19 December 2013
EMA/97103/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Cometriq

International non-proprietary name: cabozantinib

Procedure No. EMEA/H/C/002640/0000

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

BCS	
FTIR	Fourier transform infrared
HPLC	High pressure liquid chromatography
HPLC-PDA	High pressure liquid chromatography with photo-diode array detection
IM	intramuscular
IR	infrared
KF	Karl Fisher titration
MTC	Medullary thyroid carcinoma
Ph.Eur.	European Pharmacopoeia
RET	rearranged during tranfection
RH	relative humidity
SDS	sodium dodecyl sulphate
SmPC	Summary of Product Characteristics
USP	United States Pharmacopeia
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant TMC Pharma Services Ltd submitted on 29 October 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Cometriq, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011.

Cometriq was designated as an orphan medicinal product EU/3/08/610 on 6 February 2009.
Cometriq was designated as an orphan medicinal product in the following indication: Treatment of medullary thyroid carcinoma

The applicant applied for the following indication: Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Cometriq as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

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 P/0128/2012 on the agreement of a paediatric investigation plan (PIP).
At the time of submission of the application, the PIP P/0128/2012 was not yet completed as some measures were deferred.

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.

New active Substance status

The applicant requested the active substance cabozantinib (as S-malate) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

No Scientific Advice from the CHMP was sought for the indication.

Licensing status

Cometriq has been given a Marketing Authorisation in the United States on 29 November 2012.

1.2. Manufacturers

Manufacturer responsible for batch release

Catalent UK Packaging Limited

Lancaster Way, Wingates Industrial Park

Westhoughton

Bolton, Lancashire BL5 3XX

UK United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff

Co-Rapporteur: Ingunn Hagen Westgaard

- The application was received by the EMA on 29 October 2012.
- The procedure started on 21 November 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2013.
- During the PRAC meeting on 06 March 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 March 2013.

- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 May 2013.
- The summary report of the inspection carried out at the following site Catalent Pharma Solutions, Inc. between 25 February – 1 March 2013 was issued on 30 May 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 25 June 2013.
- During the CHMP meeting on 25 July 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 September 2013.
- During the PRAC meeting on 10 October 2013, the PRAC adopted an RMP Advice and assessment overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 2 October 2013.
- During the CHMP meeting on 24 October 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 18 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding issues to all CHMP members on 26 November 2013.
- During the PRAC meeting on 05 December 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 19 December 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Cometriq.

2. Scientific discussion

2.1. Introduction

Problem statement

Medullary Thyroid Carcinoma (MTC)

Carcinoma of the thyroid is the most common malignancy of the endocrine system and include mostly (85%–95%) well-differentiated tumours (papillary or follicular), about 2.5% to 10% of thyroid cancers are medullary carcinoma and other are anaplastic, both of which carry a worse prognosis for patients. MTC is a distinct subtype, arising from the parafollicular cells (C-cells) of the thyroid, that has

particular prognostic and genetic features: it presents mainly as a sporadic cancer (75% of cases) or as part of a hereditary syndrome (25%).

- The hereditary form of MTC is a rare disease commonly diagnosed in patients <20 years and characterised by Multiple Endocrine Neoplasia (MEN) with complete penetrance (virtually all patients develop MTC), but variable expressivity: Multiple Endocrine Neoplasia (MEN) type 2a, MEN type 2b, or Familial Medullary Thyroid Carcinoma (FMTC). Only 50% of patients with MEN2a and MEN2b, develop pheochromocytoma and 30% of patients with MEN2a develop parathyroid hyperplasia. All of the patients with MEN2b develop a typical ganglioneuromastosis throughout the aerodigestive tract. Patients with FMTC develop only MTC. Patients with hereditary MTC carry a germline mutation of the 'rearranged during transfection (RET) gene, leading to constitutive activation of the RET tyrosine kinase.

- The sporadic form of MTC most often presents in middle-aged patients as a solitary nodule in the thyroid. RET was found to be mutated in some tumors of patients with sporadic MTC, and patients with RET mutations (especially the common M918T mutation) are more likely to have regional lymph node involvement or distant metastases and a worse outcome.

Symptoms and Prognosis

Patients with MTC often have localization to the neck and mediastinum. Main symptoms are mostly diarrhoea, pain, opiod use, fatigue, respiratory symptoms, flushing, weight loss and dysphagia. Metastatic MTC spreads most often to the regional lymphatics as well as to the liver, lungs, and bones. Metastases can be anticipated by increasing levels of calcitonin and are often evident on radiographic imaging studies.

The 5-year survival for medullary cancer with regional spread is about 78%. For medullary cancer which spread to distant sites or lymph node the 5-year survival rate is approximately 40% and median overall survival is 2-3 years in patients with distant metastatic disease. Approximately 35% of patients present with tumor extending beyond the thyroid with regional lymph node involvement, and 13% have metastatic disease at initial diagnosis. Metastatic disease is the most common cause of death in patients with MTC, and approximately 90% of patients with metastatic disease die of progressive cancer.

Patients with the hereditary form of the disease generally have a better prognosis than patients with the sporadic form. However, if patients are matched for age and disease stage, no differences in survival are seen, suggesting that patients with sporadic disease may be diagnosed later with more advanced disease.

Treatment

Patients with MTC can be cured by thyroidectomy, performed when the tumour is confined to the thyroid gland. The tumour is relatively unresponsive to conventional doses of radiation therapy and to chemotherapeutic regimens.

Recently, in 2011, vandetanib (Caprelsa), an orally administered tyrosine kinase inhibitor (TKI) was approved for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

For patients in whom Rearranged during Transfection (RET) mutation is not known or is negative, a possible lower benefit of treatment with vandetanib should be taken into account.

About the product

Cometriq is a medicinal product that contains cabozantinib (as malate) as active substance.

Cabozantinib (also referred to as XL184, EXEL-7184, EXEL-02977184 during the development) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including RET, the GAS6 receptor (AXL), the stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 (FLT3).

Therapy with Cometriq should be initiated by a physician experienced in the administration of anticancer medicinal products. The recommended dose of Cometriq is 140 mg once daily, taken as one 80 mg orange capsule and three 20 mg grey capsules. Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs. It should be expected that a majority of patients treated with Cometriq will require one or more dose adjustments (reduction and/or interruption) due to toxicity. Patients should therefore be closely monitored during the first eight weeks of therapy (see SmPC sections 4.2 and 4.4).

