient: AT > 10 x ULN with/without TBL elevation

- 0 patients: TBL > 2 x ULN without AT elevation
- 0 patients: liver transplantation
- 0 patients: death due to liver event
- Injury type: 5 mixed / cholestatic liver injury; 1 hepatocellular
- Time to onset: 4-8 weeks
- Turalio therapy: 5 patients permanently discontinued
- Reported outcome: 5 cases resolved/resolving; 1 case data pending

2.6.1. Discussion on clinical safety

The safety profile of pexidartinib for the initially claimed indication is primarily based on safety data from the Phase 3 Study PLX108-10 (N=120) and from the TGCT expansion cohort in the Phase 1 Study PLX108-01 (N=39). The data from these TGCT subjects was integrated in the ISS with a data cut-off of March 2017. The ISS was not a proper pooling of data as the pools were not presented by dosage groups but by groups according to study (PLX108-10 or PLX108-01), treatment (placebo or pexidartinib), and PLX108-10 study part (Part 1 or both Parts 1 and 2) or crossover to Part 2. In total, 130 subjects were treated with pexidartinib in the initially intended TGCT population, and 80 TGCT subjects had a pexidartinib treatment ongoing at the March 2017 data cut-off date. Updated safety results with a data cut-off of 31 Jan 2018 have been presented for both TGCT studies (PLX108-10 and PLX108-01) and side by side with data from March 2017 data cut-off. This updated TGCT data have not been integrated in the ISS. At this updated data cut-off date, 61 TGCT subjects had a pexidartinib treatment ongoing.

In addition, supportive safety data were provided from 6 pexidartinib monotherapy studies in cancer patients (Non-TGCT monotherapy population). Of these 6 studies, 5 were pooled for analysis by dosage groups: group A 200 to 600 mg/day, group B 900 to 1200 mg/day and group C total non-TGCT pexidartinib-treated subjects. The revised dosing regimen of pexidartinib (800 mg/day, see section 2.5.3) is not comprised in one of the non-TGCT solid tumour groups. Safety data from the AML study, PLX108-05, was presented separately in the ISS (group D, 800 to 5000 mg/day) considering that the AML population has unique disease-related AEs and because doses of pexidartinib administered were much higher.

- Patient exposure and dosage

Dose exposure and dose intensity are heterogeneous among the TGCT population, which lead to limitations for comparison among the groups.

The median dose intensity for the overall TGCT population treated by pexidartinib is 3704.3 mg/week (mean: 3425.2 mg/week) and the median dose intensity for the target TGCT group at 800 mg/day of pexidartinib is 4114.2 mg/week (mean: 4038.6 mg/week). With a division per 7 to estimate the daily dose intensity, the median dose intensity is lower than the intended daily posology: 529.2 mg/day for all TGCT pexidartinib-treated subjects, 587.7 mg/day for the TGCT population that started pexidartinib at 800 mg/day. This reflects the dose reduction/interruption and discontinuation that occurred during the treatment.

Treatment discontinuations occurred in 46 (35.4%) TGCT subjects of which 25 (19.2%) were due to TEAE. Among the 30 TGCT subjects that started pexidartinib at the intended posology of 800 mg/day, 4 (13.3%) subjects had an early discontinuation of which 2 (6.7%) were due to TEAE and 11 (36.7%) subjects had a dose reduction/interruption due to TEAE. The dose tolerability of pexidartinib is therefore questionable.

Overall, the median study drug exposure is 43.0 weeks in the TGCT population of which 54 (41.5%) have been treated over 48 weeks at March 2017 cut-off date. According to the ICH E1 guideline, 100 patients exposed for a minimum of one year is considered acceptable as safety data base.

Only 30 subjects have been exposed to pexidartinib at the intended dosage of 800 mg/day in an open-label part and the median study drug duration for this subject is 31.8 weeks. The extent of exposure is therefore lower than expected.

- TEAEs and treatment-related TEAEs

Almost all the pexidartinib-treated subjects in TGCT and non-TGCT populations experienced at least one TEAE (99.2% and 97.6% respectively). Most of the TEAEs were treatment-related: 97.7% for TGCT population and 83.3% in non-TGCT population. In the controlled part of Study PLX108-10, TEAEs were more often reported in the pexidartinib than the placebo arm (98.4% and 93.2% respectively), and treatment-related TEAEs were mostly reported in the pexidartinib arm (59 [96.7%] subjects) compared to the placebo arm (38 [64.4%] subjects). In the TGCT subjects that started pexidartinib at 800 mg/day, all the subjects experienced TEAE and most of them were treatment-related (29 [96.7%] subjects).

Hair colour changes (83.3%) were the most frequent TEAE for subjects who crossed over to pexidartinib in part 2 of study PLX108-10. The frequency of TEAEs was similar between the cross-over cohort and the pexidartinib randomized cohort and the study PLX108-01 cohort, but fewer cases of fatigue and nausea were reported in the crossover group.

Severe TEAEs (CTCAE Grade ≥3) were reported in 43.1% in TGCT pexidartinib-treated subjects and were treatment-related in 36.2% TGCT subjects. No summary of reported treatment-related TEAEs of CTCAE Grade ≥3 was provided for the TGCT population.

In the controlled part of study PLX108-10, 27 (44.3%) subjects in the pexidartinib cohort and 7 (11.9%) subjects in the placebo group had CTCAE Grade ≥3 TEAEs. Among TGCT subjects starting pexidartinib at 800 mg/day, 8 (27%) subjects had a CTCAE Grade ≥3 TEAEs, of which 6 (20%) were treatment-related.

The reported TEAEs of CTCAE Grade ≥3 in the pexidartinib group in the controlled part of study PLX108-10 (reported in more than one subject) included AST increased (6 [9.8%] subjects); ALT increased (1 [1.6%] subject CTCAE Grade 4, and 5 [8.2%] subjects CTCAE Grade 3); blood ALP increased (4 [6.6%] subjects, all CTCAE Grade 3); vascular disorder, hypertension (3 [4.9] subjects each); arthralgia, GGT, and liver function test abnormal (2 [3.3%] subjects each).

A list of adverse drug reactions (ADR) has been submitted based on safety data from subjects in the controlled part of the pivotal study PLX108-10 and subjects that crossed over from placebo to pexidartinib 800 mg/day.

Exposure-adjusted rates of new AE by preferred term in all TGCT pexidartinib-treated and in placebo subjects has been submitted for March 2017 data lock point but not for each TGCT group. For most TEAEs, the rate of events in all pexidartinib-treated subjects was higher in the first 12 weeks of pexidartinib treatment.

No or only small increases in the number of TEAEs were shown in the updated safety data presented in a side by side table for the 2 TGCT studies (data cut-off March 2017 and January 2018).