The capsules should be swallowed whole and not opened. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking Cometriq.

Cometriq is contraindicated in case of hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC

The applicant proposed the following therapeutic indication: Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

Following the scientific assessment by CHMP, the therapeutic indication is:

Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1).

2.2. Quality aspects

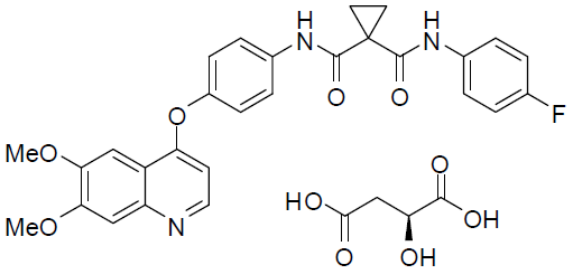
2.2.1. Introduction

Cometriq is presented as hard gelatin capsules containing 20 mg and 80 mg of cabozantinib (as malate) as active substance. Other ingredients are: silicified microcrystalline cellulose, croscarmellose sodium, sodium starch glycolate, silica colloidal anhydrous, stearic acid, gelatin, black iron oxide, red iron oxide, titanium dioxide and printing ink. The list of excipients can be found in section 6.1. of the SmPC. The product is available in blister cards.

2.2.2. Active Substance

The chemical name of cabozantinib (S)-malate is: N-{4-[(6,7-dimethoxyquinolin-4-yl)oxy]phenyl}-N′-(4-fluorophenyl) cyclopropane-1,1-dicarboxamide, (2S)-hydroxybutanedioate.

It has the following structural formula:



Cabozantinib (S)-malate is a white to off-white crystalline substance and is not hygroscopic. It is practically insoluble in water above pH 4. Cometriq contains the malate salt of cabozantinib because the freebase is insoluble in water. Cabozantinib has a non-chiral molecular structure. Polymorphism has been observed for cabozantinib (S)-malate. It is known to exist in two crystalline solid forms (N-1 and N-2) that have similar properties and one amorphous form. The N-2 form was selected for commercial development (see section on pharmaceutical development).

There is no monograph of cabozantinib in the European Pharmacopoeia. The applicant claimed that cabozantinib (S)-malate is a new active substance. The claim is accepted on the basis that cabozantinib has not previously been authorised as a medicinal product in the European Union. Furthermore, it is confirmed that it is not an isomer, mixture of isomers, a complex or derivative or salt of a chemical substance previously authorised as a medicinal product in the European Union. In addition, cabozantinib differs significantly in chemical-pharmaceutical properties and structure from vandetanib, a substance that has already been authorised in the EU for a similar indication.

Manufacture

Cabozantinib is supplied by one active substance manufacturer. It is synthesised in five main steps (with four product isolations), using well defined starting materials. Adequate specifications and control methods have been presented for the starting materials, intermediate products and reagents. Adequate in-process controls applied during the synthesis. Process validation was conducted on three consecutive production-scale batches. Detailed information on the manufacturing process of the active substance has been provided in the dossier and is considered satisfactory.

The manufacturing process has been developed using elements of Quality by Design (QbD) such as a risk assessment and design of experiment (DOE) studies. Based on these studies, proven acceptable ranges (PARS) have been defined for several process parameters for the following steps of the manufacturing process of the active substance. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

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, including potentially genotoxic

impurities (GTIs), were well discussed with regards to their origin and characterised. All potential impurities are adequately controlled in steps performed under GMP.

Specification

The active substance specification includes tests for appearance, identification (HPLC, FTIR), assay (free base, HPLC), purity (HPLC), impurities (HPLC), water content (KF), malic acid content (HPLC), organic volatile impurities (GC), residue on ignition, crystal form (XRPD), particle size distribution and heavy metals (Ph.Eur.). The analytical methods used have been adequately described and the non-compendial methods appropriately validated in accordance with the ICH guidelines. Impurities (including potentially genotoxic impurities) limits have been adequately justified considering the indication and duration of treatment for this life-threatening disease and are considered acceptable from a benefit-risk perspective.

Batch analysis data have been provided on at least eight commercial scale batches produced with the proposed commercial process. The results are within the specifications and demonstrate that the active ingredient can be manufactured reproducibly.

Stability

Five batches of the active substance, cabozantinib (S)-malate, manufactured by the commercial process at the intended commercial scale and manufacturing facility were placed on stability under long-term and accelerated storage conditions in accordance with ICH Q1A guidelines. The container closure system is representative of the intended commercial package. Up to 24 months long term stability data (25°C/60%RH) and 6 months accelerated stability data (40°C/75%RH) have been provided. The following parameters were tested: appearance, assay, impurities including genotoxic impurities, water content and crystal form. The validated analytical procedures used in the stability testing are the same as those used at release. The assay method by HPLC has been demonstrated to be stability indicating.

A photostability test following ICH guidelines Q1B was performed on one batch. Results of forced degradation studies under stress conditions (acid, base, heat, oxidation, UV/visible light) were also provided on one batch. The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The objective of the pharmaceutical development was to develop immediate release capsules for oral administration that allow dosage adjustments in accordance with the needs of the patient. It was decided that this objective could best be met by developing capsules of two strengths, 20 mg and 80 mg expressed as freebase (more precisely 19.7 mg and 78.9 mg cabozantinib freebase, respectively).

Cabozantinib is classified as a BCS class II compound (low solubility, high permeability).

Based on criteria such as crystallinity, solubility and stability, five salts were selected for further evaluation: chloride, maleate, phosphate, L-tartarate, and L-malate. Of these, the malate salt exhibited an acceptable combination of crystallinity, solubility, and stability during initial scale up and was selected for further development. During the pharmaceutical development it became clear though that cabozantinib (S)-malate exists as two closely related crystalline solid forms (N-1 and N-2) that have similar properties. An amorphous form has also been identified and characterized. Both crystalline forms, N-1 and N-2, have been thoroughly characterized.

Cometriq contains standard excipients: silicified microcrystalline cellulose (filler) which consists of microcrystalline cellulose and silicon dioxide, croscarmellose sodium (disintegrant), sodium starch glycolate (disintegrant), silica colloidal anhydrous (glidant), stearic acid (lubricant). The empty gelatine capsule consists of gelatin (capsule matrix), black iron oxide, red iron oxide (colourants), titanium dioxide (opacifier) and printing ink. The two strengths comprise the same excipients except for the iron oxide colourant. All excipients are pharmacopoeial and generally recognized as safe (GRAS) in the proposed concentrations. An excipient compatibility study was conducted and indicated that the excipients are compatible with the active substance. The excipient concentrations have been optimized by studying the effect of various excipient concentrations on the content of uniformity and dissolution.

An appropriate dissolution method was developed. Parameters such as the dissolution medium pH, surfactant type and concentration, dissolution apparatus type and agitation speed were optimized. In addition, also the HPLC method was adapted to avoid interference with the surfactant. The final dissolution method demonstrated to be able to distinguish between drug product variations.

During the manufacturing process development, the applicant used design of experiments (DOE) to optimise the mixing process parameters. Process robustness studies were executed to identify process parameters that are likely to have the greatest impact on product quality and manufacturability and to set robust ranges for the manufacturing process parameters.

The formulation used in the phase 3 clinical studies is identical to the commercial formulation and manufactured with a process representative of the final manufacturing process, and at the intended commercial scale.

The primary packaging proposed is PVC/PE/PCTFE/Al blisters. The material complies with the Ph.Eur., relevant EMA guidelines and directives and it is adequate to support the stability and use of the product.

Adventitious agents

Gelatin from bovine/limed bone is used in the finished product. Valid TSE certificates of suitability (CEP) have been provided for the gelatin suppliers. A valid TSE CEP has also been provided for stearic acid. No other excipients derived from animal or human origin have been used.

Manufacture of the product

Cometriq hard gelatine capsules are manufactured by a standard manufacturing process, the main manufacturing steps are: i) delumping of the active substance and excipients, ii) direct blending of components in a diffusion blender, iii) capsule filling and iv) weight sorting. Critical steps have been

identified and adequate in-process controls are in place. The manufacturing process will be validated prior to marketing. An adequate process validation scheme has been provided.

Proven acceptable ranges have been defined for the main steps of the manufacturing of the finished product. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

Batch analysis data have been provided for 12 commercial scale batches which were manufactured with a process representative of the final process. The results demonstrated that the manufacturing process is capable of reproducibly producing a finished product of the intended quality. Adequate in-process controls are in place for this pharmaceutical form.

Product specification

The finished product release specifications include appropriate tests for appearance (visual), identification (HPLC/UV), assay (HPLC), impurities (HPLC), genotoxic impurities (LC/MS), content uniformity (Ph.Eur.), water content (KF), dissolution (HPLC) and microbiological purity (total aerobic count and total combined yeast and molds). Impurities (including potentially GTIs) limits have been adequately justified considering the indication and duration of treatment for this life-threatening disease and are considered acceptable from a benefit-risk perspective.

Batch analysis results are provided for twelve pilot batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of seven batches of 20 mg capsules and five batches of 80 mg capsules have been placed on long term storage conditions (25ºC/60%RH) for up to 24 months, and under accelerated conditions (at 40ºC/75%RH) for up to 6 months, according to ICH guidelines. These batches were manufactured with a process representative of the final manufacturing process, at the intended commercial scale, and form representative batches of the commercial medicinal product. They were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, impurities, water content, dissolution, genotoxic impurities and microbial purity. The results are within the specifications and with no significant change from the initial data. The analytical procedures used were stability indicating.

Forced degradation studies were conducted. One development batch of each capsule strength was stressed by acid, base, heat, oxidation and light. Samples were analysed for impurities and potency. No degradation was observed under acidic and light-stressed conditions. Degradation was observed under heat and oxidative conditions, and significant degradation was observed under the basic hydrolysis. The degradation profile was similar to that observed for the neat drug substance. Photostability was tested for both capsule strengths according to ICH Q1B. No change was seen for appearance, potency, impurities GTIs, water content or dissolution.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The proposed control strategy and proposed active substance and finished product specifications are considered appropriate to ensure the quality of the product. 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.

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 SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Toxicity associated with oral administration of cabozantinib was characterized in definitive single-dose and 2-week and 26-week repeat-dose studies in rats and dogs; a fertility study in rats; embryotoxicity/teratogenicity studies in rats and rabbits; in vitro and in vivo genotoxicity bioassays; and an in vitro phototoxicity study. Cabozantinib was evaluated in GLP-compliant safety pharmacology studies for effects on cardiovascular, respiratory and central nervous systems.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamics studies with cabozantinib consisted of in vitro receptor binding assays and of several functional cell-based assays. In vivo studies focused first on target pharmacodynamic effects and tumour cellular responses to treatment. Furthermore multiple murine tumour models were used to explore the efficacy of XL184 with regard to tumour growth inhibition and regression in vivo.

In vitro it was shown that XL184 inhibits multiple receptor tyrosine kinases (RTKs) in the nanomolar range, including the proto-oncoproteins MET and RET, and the proangiogenesis protein VEGFR2. Additional targets of XL184 are FLT-3, TIE-2, AXL, TRKB, and KIT. XL184 also inhibits several mutants

forms of RET, MET and KIT, including the activated isoform RET M918T, a very common mutation in medullary thyroid carcinoma (MTC). XL184 was found to be an active site inhibitor that is competitive with ATP for each target tested (MET, VEGFR2, FLT3, TIE-2). Of all these targets only one RTK has been implicated in MTC, ie the RET tyrosine kinase.

The most important metabolites in humans are XL184 desmethyl sulphate (M2a or EXEL1644) and XL184 monohydroxy sulphate (M4). It appears that the pharmacological activity of 1644 is limited (>50% residual control activity at a concentration of 1 µM). However, human Cmax is above the tested concentration and human exposure is relative extensive. Based on the higher protein binding of the metabolite than the parent compound (99.950 to 99.996% against 99.7 to >99%) it appears likely that this metabolite does not significantly contribute of the pharmacological activity of the current product. No data on in vitro substrate/inhibition of the various Cyps have been provided for this metabolite because in vitro and in vivo data suggested that cabozantinib has minimal to no clinically-relevant CYP induction potential.

Metabolite M4 (EXEL-1646) has broader and more potent inhibition of several kinases, when compared to 1644. However, the inhibition of 48 kinases were compared between M4 and the parent cabozantinib and cabozantinib parent showed a much greater potency over a broader range of kinases than did M4. Therefore, this shows that EXEL-1646 does not contribute substantial to the cabozantinib's PD activity. The activity of two other major metabolites of XL184, M1 and M8 were found to be less active against the primary targets of XL184 (MET, VEGFR2) and both can be considered not to have a significant contribution to the pharmacologically activity of XL184.