- SAEs and deaths

- SAE

In TGCT population, 16 (12.3%) subjects treated to pexidartinib had a treatment-emergent SAEs. The most frequently reported SOC were Investigations (3.1%), Hepatobiliary disorders (2.3%) and Neoplasms benign, malignant and unspecified (2.3%).

A total of 9 (6.9%) subjects in TGCT population had treatment-related SAEs. Most of them were hepatic TEAEs (6 cases): 2 cases of liver function test abnormal, one case of hepatic enzyme abnormal, one case of transaminase increased, one case of hepatotoxicity and one case of liver disorder. The others treatment-related serious TEAEs reported with pexidartinib were 2 cases of skin and subcutaneous tissue disorders, one case of hyponatremia and one case of adenosquamous carcinoma.

In part 1 of study PLX108-10, one (1.7%) subject reported SAE in the placebo arm which was not considered treatment-related *vs* 8 (13.1%) in pexidartinib arm of which 6 (9.8%) were considered treatment-related (6 hepatic SAEs and one rash). Among the 30 subjects that crossover in part 2, 3 (10%) subjects presented SAEs of which one (3.3%) was considered treatment-related (one case of adenosquamous carcinoma of the cervix).

- Deaths

In the pooled TGCT population, one death due to cardiac arrest was reported in the pivotal study PLX108-10 and it was considered unrelated to pexidartinib.

In the non-TGCT solid tumour population, 18 (10.7%) deaths were reported. Most of them were related to progressive disease (14 [8.3%] subjects). Of all the deaths reported, 16 (11.1%) occurred in the pooled pexidartinib 900 mg/day to 1200 mg/day dose group and 2 (8.3%) occurred in the pooled pexidartinib 200 mg/day to 600 mg/day dose group. One (0.6%) death was related to AEs and 3 (1.8%) deaths related to "other".

One death occurred in a context of cholestatic liver disease in Study PLX108-13.

- Discontinuation and dose reduction/interruption due to TEAEs

Overall in the TGCT population pexidartinib-treated, 26 (20%) subjects had TEAE leading to discontinuation and 70 (53.8%) subjects experienced TEAE leading to dose reduction/interruption.

In the controlled part of the pivotal study PLX108-10, 8 (13.1%) subjects had a TEAE leading to discontinuation in pexidartinib arm whereas none occurred in placebo arm. Regarding the TEAEs leading to dose reduction/interruption, they also occurred more frequently in pexidartinib arm (23 [37.7%] subjects) compared to placebo arm (6 [10.2%] subjects).

Among the TGCT subjects that started pexidartinib at 800 mg/day, 3 (10%) discontinued the treatment due to TEAE and 11 (36.7%) had a dose reduction or interruption due to TEAE, which is similar to the pexidartinib arm in the controlled part of the pivotal study.

In the overall TGCT pexidartinib-treated subjects, the most frequently TEAEs leading to discontinuation, dose reduction or interruption were ALT or AST increased.

The TEAEs leading to discontinuation occurring in more than one subject were ALT or AST increased (4 [3.1%] subjects each). Other frequently reported TEAEs that resulted in discontinuation of pexidartinib were cognitive disorder, fatigue (3 [2.3%] subjects each) and arthralgia (2 [1.5%] subjects).

The TEAEs leading to dose reduction or interruption occurring in more than one subject were fatigue (15 [11.5%] subjects), ALT increased and AST increased (14 [10.8%] subjects each); nausea (10 [7.7%] subjects); vomiting and blood ALP increased (8 [6.2%] subjects); periorbital oedema (7 [5.4%] subjects each); pruritus (5 [3.8%] subjects); cognitive disorder, dysgeusia, and rash maculopapular (4 [3.1%] subjects each); blood bilirubin increased, headache, memory impairment, diarrhoea, influenza, hypophosphataemia (3 [2.3%] subjects); GGT increased, liver function test abnormal, neutrophil count decreased, weight increased, amnesia, dizziness, pyrexia, abdominal pain, stomatitis, rash, upper respiratory tract infection, joint effusion, myalgia, neutropenia, and hypertension (2 [1.5%] subjects).

The updated safety data at January 2018 cut-off date showed a similar frequency of reported TEAEs leading to discontinuation in study PLX108-10 and TGCT cohort of study PLX108-01 compared to March 2017 data cut-off date. A similar frequency of reported TEAEs leading to dose reduction/interruption in TGCT cohort of study PLX108-01 was also noted. However, there was an increase of frequency of TEAEs leading to dose reduction/interruption for pivotal study PLX108-10: 39 (42.9%) subjects at March 2017 data cut-off vs 54 (59.3%) subjects at January 2018 data cu-toff.

Dose modifications for adverse reactions were proposed by the applicant (Table 41). The applicant also proposed to monitor ALT, AST, ALP and bilirubin prior to initiation of treatment, weekly for the first 12 weeks of treatment, every 2 weeks for the next month and every 3 months thereafter.

Nevertheless, the effectiveness of these proposed dose modifications (Table 41) cannot be assessed at this time because limited information is available. According to an analysis submitted by the applicant on the impact of the dose modifications (Table 41) and dose reductions (Table 28), among the 5 TGCT patients with mixed or cholestatic liver injury in clinical trials with pexidartinib, 4 would have received a lower (<800 mg) pexidartinib dose and 4 would have had an earlier interruption/discontinuation of pexidartinib, and no patient would have been rechallenged.

- Hepatotoxicity and hepatic TEAEs

A total of 50 (38.5%) subjects in TGCT population experienced a hepatic TEAE, 32 (19.0%) subjects in non-TGCT population and 34 (37.8%) subjects in AML population, including liver abnormalities or mixed and cholestatic hepatotoxicity. In some cases, the hepatotoxicity was serious and prolonged, and biopsies confirmed ductopenia and/or cholestasis. Most of the hepatic TEAEs reported were CTCAE grade ≥3 (20 [15.4%] subjects). The most frequently reported hepatic TEAEs were AST and ALT increases, reported in 38 (29.2%) and 33 (25.4%) subjects respectively.

In the target TGCT subjects that started pexidartinib at the posology of 800 mg/day (N=30), 9 (30%) subjects experienced hepatic TEAEs. Two (6.7%) of these subjects experienced hepatic TEAEs of CTCAE Grade ≥3.

A total of 46 subjects in TGCT population experienced treatment-related hepatic TEAEs, 9 (6.9%) had a treatment-related hepatic TEAE leading to discontinuation and 19 (14.6%) had a treatment-related hepatic TEAE leading to dose reduction or interruption.