Also in cellular systems exposure to XL184 inhibited basal or growth factor-induced auto-phosphorylation of RTKs, proliferation of tumour cell lines (including only one cell line relevant for the current indication, ie TT medullary thyroid tumour cell line containing a RET mutation, Ret C634W), microvascular endothelial cell migration, and VEGF-driven tube formation. These data indicate that XL184 may have an anti-tumour effect in vivo on tumours that depend on signalling via one of several RTKs RET/MET/VEGFR/… for growth and/or migration/metastasis formation. In these studies only limited attention has been paid to the RET tyrosine kinase and its clinically relevant mutations. In vitro inhibition generally is seen in the nM range. Extrapolation of these concentrations to in vivo situation is not always possible due to the extremely high protein binding of XL184 (>99.9%). However it is noted that human plasma concentrations are in the low µM range suggesting that the free plasma concentrations may be within the pharmacological active range.

The relationship between dosing, plasma concentration and target RTK inhibition was studied in several studies in nude athymic mice tumour models. Prolonged inhibition of several RTKs was noted which corresponded to the plasma concentrations of XL184 in that inhibition was diminished when plasma levels fell below approximately 10 µM (5 µg/ml) for MET, 15 µM for RET (7,5 µg/ml), and 5 µM (2,5 µg/ml) for VEGFR2. This is within the range or slightly above the clinical plasma levels (2-4 µM). In the target tissue the concentrations of XL184 behaved in a similar manner to plasma concentrations. The concentration in lung was similar (study XL184-disc-010) or ~ 2 fold higher (study XL184-disc-015) to plasma, the concentration in tumour was the similar to (study XL184-disc-011) or ~ 2-fold lower (study XL184-disc-009 and disc-014) than plasma concentration. In liver the concentration was ~2-3 fold higher than in plasma (study XL184-disc-013).

Data from several rat or murine tumour models indicate that once daily administration of XL184 can inhibit tumour growth, and even tumour regression at high doses when plasma levels are in low µM

range. Histopathology of tumour tissue revealed reduced cellular proliferation and microvessel density and increased necrosis in XL184 treated animals. Also relatively large sized tumours were sensitive to XL184 treatment. No data is available on regrowth of tumour following multiple dosing, it is assumed that tumours regrow following end of treatment, however it is not clear if there may be a rebound effect (increased tumour growth) following end of treatment. In only one study a tumour cell line relevant for the indication was used (TT). In this xenograft model (study XL184-disc-025) clear tumour growth inhibition was shown, but regression was only seen at the highest dose.

The effect of XL184 treatment on metastasis formation was evaluated in several studies. In most, but not all studies inhibition of metastasis formation was noted. No MTC cell line was used on these studies.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies were performed.

In a screen consisting of 75 pharmacological targets, including receptors, transporters, and enzymes, specific inhibition was seen only for the adenosine A3 receptor (IC50 <0.9 µM) and the ML1 (melatonin) receptor (IC50> 1 µM). These potential interactions do not represent a toxicologically or clinically significant risk.

Safety pharmacology programme

In in vivo safety pharmacology studies, no adverse effects on neurobehavioral function at up to 300 mg/kg or respiratory-system function at up to 900 mg/kg occurred in rats administered XL184.

The in vitro safety pharmacology data were not performed according to GLP, and data provided in several study reports was limited. The data suggest that cabozantinib is not a potent hERG inhibitor, but has an effect on hERG trafficking, which might lead to delayed QT prolongation in patients. In vivo in dogs, no effects on ECG parameters were observed after a single dose, nor after 26 weeks of dosing (see repeated dose toxicity). In patients, detailed evaluation of the effect of cabozantinib on QT interval was performed in a clinical trial, which revealed a slight, but not clinically relevant prolongation of the QT interval. Considering the available clinical data and the lack of a relevant effect on ECG parameters, further non-clinical data or discussion are not required. In vivo, no effect other than a transient effect on diastolic blood pressure was seen. Hypertension is a known class effect of these type of products and this has also been observed in clinical trials. Further monitoring on a clinical level is warranted.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were performed (see discussion on Non-clinical aspects).

2.3.3. Pharmacokinetics

Cabozantinib is a highly permeable compound with a generally rapid absorption after oral administration. Absolute bioavailability of the malate salt of cabozantinib administered via an oral capsule (clinical formulation) is moderate to high in dog and rat, respectively.

Kinetics of cabozantinib after repeated once-daily dosing were generally linear in rats over the dose range 0.1 – 15 mg/kg, but increased more than dose-proportional over the dose range 5 – 15 mg/kg. In dogs, cabozantinib exposure increased less than linearly with dose over the dose range 0.2 – 5 mg/kg but more than linear with dose over the range 10 – 100 mg/kg.

Cabozantinib is highly bound to plasma proteins in all pre-clinical species and in humans (>99.7%) and widely distributed into body tissues, including passage over the blood-brain barrier, the blood-testes barrier and the placenta, as expected based on the moderate to high volume of distribution. In addition, cabozantinib has potential to bind to melanin. Partitioning into red blood cells has not been studied pre-clinically but data provided in the clinical section showed that XL184 is mainly present in plasma and to a limited extent distributed into erythrocytes. Elimination from plasma is slower in rat than in the other pre-clinical species as indicated by lower plasma clearance values. In addition, excretion data in rat show that within 24 hours only about a third was excreted. Cabozantinib is mainly excreted via faeces in rats.

Entero-hepatic recirculation of cabozantinib may occur in humans as well as in rats and dogs. However, based on the chemical structures of the metabolites readily enabling back-transformation to parent cabozantinib is not expected. For the glucuronide conjugates however back transformation is possible by the intestinal flora. At this stage, it is unclear whether drug-drug interactions with antibiotics or disruption of the enterohepatic recirculation of cabozantinib by other drugs, such as cholestagel or cholestyramine, could occur. Further studies are being conducted to clarify this (see Discussion on non-clinical aspects).

Hepatic clearance does not play a large role in the elimination of cabozantinib in the pre-clinical species as cabozantinib has a low intrinsic clearance value and in vivo only approximately a tenth in rat and a third in mouse is metabolised by CYP3A4 and to a much lesser extent CYP2C9. However, not all CYPs are studied for involvement in the formation of these metabolites (except for M1). In addition, no data on enzyme involvement are available for the other metabolites. In humans however, metabolism is more prominent than in the pre-clinical species. The major component in plasma is unchanged parent and exposure to XL184-monohydroxysulfate (M4), the main human metabolite, was 25% relative to total plasma exposure. No data were provided on the metabolite profile of the excreta (see Discussion on non-clinical aspects).