There was a major change of conduct in September 2016 after 2 SAEs in the pivotal study PLX108-10 consistent with cholestatic liver dysfunction. The study DMC was requested to review the unblinded safety data related to these cases and recommended safety measures that changed the conduct of this study

(see section 2.5.2). In Study PLX108-10, AEs that were considered to be hepatotoxicity included cholangitis, hepatocellular injury, hepatotoxicity, and liver disorder, and 3 of 61 subjects in pexidartinib arm in the controlled part of the phase 3 Study experienced mixed or cholestatic liver injury. At the time of implementation of safety measures in the pivotal study in September 2016, 7 cases of cholestatic/mixed liver injuries occurred in the whole development programme among approximatively 550 subjects. After the updated data cut-off date January 2018, two new cases of mixed/cholestatic liver injury occurred in one study enrolling 32 subjects at pexidartinib dose 800 mg/day. However, it is unclear how many cases of mixed/cholestatic liver injury occurred at the latest data cut-off date and under which preferred term these cases have been referred in TGCT and non-TGCT monotherapy populations.

All cases of mixed or cholestatic hepatic injury occurred during the first 8 weeks of treatment in the clinical development. Treatment discontinuation is required in these cases. While most such hepatotoxicity cases resolved upon treatment discontinuation with a duration of hyperbilirubinaemia of 1 to 7 months or jaundice, there are 2 hepatotoxicity cases across the clinical program that were not reversible: one death of a subject with vaginal melanoma in a context of cholestatic liver injury (pexidartinib at 1000 mg/day) and one case of cholestatic hepatotoxicity leading to liver transplant in a subject with breast cancer (pexidartinib 600 mg twice daily and paclitaxel 155 mg weekly).

Brief narratives of the most notable hepatic events were provided for the pexidartinib program, all cases with liver biopsy taken in the context of a hepatic event, and all cholestatic liver injury cases across the program. Liver biopsy was performed for 8 hepatic cases whereas 18 notable hepatic events occurred. In some cases, the hepatotoxicity was serious and prolonged such that biopsies confirmed structural changes (ductopenia and/or cholestasis). The main effect in the liver biopsy reports is ductopenia that can lead to vanishing bile duct syndrome. A steatosis can also be associated as well as lobular or centrilobular cholestasis. Among the notable hepatic events, it is noted that the re-challenge with pexidartinib further to elevation of AST/ALT is positive. Therefore, the restart of treatment after interruption is questionable.

A dose-exposure analysis has been performed to evaluate the relationship of pexidartinib and AST and ALT increases and with TBIL increases (see section 2.4.3). Taking into consideration that the dose-dependency of pexidartinib and hepatotoxicity cannot be excluded, further data will need to be generated with the planned post-authorisation study to substantiate the revised dosing regimen (see section 2.5.3).

The mechanism of hepatotoxicity remains unknown and the occurrence of liver injury cannot be predicted.

It is uncertain if the risk of mixed or cholestatic hepatic injury can be adequately managed and hepatotoxicity can be life-threatening. AST and ALT elevations can be decreased by dose interruption. However, in the hepatic toxicity cases presented as notable in the dossier, the re-challenge appeared positive. Therefore, the occurrence of hepatotoxicity in case of re-administration of pexidartinib cannot be excluded: the re-administration of pexidartinib should be considered as a high risk. Moreover, it is unclear if the re-administration of pexidartinib can lead to a more severe hepatotoxicity. Indeed, in some cases jaundice or hyperbilirubinaemia persisted up to 7 months after pexidartinib interruption/discontinuation.

Dose modifications criteria have been proposed by the applicant to manage the hepatotoxicity. There is only little evidence that these risk management procedures could have prevented cases of cholestatic liver injury. However, prompt interruption of pexidartinib might help to reduce the severity and duration of ductopenia and/or cholestasis.

Safety monitoring measures have been set up in the pivotal study PLX108-10 in September 2016 (see section 2.5.2). Amongst others, the liver test monitoring was strengthened, but the effectiveness of the proposed liver test monitoring frequency was not established. The submitted safety data do not permit to

conclude on the effectiveness of the safety management procedures in preventing severe cholestatic liver injury (exclusion of patients with elevations of serum transaminases or bilirubin, or active liver or biliary tract disease and weekly monitoring of liver tests), because no new study participants and no cross-over from placebo to pexidartinib was permitted subsequent to the safety measures implemented in the trial. The effectiveness of the proposed safety measures can only be assessed in future trials or at least in new subjects starting pexidartinib treatment such as expected from the post-authorisation study to be conducted.

Other adverse events of special interest

- Cognitive disorders

In the TGCT population, the frequency of cognitive TEAEs was higher in the TGCT cohort of phase 1 study than in the phase 3 study, in which no difference between the pexidartinib and placebo treatments was noticed, with 3 (5%) in each treatment arm. It is noted that the subjects from this phase 1 TGCT group were exposed to higher pexidartinib dose among the TGCT population (1000 mg/day) and longer drug exposure (median exposure: 73 weeks; median exposure for all the pexidartinib treated TGCT population: 43.0 weeks). Consequently, it is stated in the proposed SmPC section 4.7 and 4.8 that Turalio can cause neurotoxic effects including cognitive disorder, which should be considered when performing tasks that require judgment, motor or cognitive skills.

- Cardiac disorders

Overall, no pexidartinib-relative TEAEs of cardiac interest was reported. Two cases of cardiac arrest were reported but were unrelated to pexidartinib. A thorough QTc prolongation study has been conducted in healthy volunteers, and no QT prolongation was noted with pexidartinib at supratherapeutic dose.

- Myelosuppression

A total of 26 (20.0%) subjects experienced a myelosuppression TEAE in TGCT population, of which 23 (17.7%) were treatment-related. There were 4 (3.1%) pexidartinib-treated subjects who experienced CTCAE Grade ≥3 myelosuppression TEAEs: neutropenia (2 subjects [1.5%]) and neutrophil count decreased (1 [0.8%]), all of which were treatment-related; and 1 (0.8%) subject experienced lymphocyte count decreased, which was not treatment-related.

Pexidartinib might have an impact on the bone-marrow microenvironment and the macrophage/monocytic system, which may induce potentially dangerous irreversible changes in bone marrow function during longer treatment periods not assessable at present. Moreover, infection rates may increase and types of infections may shift to unusual agents.

- Immunological events

No data regarding immunological were submitted provided and it remains unknown whether antibody formation against pexidartinib could occur. Moreover, it remains unknown whether pexidartinib has any impact on the immune system. While vasculitis was observed in animals, no systematic approach to assess potential vasculitis in the human target population was implemented. Many of the cutaneous adverse events reported might mimic vasculitis.

Safety related to drug-drug interactions and other interactions

Data available for drug-drug interaction (see section 2.4) showed that several clinically relevant interactions on the level CYP and UGT enzymes and systemic gastric acid reducers could be expected.

Although the applicant summarised that no effect of prior therapy or medical history was identified as a risk factor for hepatotoxicity or other AE, this seems not to be fully in line with information provided in the patients' narratives. Several patients who developed significant hepatotoxicity had concomitant treatment with potential hepatotoxic medication, which are likely to increase the risk for DILI. Since the adverse effect of pexidartinib on hepatic function can be severe and prolonged, it seems unlikely that additional risks for increasing pexidartinib hepatotoxicity can be sufficiently controlled in clinical practise, in particular as these may be over-the-counter medications. The narratives seem to indicate that even under study conditions (more restrictive than clinical practice and routine administration), co-administration of other hepatotoxic medicines will occur and may additively increase the risk for DILI in the target population. Currently, the impact of DDI on pexidartinib metabolism is also unknown but may further increase the risk for DILI.

The applicant acknowledges that a careful assessment of baseline liver function, medical history, and concomitant medications is required to evaluate the potential clinical impact in an individual patient of liver function impairment by pexidartinib. However, it remains currently unknown whether the proposed methods are sufficient to lower the risk for DILI to an acceptable level. Data to confirm the proposed approach were not presented.

TGCT is a slow-growing non-malignant tumour; the treatment duration needed to control durable and clinically relevant TGCT is unknown. The applicant claims that no notable withdrawal or rebound has been reported after interruption or discontinuation of pexidartinib, but this is based on a very short follow-up period of up to 10 weeks, which in this disease is neither informative nor reassuring. The planned post-authorisation study will provide 7-year follow-up data.

- Safety in special populations

Most of the TGCT subjects in the clinical trials were less than 50 years (N=84), 38 subjects were 50-65 years and 8 subjects >65 years of age. As pexidartinib is intended for long-term treatment, safety is in elderly a concern because of higher exposure in these patients. A dose reduction by 200 mg/d is part of the revised dosing regimen (see Table 28) for patients >= 65 years of age, and the planned post-authorisation study will include such patients to provide PK and clinical data.

- Pregnancy and fertility

Considering outcomes of 2 pregnancies, data are very scarce in pregnant women using pexidartinib. In embryo-foetal development toxicity studies, a teratogenic potential was demonstrated for pexidartinib in both rats and rabbits.

No data were submitted regarding the potential inactivation of oral contraception.

Moreover, nonclinical findings raised a potential risk on fertility; as concluded in non-clinical section 2.3.7, a clinical relevance seems likely. Therefore, male patients treated with Turalio should be advised to have sperm sample frozen and stored before treatment.

Changes in female reproductive organs were observed in repeat-dose toxicity studies conducted in rats and dogs, attributed to the pharmacological activity of pexidartinib. Therefore, an effect on female fertility/reproductive capacity cannot be ruled out in humans.

Based on findings in animals, male and female fertility may be compromised during treatment with pexidartinib, and patients should be advised of this risk as per the proposed SmPC section 4.4.

Additional expert consultation

The Scientific Advisory Group (SAG) in Oncology was consulted during this procedure. See section 2.5.3 for SAG answers to questions concerning safety and efficacy of pexidartinib and an integrated discussion.

2.6.2. Conclusions on the clinical safety

The main safety issue of pexidartinib is hepatotoxicity. It occurred during the first 8 weeks for all mixed/cholestatic liver injuries observed during the development program, but its occurrence cannot be predicted. The mechanism of action of hepatotoxicity remains unknown and no predictive factor has been identified. Moreover, the effectiveness of the proposed risk minimisation measures remains uncertain at this time. The risk of potentially life-threatening hepatotoxicity and the lack of proof of effectiveness of its monitoring and the dose modifications are worrying, especially for a non-fatal condition. Specifically, the high degree of potentially fatal hepatotoxicity and the high risk for DILI is illustrated by one case of death that occurred in the context of ongoing cholestatic liver injury (although considered unrelated) and the need for liver transplantation in another case during the clinical development program (both in non-TGCT subjects).

In addition, the safety data for patients who received 800 mg/day as of treatment initiation is based on 30 subjects with a median drug exposure of 31.8 weeks, which is considered weak evidence for a non-life threatening condition and for a long-term treatment intention. Moreover, these 30 subjects were those from placebo arm in controlled part of the pivotal study who crossed-over to open-label part.

The potential long-term safety concerns of pexidartinib are mainly cognition disorders, myelotoxicity, skin rash and potentially cardiovascular toxicity have to be addressed in the planned post-authorisation study that will provide PK and clinical data, including longer-term safety data.

2.7. Risk Management Plan

Safety concerns

Table 42: Summary of safety concerns (RMP version 1.0, DLP 22 April 2020)

Summary of safety concerns	
Important identified risks	Hepatotoxicity Blood disorders
Important potential risks	Embryo-foetal toxicity Fertility toxicity Serious infection Neurotoxicity Cumulative toxicity in uvea, thyroid, and skin Vasculitis Malignancies
Missing information	Use in elderly patients (≥65 years of age) Long-term safety

Pharmacovigilance plan

- Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for the safety concerns hepatotoxicity and embryo-foetal toxicity follow-up questionnaires to capture specific data related to these safety concerns in the post-marketing period.

- Additional Pharmacovigilance Activities

The Applicant proposed a Post-authorisation Safety Study (PASS) entitled "Non-interventional study on pexidartinib treatment in routine clinical practice for patients with Tenosynovial Giant Cell Tumours (TGCT)".

Table 43: Summary table of additional PV activities (RMP dated 22 April 2020)

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT)	The primary objectives are: Collect and evaluate real world, long-term safety data for pexidartinib with a focus on liver related AEs, all-cause mortality, and other drug related AEs in all patients treated with pexidartinib in routine clinical practice for up to 7 years. Special focus will be given to elderly patients (≥65 years). Safety data will also be evaluated according to the sex	Hepatoxicity; Blood disorders; Serious infection; Neurotoxicity; Cumulative toxicity in uvea, thyroid, and skin; Vasculitis; Malignancies; Use in elderly patients; Long-term safety	Final report	To be supplied with the study milestones in the protocol (final report expected by 30 October 2029)

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Post-Marketing Safety Study (PASS) PROPOSED	and body weight-based dosing regimen. An evaluation will also be made of safety relative to re-initiation of pexidartinib treatment after an interruption of >1 month. Collect and evaluate all adverse events, with a special focus on important identified and/or potential risks such as blood disorders, serious infections, neurotoxicity, cumulative toxicity in uvea, thyroid and skin, malignancies and vasculitis. Compare rate, the severity, the duration and the outcomes of the adverse events reported in this PASS to those observed in the clinical studies submitted during the application procedure.			