Cabozantinib is an inhibitor, but not a substrate, of P-glycoprotein with an IC50 value of 0.5 µM. The Applicant will perform a study investigating whether cabozantinib is a substrate or inhibitor of MRD1, BCRP, BSEP, MRP2, OAT1, OAT3, ACT1, OCT1, OCT2, OATP1B1 and OATP1B3 in 2Q13. Potential inhibitory effects on MATE1 and MATE2k also will be addressed. Evaluation of CYP2B6 inhibition by cabozantinib showed a concentration dependent inhibition over the range 0.41 to 16 µM with an IC50 value of 10.1 µM. As this IC50 value is higher than the IC50 value for CYP2C8 and a clinical drug-drug interaction study did not show inhibitory effects of cabozantinib on CYP2C8 in vivo, it is not expected that cabozantinib will inhibit CYP2B6 in vivo. Cabozantinib is not expected to inhibit or induce CYPs in humans at clinically relevant concentrations.

2.3.4. Toxicology

Single dose toxicity

Acute effects in rats showed as possible hepatotoxicity and hematopoietic tissue toxicity with death at 300 mg/kg. Dogs showed less sensitive for acute doses with minimal evidence of toxicity at 2000 mg/kg.

Table 1. Single dose toxicity studies with cabozantinib (XL184)

Study ID	Species/ Sex/Number /Group	Dose/Route	Observed max non-lethal dose	Major findings
XL184-Disc-038 Dose range-finding Non-GLP	Rat F/2	500, 1000, 2000 mg/kg Oral gavage	500 mg/kg	≥1000: death, weight↓, ALT↑, AST↑, CK↑, GGT↑, LDH↑
XL184-NC-003 GLP	Rat M+F/5	100, 300, 900 mg/kg Oral gavage	100 mg/kg	≥100: ALT, AST, ALP, cholesterol, total bilirubin↑ ≥300: death, histopathologic changes in adrenal gland, lung 900: prostration, coldness to touch, abnormal respiration; clinical pathology changes indicative of liver and hematopoietic toxicity, dehydration; histopathologic changes in GI tract, lymphoid tissues, bone marrow, adrenal gland, lung, testes, kidney, pancreas
XL184-NC-001 Dose range-finding Non-GLP	Dog M/2	30, 60, 120, 240, 480 mg/kg Oral gavage	>480 mg/kg	≥120: hypoactivity (F) ≥240: Ca, PO4↓ 480: WBC, neutrophil, and monocyte counts, cholesterol, ALT, AST↑
XL184-NC-004 GLP	Dog M+F/2	400, 1000, 2000 mg/kg Oral gavage	>2000 mg/kg	2000: excessive salivation

Repeat dose toxicity

In rats the most important target tissues for cabozantinib-related toxicity after 2 weeks of oral gavage are GI tract, bone marrow, lymphoid tissues, reproductive tract tissues, endocrine tissues, liver and kidney. The adverse effects were generally dose related and seen from 5 mg/kg/day and above and were generally reversible upon discontinuation of treatment. At the maximum dose of 1 mg/kg/day during the 6 month study, mild and mostly reversible effects were seen on liver and kidney. Because one animal died possibly test article-related, the NOAEL was considered 0.3 mg/kg/day, which is

agreed. Based on the AUC of plasma exposures this is 0.2- to 0.3-fold of the intended clinical exposure.

At high dose (⩾100 mg/kg for 4-14 days), cabozantinib causes hematopoietic- and hepatotoxicity, and dehydration in dogs. Also targets for toxicity are GI-tract, lymphoid tissues, testes, bone, pancreas, gallbladder, eye and possibly CNS tissues. Lesions were reversible at 100 mg/kg. No treatment-related histopathologic changes were present at 10 mg/kg for 14 days. At the maximum dose of 5 mg/kg/day during the 6 month study, no signs of toxicity were evident, but some effects occurred in reproductive tissues. An extra chronic study with 20 mg/kg showed some reversible hematopoietic- and hepatotoxicity, and effects on skin. The histological appearance of testes, epididymis, ovaries, mammary glands, and uterus was similar to animals that have not attained complete sexual maturity, which was not the case in the control animals. The NOAEL was considered to be 5 mg/kg, which is about 0.2-fold of the intended clinical exposure.

Moderate to severe hypopigmentation was observed in a 6-month repeat-dose toxicity study in dogs (XL184-NC-018), at exposure levels below expected human exposure level, leading to discoloured skin and hair, resembling vitiligo in humans. Rat distribution studies have demonstrated that XL184-related radioactivity is retained and accumulated in pigmented ocular tissue. Due to the use of non-pigmented animals in the long-term repeat-dose rat study, similar findings in pigmented rats cannot be excluded. Although cabozantinib appears to accumulate and retain in ocular tissue, the skin and hair depigmentation observed with cabozantinib is most likely related to inhibition of c-KIT, and is not considered a concern for the pigmentation of the eye.

Table 2. Repeat-dose toxicity studies with cabozantinib (XL184).

Study ID	Species/ Sex/Number/Group	Dose/Route	Duration	NOAEL (mg/kg/ day)	Major findings
XL184-Disc-036 Dose range-finding Non-GLP	Rat F/6	1, 3, 10, 30, 100 mg/kg Oral gavage	8 days	<1	≥1: follicular necrosis, submucosal edema and inflammation in stomach ≥3: ALT, AST, LDH, GGT, lipase, amylase↑ ≥10: CK↑ 100: death, histopathologic changes in adrenals, bone marrow, kidney, lungs, lymph nodes, ovaries, stomach
XL184-NC-005 GLP	Rat M+F/10	1, 5, 15 mg/kg Oral gavage	14 days	1	≥5: Bodywght, food cons↓, bonemarrow depletion, necrosis in thymus, spleen, ileum 15: death; hematopoietic, liver, GI, and/or renal toxicity; histopathologic changes in adrenals, lymphoid tissues, GI tract, bone marrow and pancreas
XL184-NC-013 GLP	Rat M+F/20	0.1, 0.3, 1 mg/kg Oral gavage	6 months	0.3	1: death (1M), bodywght (F)↓, ALT↑, chronic progressive nephropathy
XL184-NC-002 Dose range-finding Non-GLP	Dog M/2	500, 2000 mg/kg Oral gavage	500: 4 days 2000: single dose	<500	≥500: Vomitus and abnormal feces; bodywght, food cons↓, histopathologic changes in GI tract, lymphoid tissues, and/or testes