Risk minimisation measures

Next to the routine risk minimisation measures (Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL)) the Applicant proposes the following additional risk minimisation measures:

- HCP guide
- Patient Reminder Card (PRC)

Table 44: Summary table of pharmacovigilance activities and risk minimisation measures by safety concern (RMP dated 22 April 2020)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hepatotoxicity	Routine risk minimisation measures: SmPC Section 4.2 Posology Section 4.3 Contraindications Section 4.4 Special warnings and precautions for use Section 4.5 Interaction with other medicinal products and other forms of interaction	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction, specific for hepatic events

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Section 4.8 Undesirable effects Section 5.2 Pharmacokinetic properties Patient Information Leaflet (PIL) Section 1 What Turalio is and what it used for Section 2 What you need to know before you take Turalio Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Recommendations for liver function monitoring is included in the SmPC sections 4.2 and 4.4 and in the patient information leaflet (PIL) sections 1 and 2. Information on detection of symptoms of liver problems is provided in the PIL section 2. Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription. Additional risk minimisation measures: HCP guide Patient reminder card (PRC)	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)
Blood disorders	Routine risk communication: SmPC: Section 4.8 Undesirable effects Section 5.3 Preclinical safety data PIL Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)
Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Section 4.3 Contraindications Section 4.4 Special warnings and precautions Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data PIL Section 2 What you need to know before you take Turalio	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: AE follow-up form for adverse reaction, specific to pregnancy Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Women of childbearing potential must undergo pregnancy testing before starting treatment with Turalio (SmPC sections 4.4 and 4.6 and PIL section 2). Women of childbearing potential must use an effective non-hormonal method of contraception during treatment with Turalio and for 1 month after the last dose (SmPC sections 4.4 and 4.6 and PIL section 2). Male patients with female partners of childbearing potential should use an effective method of contraception during treatment with Turalio and for 1 month after the last dose (SmPC sections 4.4 and 4.6 and PIL section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription. Additional risk minimisation measures: HCP guide Patient reminder card (PRC)	
Fertility toxicity	Routine risk minimisation measures: SmPC: Section 4.4 Special warnings and precautions Section 4.6 Fertility, pregnancy and lactation Section 5.3 Preclinical safety data PIL Section 2 What you need to know before you take Turalio Routine risk minimisation activities recommending specific clinical measures to address the risk: Turalio may reduce fertility in women and men. You should discuss this with your doctor before starting treatment (PIL section 2). Men being treated with this medicine are advised to have sperm samples preserved and stored before treatment (SmPC sections 4.4 and 4.6 and PIL section 2). Women should be advised of the risk of decreased female fertility (SmPC sections 4.4 and 4.6). Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription. Additional risk minimisation measures: None	Additional pharmacovigilance activities: None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Serious infection	Routine risk communication: SmPC: Section 4.8 Undesirable effects Section 5.3 Preclinical safety data PIL Section 4 Possible side effects Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)
Neurotoxicity	Routine risk communication: SmPC: Section 4.7 Effects on ability to drive and use machines Section 4.8 Undesirable effects Section 5.3 Preclinical safety data PIL Section 2 What you need to know before you take Turalio Routine risk minimisation activities recommending specific clinical measures to address the risk: Turalio can affect your ability to drive and use machines. Consider the following side effects when driving or using machines: feeling weak, tired or overly tired, vision changes, including blurred vision, double vision, increased sensitivity to light and changes in attention or ability to concentrate. Talk to your doctor, if you are uncertain about your ability, before driving or using machines (PIL section 2). Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)
Cumulative toxicity in uvea, thyroid, and skin	Routine risk communication: SmPC: Section 4.8 Undesirable effects Section 5.3 Preclinical safety data PIL Section 4 Possible side effects	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription Additional risk minimisation measures: None	(Study Number: to be determined)
Vasculitis	Routine risk communication: SmPC: Section 5.3 Preclinical safety data Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)
Malignancies	Routine risk communication: SmPC: Section 4.4 Special warnings and precautions for use Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable. Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription. Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)
Use in elderly patients (≥65 years of age)	Routine risk minimisation measures: SmPC Section 4.2 Posology Section 5.1 Pharmacodynamic properties PIL Section 2 What you need to know before you take Turalio Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription. Additional risk minimisation measures: None	
Long-term safety	Routine risk minimisation measures: PIL Section 3 How to take Turalio Routine risk minimisation activities recommending specific clinical measures to address the risk: Not applicable Other routine risk minimisation measures beyond the Product Information: Legal status: Turalio is on restricted prescription. Additional risk minimisation measures: None	Additional pharmacovigilance activities: PASS: Non-interventional study on pexidartinib treatment in routine clinical practice for patients with symptomatic tenosynovial giant cell tumour (TGCT) (Study Number: to be determined)

Conclusion

The CHMP and PRAC, having considered the data submitted in the application, was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant compared the structure of pexidartinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers pexidartinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the

applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* Since the product information has changed further to the procedure with a more restricted indication and posology recommendations by age, sex and body weight, it is recommended to perform an additional test taking into account these points.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed restricted indication is, "Turalio is indicated as monotherapy for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability."

TGCT is a rare, non-malignant proliferative neoplasm involving the synovium and tendon sheaths that typically presents in young and middle-aged adults. Symptoms often include pain, stiffness, swelling and reduced range of motion (ROM) of the affected joint(s), which may result in marked functional limitation and, potentially, chronic debilitation. Localized forms of TGCT usually allow total resection with excellent or good clinical results and show little recurrence. However, diffuse forms of TGCT can be challenging to manage surgically and local control is uncertain and carries a risk of multiple recurrences. Affected patients often have more extensive involvement and a poorer likelihood of success with surgery. Surgical resection may involve removal of major tendons, neurovascular structures, or limbs, leading to significant postsurgical morbidity.

The aim of systemic therapy of TGCT is to reduce surgical morbidity and to preserve function and patient quality of life.

3.1.2. Available therapies and unmet medical need

Surgical resection is the standard of care for TGCT. Localized-type TGCT is in most instances managed by direct excision of the tumour nodule, with excellent or good clinical results. Patients with diffuse-type TGCT often have more extensive involvement and a smaller likelihood of success with surgery. The management of these tumours is more complex and could involve total synovectomy, joint replacement or, in very rare cases, amputation. The goal is to prevent total joint replacement or amputation and to preserve function as much as possible.

Anti-inflammatory and analgesic medications, including opioids, are commonly used as supportive therapy.

Radiation therapy (RT) is the most widely used adjuvant therapy and seems to reduce recurrence in diffuse-type TGCT, especially when synovectomy was partial. RT is not expected to lead to functional improvement and may be associated with accelerating degenerative arthritis.

No anti-tumour medicinal products are approved for this disease.

A treatment that would shrink tumours to such an extent that function, pain or aesthetic deterioration is limited or improved, or that would avoid or delay mutilating or debilitating surgery, would cover an unmet need.

3.1.3. Main clinical studies

The main evidence of efficacy submitted is a pivotal phase 3, multi-centre, 2-part study. The first part was a randomized, placebo-controlled, double-blind study comparing pexidartinib (n=61) versus placebo (n=59) in patients with symptomatic TGCT for whom surgical resection would be associated with potentially worsening functional limitation or severe morbidity (locally advanced). The primary efficacy endpoint was ORR (CR+PR) at week 25 according to centrally read MRI and RECIST 1.1 criteria. Secondary endpoints were ROM, PROMIS physical function, worst stiffness, worst pain and response by TVS at week 25. At week 25 or progression, subjects could continue open-label pexidartinib twice daily (up to 800 mg/d) for additional 24 weeks. The trial was stopped early for the protection of subjects after the emergence of serious safety signals of hepatotoxicity.

3.2. Favourable effects

In the subgroup of the main study that corresponds to the claimed, restricted indication (20 pexidartinib-treated patients), the best overall response (BOR) as per RECIST 1.1 was 55% objective response rate (ORR) after 25 weeks of pexidartinib.

To explore the clinical effects of objective response, ROM was assessed in a case-by-case approach to explore the clinical effects of the BOR. Since 2 subjects of the restricted indication population were not adequately evaluable, only 18 patients were assessed case-by-case.

Among the 18 evaluable patients, 4 patients had a probably clinically relevant ROM improvement (more than 15 percentage points improvement in relative ROM in the worst affected joint at the latest evaluable ROM assessment) based on a responder analysis.

In 9 of the 20 subjects, ROM measurements related to the knee; the knee ROM change from baseline was 3.4% (mean; SEM 3.4) at week 25 (6 evaluable subjects) and 4.6% (4.7) at the visit with the smallest post-baseline sum of longest TGCT diameters (8 evaluable subjects), respectively, corresponding to an absolute increase of about 5° and 7° in ROM of the knee, which normally is about 150°.

Supportive data on pexidartinib are the overall results of the phase 3 study, which was intended to support the initially claimed TGCT indication. The study demonstrated that pexidartinib achieved an ORR of 39% (95% CI 26.5-51.8) at week 25 compared to 0 in placebo-treated patients (1-sided p <0.001); 9/59 subjects (14.8%) experienced a complete response (CR) and 15/59 (24.6%) a partial response (PR) as per RECIST 1.1. Subgroup analyses for ORR showed a consistent effect over most subgroups including disease location, joint size, US versus non-US study sites and type of TGCT (diffuse or localized).

At the data cut-off of 31 May 2019, the best objective response rate was 61.5% (95% CI 51.3-70.9) among all pexidartinib treated TGCT subjects (N=91) across studies. A median duration of response based on RECIST had not been reached as of the 31 May 2019 data cut-off, at which time the median follow-up from first dose was 36 months (range 31-47 months).

An improvement was seen in clinical secondary endpoints encompassing ROM and PROs (PROMIS Physical Function, worst stiffness, pain BPI-30), and results were statistically significant for all endpoints except for pain improvement (BPI-30) (see Effects Table). There appears a reasonable correlation between shrinkage and pain control or function, at least on a short term.

The long-term effect of pexidartinib (as per the data cut-off of 31 May 2019) on TGCT in terms of CR seems dependent upon tumour size because fewer CRs (10%) occurred in large tumours (defined as >11.6 cm) compared to small or medium-sized tumours (40%).

3.3. Uncertainties and limitations about favourable effects

The observed reduction in tumour size was not associated with a significant improvement of joint function in terms of change in relative ROM. Even in a best-case scenario, a possible clinically relevant improvement in joint functionality could only be considered in a few patients. However, the favourable trends in clinical secondary endpoints are difficult to interpret due to many missing observations (increasing bias since patients with observations may not reflect the study population) and due to high variability of observed effects (the effect on pain thus lacked statistical significance).

It remains impossible to understand in how many patients tumour regression and/or improvement in ROM was associated with a measurable clinical advantage (e.g. return to work, ability to run or performing certain activities), lacking a comprehensible description of the nature and the importance of the clinical response.

The duration of the tumour shrinkage during pexidartinib and especially off treatment is an important source of uncertainty. Lifelong treatments may be poorly acceptable (see safety below), and the main clinical study did not bring reliable information on outcomes after temporary or definite treatment withdrawal. These questions have to be addressed in a long-term study investigating Pk, safety, and activity.

Given the available data and based on pharmacological and mechanistic considerations, it is likely that the tumour could re-start progression and that continuous -or at least long-term- treatment is necessary to control the disease. This crucial information is not available. This question will need to be addressed in a corresponding cohort in the above-mentioned long-term study.

3.4. Unfavourable effects

Hepatotoxicity is the most important safety concern with pexidartinib. Pexidartinib is associated with two clinically distinct types of hepatic adverse reactions both occurring in the first 8 weeks of treatment in the clinical development: isolated liver enzyme elevations which occurred frequently and resolved in most cases within 15 days after dose reduction or discontinuation, and mixed or cholestatic hepatotoxicity which occurred at low incidence and is potentially irreversible and appears non-manageable.

Higher pexidartinib exposures are correlated with higher probabilities of liver enzyme (ALT/AST) elevations. This concentration effect levels off, and the probability diminishes, after the first 12 weeks of treatment. Exposure-response analyses indicate that females and low-weight patients have increased exposure and a reduced clearance of flat dose pexidartinib, requiring dose reductions.

The mixed or cholestatic hepatotoxicity related to pexidartinib may be fatal and is likely not manageable because the mechanism of liver toxicity in animals and in humans is unknown and its occurrence cannot be predicted. Intensive monitoring of liver enzymes may partly mitigate the severity and possibly the risk of severe hepatotoxicity, but even with monitoring the risk remains poorly predictable. A review of the hepatotoxicity cases did not suggest predictive factors.

A total of 10 serious hepatotoxicity cases have been assessed as probably related to pexidartinib by an adjudication committee (5 cases each in the TGCT population and in the non-TGCT clinical safety dataset), including one death and one liver transplant. In addition, two cases of serious hepatotoxicity were assessed as possibly related to pexidartinib. As of 22 May 2020, the US post-marketing data reported six cases of serious hepatotoxicity among 125 registered TGCT patients treated with pexidartinib.