Study ID	Species/ Sex/Number/Group	Dose/Route	Duration	NOAEL (mg/kg/ day)	Major findings
XL184-NC-006 GLP	Dog M+F/2-5	Phase 1: 100, 300, 1000 mg/kg Phase 2: 10, 100 mg/kg Oral gavage	Phase 1: 7, 6, 5 days Phase 2: 14, 5 days resp.	10	100: death (3/3 M and 3/3 F following Dosing D 7); reversible histopathologic changes in bone marrow, lymphoid tissues, GI tract; secondary changes in bone, pancreas, eye, gallbladder, and central nervous system 300: histopathologic changes not reverible; ALT, AST↑ urea nitrogen, creat, PO4↓
XL184-NC-012 GLP	Dog M+F/4	0.2, 1, 5 mg/kg Oral gavage	26 weeks	5	≥0.2: Microscopic findings in ovaries (corpus luteum absent) considered to reflect incomplete sexual maturation in young adult dogs
XL184-NC-018 GLP	Dog M+F/4	30 mg/kg × 10 days→11 non-dosing days→20 mg/kg × 111 days (M) or 161 days (F) Oral gavage	20 mg/kg: 16 weeks (M) 23 weeks (F)	nd	death (2 M, 1 F); body wght, food cons↓; testes and ovary wght↓; microscopic findings in testes (bilateral hypospermatogenesis), ovaries (corpus luteum absent), thymus (lymphoid depletion), mammary gland and uterus (decreased glandular tissue)

Nd = not determined

Genotoxicity

Table 3. Overview of genotoxicity studies in cabozantinib:

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/equivocal
Gene mutations in bacteria 7359-193 Non-GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	10–5000 µg/plate +/- S9	negative
Gene mutations in bacteria XL184-NC-010 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	10–5000 µg/plate +/- S9	negative
Gene mutations in mammalian cells 7359-194 Non-GLP	L5178Y/TK+/- mouse lymphoma cells	50-500 µg/ml +/- S9	negative
Gene mutations in mammalian cells XL184-NC-011 GLP	Human peripheral blood lymphocytes	5-750 µg/ml +/- S9	negative
Chromosomal aberrations in vivo XL184-NC-019 GLP	Mouse, micronuclei in bone marrow	500, 1000, 2000 mg/kg	negative

Carcinogenicity

Carcinogenicity evaluations of XL184 have not been conducted based on the absence of genotoxicity in both in vitro and in vivo bioassays, the lack of preneoplastic lesions in chronic repeat-dose toxicity studies in rats and dogs, the lack of demonstrated carcinogenic potential in the RTKi product class, and the intended treatment population of subjects with advanced, progressive MTC with limited treatment options and a relatively short life expectancy (which is supported by the interim overall survival results from the pivotal study XL184-301), in accordance with ICH S1A and ICH S9.

Reproductive Toxicity

Cabozantinib-related effects on male and female reproductive organs were observed in rats, leading to reduced fertility at ≥1 mg/kg/day for females and ≥2.5 mg/kg/day for males. Paternal toxicity showed from 2.5 mg/kg/day (death, pale ears, thin appearance, missing teeth, extremely white, excessively long, malocclusion, cut or curved upward; hair coat yellow, red or rough in appearance, and fecal changes). Comparable toxicity showed in females also from 2.5 mg/kg, but less severe. Weights of testes, epididymis, prostate and seminal vesicles decreased and reductions occurred in sperm count and concentration from 2.5 mg/kg. No fertile males were present at 2.5 and above. A dose-related prolongation of diestrus showed at 2.5 mg/kg. Although the majority of females had confirmed matings, the male/female fertility index was 0% at 2.5 and 5 mg/kg; there were no pregnancies in either group. Female fertility and embryo/fetal viability were reduced at 1 mg/kg. Effects are below or around the intended human exposure.

In line with these findings, histopathological findings were observed in repeat-dose toxicity studies in dogs (reduced testes weight and hypospermatogenensis at > 1 mg/kg/day; reduced ovary weight at ⩾0.2 mg/kg/day). At present, the reversibility of the effects on male and female fertility is not known. Consequently, the need for advice regarding fertility preservation measures is stated in the SPC section 4.6.

In rats, maternal toxicity showed at 5 mg/kg cabozantinib. Embryo/fetal viability and development were adversely affected at ⩾ 0.6 mg/kg. Based on a treatment-related increase in post-implantation loss at ⩾0.03 mg/kg/day, the NOEL for embryo/fetal viability was determined to be 0.01 mg/kg/day, which is <1% than the human exposure.

In rabbits, the NOAEL for maternal toxicity and embryo-fetal viability and growth was 3 mg/kg. The NOEL for teratology was 1.0 mg/kg, equating to a plasma exposure <0.1-fold of the intended human dose.

Malformations were not observed in the decisive embryo-foetal study in rats dosed up to 0.1 mg/kg/day. However, edema, cleft palate/lip, dermal aplasia and kinked/rudimentary tail were observed in the dose-range study at 0.6 mg/kg/day, without maternal toxicity. In rabbits, cabozantinib-related foetal visceral variations / malformations occurred at 3 mg/kg/day in the decisive study, reflected by small or missing intermediate lobe of lungs, reduced spleens (7 foetuses in one litter), and a significant increase in the foetal incidence of total malformations, albeit at a maternally toxic dose.