Adverse events were more often reported with pexidartinib than placebo. The following main toxicities can be clearly identified to be related to pexidartinib (difference to placebo at least 10% and not in favour of pexidartinib): hair colour changes (+70.4% compared to placebo), fatigue (+21.3%), AST (+29.2%), ALT (+23.7%), ALP increased (+10.8%), dysgeusia (+26.8%), pruritus (+22.8%), periorbital oedema (+22.9%), rash (+20.4%), vomiting (+14.9%), peripheral oedema (+15.1%), constipation (+10.3%), face oedema (13.7%), macular rash (+12.9%) and erythema (+10.8%).

The myelosuppressive and immunosuppressive effects of pexidartinib may increase the risk of serious infection and malignancies. Vasculitis and neurotoxicity were observed in animals, and these toxicities were only partially identifiable in the human target population. However, adverse events of cognitive disorders occurred in patients receiving pexidartinib and have to be seen as clear evidence for potential clinically relevant neurotoxicity associated with pexidartinib. A risk for accumulation seems to be most pronounced in the uvea, the thyroid and the skin.

Severe TEAES (CTCAE Grade 3 or higher) were more often reported in the pexidartinib arm than the placebo arm, 44.3% and 11.9%, respectively. The most frequently reported CTCAE grade 3 or higher TEAEs were in the SOC Investigations in the TGCT population, mostly hepatic enzymes elevations (AST, ALT and ALP increases).

Serious AE were more often reported in pexidartinib arm compared to the placebo arm in the controlled part 1 of the pivotal study, 13.1% and 1.7%, respectively. Among the reported SAEs in pexidartinib arm, most were hepatic events. Overall, 20% of TGCT subjects treated by pexidartinib had a TEAE leading to discontinuation. The most frequently reported TEAEs were ALT or AST increased, cognitive disorder, fatigue and arthralgia. A total of 53.8% of TGCT subjects treated with pexidartinib had a TEAE leading to dose reduction or interruption. The most frequently TEAEs reported were ALT or AST increased, followed by nausea, vomiting, ALP increased and periorbital oedema.

3.5. Uncertainties and limitations about unfavourable effects

There is no reliable estimate of the frequency of mixed or cholestatic hepatotoxicity, and it remains uncertain if the risk of mixed or cholestatic hepatotoxicity could be mitigated in terms of frequency and / or severity by appropriate measures (e.g., through progressive dosing, drug monitoring, shorter duration of treatment or treatment interruptions). The effectiveness of proposed measures to reduce mixed or cholestatic hepatotoxicity (intensive liver enzyme monitoring, age-, sex- and weight-based dosing as well as dose modifications for adverse reactions) has to be addressed in a long-term post authorisation study investigating PK, safety and activity.

There are uncertainties on the long-term safety since the extent of exposure is limited and no conclusion about possible risks for humans with continued long-term treatment can be drawn from nonclinical data. Despite the updated safety data provided by the applicant at data cut-off date of 31 May 2019, the extent of exposure remains insufficient to address potential safety concerns, with 86 TGCT subjects exposed for one year or longer at different pexidartinib dosages. This is particularly important since persistence of

tumour shrinkage after treatment discontinuation has not been demonstrated (see efficacy issues above). This issue will be addressed with further safety data to be generated in the context of the above-mentioned long-term study.

The full safety profile of pexidartinib was not sufficiently characterized during clinical development as the applicant could not provide evidence whether or not toxicological findings could be related to off-target activity of pexidartinib. Identification of potential long-term safety concerns remains difficult since the pexidartinib full selectivity profile is unclear and binding to CSF1R, KIT and potential other kinases could contribute to the adverse event profile of pexidartinib. Considering the drug's mode of action, pexidartinib might have an impact on the bone-marrow microenvironment and the macrophage/monocytic system. This issue will be addressed with further safety data to be generated in the context of the above-mentioned long-term study.

There is lack of evidence for the recommended dosing regimen of 800 mg/day, and the tolerance at this dose is uncertain taking into account the frequent dose reductions or dose interruptions (53%) and dose discontinuation (20%) in the TGCT study population. This issue will be addressed with further PK and safety data to be generated in the context of the above-mentioned long-term study.

Teratogenic potential was demonstrated for pexidartinib, with non-reversible findings on male reproductive organs in rats and dogs, effects on male fertility in rats and changes in female reproductive organs in rats and dogs at exposure levels mostly lower than those in patients. A clinical relevance seems likely, in view of the concordance across species and the lack of reversibility, the absence of safety margin and the underlying mechanism involving pharmacological effects of pexidartinib. Male patients treated with Turalio should be offered to have sperm sample preserved and stored before treatment. Effects observed on female fertility with pexidartinib have been reported to be induced by progesterone receptors; the overall weight of evidence suggests that the effects on female fertility are likely reversible.

3.6. Effects Table

Table 45: Effects Table for Turalio as monotherapy for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability (ITT population, data cut-off 27 March 2017, unless stated otherwise)

Effect	Short Description	Unit	Pexidartinib arm	Control arm (placebo)	Uncertainties / Strength of evidence	References
Favourable effects						
Best overall response (BOR)	Objective response rate (CR + PR) based on RECIST 1.1 at any time after pexidartinib start	% of subjects	55	NA	- Patients selected on baseline criteria - blinded central MRI reading - Uncertainties on clinical relevance - not supported by PRO and function endpoints	Corresponding to restricted indication (N = 20, only pexidartinib-treated, including after cross-over, see discussion clinical efficacy, data cut-off 31 May 2019)

Effect	Short Description	Unit	Pexidartinib arm	Control arm (placebo)	Uncertainties / Strength of evidence	References
ROM Range of motion responders	More than 15 percentage points change from baseline to latest available ROM assessment in % of normal ROM for most affected joint	Number of responding subjects / number of evaluable subjects	4 / 18	NA	- Responder analysis, threshold not validated - Patient selection based on baseline criteria	Corresponding to restricted indication (N = 20, only pexidartinib-treated, including after cross-over, data cut-off 31 May 2019)
ROM Range of motion	LS Mean change from baseline in % of normal ROM for knee as most affected joint	%	3.4 (after 25 weeks, 6 evaluable subjects); 4.7 (at visit with smallest post-baseline sum of longest TGCT diameters, 8 evaluable subjects)	NA	- Small patient numbers (N=9) - Patient selection based on baseline criteria (see discussion of clinical efficacy)	Corresponding to restricted indication (N = 20, only pexidartinib-treated, including after cross-over, data cut-off 31 May 2019)
Unfavourable effects						
Treatment-related Grade ≥3 AEs		N (%)	23 (37.7)	2 (3.4)	Limitation for interpretation because of differences in dosage and exposure in TGCT patients	
Severe Hepatic AEs		N (%)	12 (19.7)	1 (1.7)		
AESI Cognitive disorders		N (%)	3 (4.9)	3 (5.1)		
AESI Myelosuppression AE		N (%)	11 (18.0)	2 (3.4)		

Abbreviations: ORR: overall response rate; LS: least-squares fit; ROM: range of motion; TVS: tumour volume score; NRS: numeric rating scale; BPI: brief pain inventory; AE: adverse event; TEAE: treatment-emergent adverse event; SAE: Serious adverse event; AESI: adverse event of special interest; NA: not applicable

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the claimed, restricted indication, pexidartinib was associated with tumour shrinkage and improvement in joint function and/or alleviating pain only in a small number of patients severely affected by a TGCT. This benefit appeared small and dependent on baseline conditions related to the tumour and to the patient's status.

The pexidartinib effects measured for clinically relevant outcomes (in particular pain, range of motion and physical functioning) were small and varied across the outcomes and timepoints, notwithstanding the difficulties in estimating effects due to missing data (including missing valid PRO data as a consequence of subject noncompliance and technical issues).

It is unclear in how far improvements in ROM were associated with measurable clinical advantages (e.g., return to work, ability to run or perform certain activities); the nature and importance of responses in the clinically relevant outcomes is unclear.

Additionally, there is high uncertainty with data on the clinically relevant outcomes due to substantial missingness and changes to their analyses (hierarchical significance testing sequence) after the data were collected.

Therefore, the observed reduction in TGCT size is not considered supported by relevant improvements of joint function (relative ROM) or clinically relevant outcomes (e.g., pain and physical functioning), even when objective responses were durable in a high proportion of patients.

The population in whom pexidartinib could bring a benefit is difficult to define prospectively with objective elements. Furthermore, uncertainties on the maintenance of these benefits on a long term and the unknown outcomes after treatment interruption or re-introduction do not allow a clear estimation of benefits.

TGCT is not a condition with reduced life-expectancy and it progresses in most patients slowly. This makes it necessary that severe adverse reactions must be prevented, especially when these are potentially fatal such as the mixed or cholestatic liver injury that is associated with pexidartinib.

Pexidartinib was developed in analogy to the classical oncology maximal tolerated dose-concept. Crucial uncertainties remain on the risk of hepatotoxicity of pexidartinib despite age-, sex- and weight-based dosing as well as dose modifications for adverse reactions, clinical and laboratory monitoring in this condition, the effectiveness of which remain uncertain.

These major uncertainties prevent to conclude on a positive benefit/risk balance.

The CHMP had consulted the SAG and considered their answers but found that the risk of hepatic toxicity of pexidartinib will remain unpredictable even when pexidartinib treatment should only be given in expert centres in a multidisciplinary setting by professionals experienced with targeted therapies, that the effectiveness of the measures to mitigate the risk of liver injury is uncertain and that results on clinically relevant outcomes did not support attributing clinical benefit to the tumour shrinkage (see section 2.5.2).

The applicant proposed to supplement the efficacy data with long-term treatment experience expected from post-authorisation measures and a post-authorisation safety study. However, these post-authorization studies could be of relevance only in case the benefit/risk balance was established to be positive.

3.7.2. Balance of benefits and risks

TGCT treatments would be expected to show clear and sustained improvement in relevant patient-reported outcomes and normalisation of patient functioning. However, the available data did not establish that pexidartinib activity was associated with relevant clinical benefit.

Given the nature and disease course of TGCT and the uncertain clinical importance of the effects associated with pexidartinib, the currently known frequency and life-threatening severity of hepatic injury associated with pexidartinib is not acceptable.

Considering all favourable and unfavourable effects, existing uncertainties and possible risk minimisation measures, the benefits do not outweigh the risks of pexidartinib in the sought indication.

3.8. Conclusions

The overall B/R of Turalio is negative.

Divergent positions are appended to this report.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Turalio as monotherapy for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability, the CHMP considered by majority decision that the safety and efficacy of the above-mentioned medicinal product is not sufficiently demonstrated and therefore recommends the refusal of the granting of the Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- the single pivotal study confirmed activity in terms of tumour shrinkage but did not establish that the activity was associated with relevant clinical benefit; the measured clinical effects are lacking validity and relevance, and are uncertain due to missing data;
- the hepatic toxicity of pexidartinib remains a crucial concern, considering the potential mortality (or need for organ replacement) from this adverse reaction and the unpredictability of this adverse reaction, in the context of a disease that is chronically debilitating but does not reduce life expectancy; it is uncertain if the proposed risk mitigation measures will be able to effectively reduce the risk and severity of hepatotoxicity.

These major uncertainties on efficacy and safety lead to a negative benefit/risk balance.

Due to the aforementioned concerns, a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the latest Rapporteurs' Joint Assessment Report cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant's claim of new active substance status, the CHMP position at the time of this report is reflected in section 2.9 (new active substance). However, in light of the negative recommendation, the CHMP is of the opinion that it is not appropriate to conclude on the new active substance status.

Divergent positions to the majority recommendation are appended to this report.

APPENDIX

DIVERGENT POSITION DATED 25 June 2020

DIVERGENT POSITION DATED 25 June 2020

Turalio EMEA/H/C/004832/0000

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of the marketing authorisation of Turalio indicated for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability.

The reason for divergent opinion was the following:

A phase 3 study showed that pexidartinib met its primary endpoint showing an ORR of 39% at week 25 compared to 0% in placebo-treated TGCT patients according to RECIST 1.1 criteria (95% CI: 26.5-51.8, 1-sided p value <0.001).

Subgroup analyses showed consistent favourable effects over most subgroups including disease location, joint size and type of TGCT (diffuse or localized). Importantly, in an analysis across studies, at the latest data cut-off of May 2019 with continued pexidartinib treatment, the best objective response rate increased to 61.5%. Furthermore, a median duration of response had still not been reached as of the May 2019 data cut-off, at which time the median follow-up from first dose was 36 months (range: 31-47 months).

In general, patients experienced decreased pain, decreased stiffness and increased physical functioning. In some cases, the reduction of the tumour size enabled substantial relief of symptoms and improvement in performing some daily activities.

Hepatotoxicity is the most important safety risk with pexidartinib. However, post-marketing data from US did not reveal any new fatal cases. The Applicant has proposed a number of risk minimisation measures.

Taken together, efficacy has been established and safety is well-characterised and could be acceptable in the proposed patient population. Thus, the benefit/risk balance could be considered positive for the treatment of adult patients with tenosynovial giant cell tumour (TGCT), which is associated with clinically relevant physical function deterioration and in whom other surgical or therapeutic options have been exhausted or would induce unacceptable morbidity or disability.

Sinan B. Sarac

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Kolbeinn Gudmundsson