Table 4. Overview of reproduction toxicity studies performed with cabozantinib

Study type / Study ID / GLP	Species; Number /group	Route & dose	Dosing period	Major findings	NOAEL / AUC ng.h / ml
Fertility XL184-NC-020 GLP	Rat M+F/22	Oral 1, 2.5, 5 mg/kg	M: 10 weeks (4 weeks prior to mating) F: 2 weeks prior to mating through GD 7	**≥1: (F)** % pre- and post-implantation losses and resorptions ↑ **≥2.5: (M)** body weights, food consumption, reproductive tissue weights, fertility, and sperm counts↓ **(F)** altered estrus cycling; 100% non-pregnant **5: (M)** moribund sacrifice (Day 39)	1 mg/kg (M) AUC: 20700 (M) 19300 (F)
Embryo-fœtal development XL184-NC-021 Non-GLP	Rat F/6	Oral 0.03, 0.1, 0.6, 1, 2.5, 5, 7.5 mg/kg	GD 6-17	**≥0.03:** uterine weights ↓ (primarily due to fetal weights↓) **≥0.6:** external variations (swollen hindpaw, curly tail) and malformations (edema, cleft palate, hare lip, kinked/ rudimentary tail, dermal aplasia); uterine weights ↓ (primarily due to post-implantation loss↑) **≥1:** complete early resorption of all fetuses **≥5:** body weights, food consumption↓ ; unscheduled deaths	ND
Embryo-fœtal development XL184-NC-022 GLP	Rat F/25	Oral 0.01, 0.03, 0.1 mg/kg	GD 6-17	**≥0.03:** post-implantation loss ↑	0.01 mg/kg AUC: 168
Embryo-fœtal development XL184-NC-023 Non-GLP	Rabbit F/6	Oral 0.5, 2.5, 7.5, 15, 30 mg/kg	GD 7-20	**≥2.5:** incidence fetal variations↑ (swollen hind paws) **≥7.5:** unscheduled deaths; body weights, food consumption, uterine weights, fetal viability ↓ (early and total resorptions and post-implantation losses↑); abortions↑	0.5 mg/kg AUC: ND
Embryo-fœtal development XL184-NC-024 GLP	Rabbit F/20	Oral 0.3, 1, 3 mg/kg	GD 7-20	**3:** fetal spleen size↓ (no maternal toxicity or fetal skeletal or external malformations)	1 mg/kg AUC: 984

Juvenile toxicity

Juvenile animals were dosed at PND 21-70. Major, reversible findings following treatment from PND21-35 (cohort 1) were limited to increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), and reduced

bone mineral content and density. Major findings following treatment from PND21-70 (cohort 2) were increased WBC parameters, increased haematopoiesis, tooth abnormalities, reduced bone mineral density and content, liver pigmentation and bile duct hyperplasia. The observed effects on uterus/ovaries and decreased haematopoiesis seen in cohort 1 were not seen in cohort 2, suggesting transient effects, while effects on bone parameters and liver pigmentation were sustained. Findings from the juvenile toxicity study have been included in the SPC section 5.3.

Toxicokinetic data

An overview of the toxicokinetics of XL184 in rat and dog is provided in Table 5. For comparison, human data are also added and the ratio between animal exposure and human exposure is calculated.

Table 5. Toxicokinetics and interspecies comparison of cabozantinib.

Species/ Time/ Study ID	**Daily Dose (mg/kg)**	**Animal AUC (ng.h/ml)**		**Cmax (ng/ml)**		**T ½ (h)**		**A:H exp****
		♂	♀	♂	♀	♂	♀	
Rat 8 days XL184-Disc-036	1	-	24484	-	1408	-	13.1	**0.65**
	3	-	57700	-	3231	-	12.3	**1.5**
	10	-	286332	-	15010	-	21.7	**7.6**
	30	-	640268	-	29925	-	-	**17**
Rat 14 days XL184-NC-005	1 (NOAEL)	10978	-	853	-	9.62	-	**0.29**
	5	52152	-	4690	-	16.0	-	**1.4**
	15	512771	-	26733	-	21.5	-	**14**
Rat * 14 days XL184-NC-014	1 (NOAEL)	6780	-	464	-	10.1	-	**0.18**
	5	36200	-	2650	-	8.04	-	**0.96**
Rat 26 weeks XL184-NC-013	0.1	2632	4753	165	298	-	-	**0.07/0.13**
	0.3 (NOAEL)	7851	14416	523	881	26.1	-	**0.21/0.38**
	1	29736	44086	2590	2740	22.8	-	**0.79/1.2**
Dog 4/1 days XL184-NC-002	500	784626	-	23332	-	25.6	-	**21**
	2000	377233	-	16989	-	17.6	-	**10**
Dog * 5-14 days XL184-NC-006	100	199566	135198	12967	10163	5.06	4.65	**5.3/3.6**
	300	464851	310576	26500	19120	8.34	8.06	**12.3/8.2**
	1000	447389	431916	25134	25120	-	-	**11.8/11.4**
	10 (NOAEL)	8406	11408	824	1400	6.02	6.01	**0.22/0.30**

Species/ Time/ Study ID	Daily Dose (mg/kg)	Animal AUC (ng.h/ml)		Cmax (ng/ml)		T ½ (h)		A:H exp**
		♂	♀	♂	♀	♂	♀	
	100	237419	222059	15650	13500	7.62	9.96	**6.3/5.9**
Dog 26 weeks XL184-NC-012	0.2	285	323	33.8	73.4	4.89	5.09	**0.01/0.01**
	1	2027	2012	317	426	8.53	9.97	**0.05/0.05**
	5 (NOAEL)	7757	6327	706	1008	12.6	8.58	**0.20/0.17**
Dog 16/23 weeks XL184-NC-018	20	18800	24800	2600	2500	6.06	7.65	**0.50/0.66**
Rabbit Gestation days 7-20 XL184-NC-024	1 (NOEL)	-	984	-	86.2	-	8.3	**0.03**
	3	-	4240	-	295	-	7.6	**0.11**
Human	2.9	37850		-		91		**1**

*) Day 1 post-dose values.
**) A:H exp = Animal:Human Exposure Multiple

Interspecies comparison

There are some differences in oral bioavailability of the L-malate salt between the pre-clinical species investigated: ~90% in rats and ~55% in dogs. No absolute bioavailability was determined for humans.

Volume of distribution was comparable across mouse and rat (i.e. ~0.9 and ~0.6 L/kg, respectively) but was significantly lower than in dog and monkey (i.e. ~2.1 and ~2.7 L/kg). Further, plasma clearance was approximately one order of magnitude lower in rat (i.e. ~0.030 – 0.045 L/kg/hr) than in the other pre-clinical species (i.e. 0.23 – 0.64 L/kg/hr). In line with this, plasma half-lives were also comparable between mouse, dog and monkey (i.e. ~3 – 4 hours) and longer in rat (i.e. ~12 – 13 hours). In humans, elimination of XL184 was much slower than in the pre-clinical species. The volume of distribution (Vc/F) was much larger in humans than in the pre-clinical species, i.e. ~5.8 L/kg. The clearance (CL/F) was in the same order of magnitude as in rats (0.07 L/kg/hr), but plasma half-life was much longer with 120 hours.

Plasma protein binding of XL184 was high in all species, including humans.

Metabolism of XL184 is more prominent in humans than in the pre-clinical species. However, no unique human metabolites were found. Furthermore, XL184 is mainly excreted via faeces in both rats and humans but urine is a more important route of excretion in humans than in rats. Further comparison of metabolism and excretion across pre-clinical species and humans is hampered by several facts: 1) *in vivo* metabolism of XL184 in the different species is elucidated at different dosages and dosing regiments; 2) the excretion of XL184 has not been investigated in dog, which is considered as a key animal species for preclinical assessment; 3) the excretion of XL184 in bile has not been

investigated while the presence of entero-hepatic recirculation is assumed in humans; 4) the metabolite profile of the excreta has not been determined.

Local Tolerance

No studies on local tolerance were submitted.

Other toxicity studies

<u>Reproductive and developmental toxicity</u>

<u>Metabolites and impurities</u>

Table 6. Overview of genotoxicity studies in metabolites:

Metabolite / Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**
XL184 n-oxide (M1) Gene mutations in bacteria BMSAmes-927982 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate - S9	negative
parafluoroaniline (p-FA) Gene mutations in bacteria BMSAmesSQ-008953 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	Positive

Table 7. Repeat-dose toxicity study with cabozantinib and impurity.

Study ID	**Species / Sex / Number / Group**	**Dose / Route**	**Duration**	**NOAEL (mg / kg / day)**	**Major findings**
XL184-NC-014 GLP	Rat M+F/10	1, 5 mg/kg Oral gavage	14 days	1	5: Bodywght, food cons↓ glomerular membrane thickening, tubular Degeneration in kidney, corpora lutea necrosis, pituitary and adrenal gland necrosis

Table 8. Overview of genotoxicity studies in impurities

Metabolite / Type of test / study ID / GLP	**Test system**	**Concentrations / Concentration range / Metabolising system**	**Results Positive / negative / equivocal**

Metabolite / Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
XL184-1-1 Gene mutations in bacteria BMSAmes-655335 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	Positive
XL184-1-4 Gene mutations in bacteria BMSAmes908145 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	positive
4-Fluoroaniline Gene mutations in bacteria BMSAmesSQ-008953 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	positive
4-aminophenol Yoshida et al, 1998 Non-GLP	E. coli WP2uvrA/pKM101	500 - 1500 µg/plate - S9	positive
XL184-1-2 Gene mutations in bacteria BMSAmes-908148 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	negative
XL184-2-2 Gene mutations in bacteria BMSAmes-908146 GLP	Salmonella strains TA98, TA100, TA1535 and TA1537 E. coli tester strain WP2 uvrA.	40–5000 µg/plate +/- S9	negative

Phototoxicity

Cabozantinib showed no phototoxicity in the 3T3 NRU-PT test (data not shown).

2.3.5. Ecotoxicity / environmental risk assessment

The Applicant has submitted an ERA based on the EMEA/CHMP/SWP/4447/00 guideline (EMEA, 2006).

The Applicant refined the F_{pen} based on the prevalence of medullary thyroid cancer. This refinement resulted in an F_{pen} of 0.00007 and a PEC_{sw} of 0.0049 µg/L. Since this value is lower than the action limit of 0.01 µg/L, no unacceptable adverse effects to the environment are expected. No further environmental risk assessment is required.

Table 9. Summary of main study results

Substance (INN / Invented Name): cabozantinib
CAS-number (if available): 1140909-48-3

PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	Log K_{ow} = 3.96, no study report provided	Inconclusive
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence)	0.0049	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)			(N)

Based on the refined PECsw, no unacceptable risk for the environment is expected from cabozantinib. However, the determination of the log Kow according to OECD guidelines. (including reports) should be submitted post-authorisation (see Discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodeling, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including RET, the GAS6 receptor (AXL), the stem cell factor receptor (KIT), and Fms-like tyrosine kinase-3 (FLT3).

Cabozantinib exhibited dose-related tumour growth inhibition, tumor regression, and/or inhibited metastasis in a broad range of preclinical tumour models. A clear anti-tumour effect of XL184 is evident from the primary pharmacodynamic studies. XL184 clearly potently inhibited RET in vitro, a RTK that is implicated in MTC, and had an anti-tumour effect in vivo against RET mutated MTC cell lines. Dysregulation of MET signalling has been observed in many tumour types, but thus far not in MTC. So while MET inhibition may, in theory be beneficial for MTC patients, no solid evidence has been provided. In principle inhibition of VEGFR may also add to an anti-tumour effect of XL184 in MTC patients, however data to substantiate this claim are not available. Thus, while inhibition of several signalling pathways may be potential targets for MTC treatment, for only one RTK, RET, a clear association with MTC has been proven. Since XL184 clearly inhibits this RTK, in vitro and has an antitumour effect in vivo against RET mutated MTC cell lines proof of principle for XL184 treatment in MTC patients is considered to be provided.

No pharmacodynamic drug interaction studies were performed. It is agreed that co-medication with products having the same pharmacological targets is unlikely. Therefore the absence of pharmacodynamic drug interaction studies is agreed.

The bioavailability of cabozantinib is moderate to high, and it is highly bound to plasma proteins. There are four major metabolites, of which the 6-desmethyl half-dimer sulphate (M2a) and the monohydroxysulphate (M4) are the most important. In rats Cabozantinib is mainly excreted via faeces. Cabozantinib is an inhibitor, but not a substrate, of P-glycoprotein with an IC50 value of 0.5 µM. No other transporters were investigated. Cabozantinib is not expected to inhibit or induce CYPs in humans at clinically relevant concentrations.

Excretion data should have been provided for dogs as these data are important for the assessment of possible toxicity and interspecies comparison. The Applicant will provide information on the excretion of XL184/radioactivity in dog post-approval. Also, the Applicant is requested to provide metabolite

profiling data of the excreta for rats and dogs. In light of the presumed enterohepatic recirculation, the Applicant is currently performing excretion experiments in bile duct-cannulated and non-cannulated rats and dogs. The evaluation of enterohepatic recirculation evaluation in dogs and rats is included in the RMP. Based on the outcome of these non-clinical studies, the CHMP recommended the applicant to consider drug interaction studies with the antibiotic neomycin, or with drugs that may disrupt the enterohepatic recirculation of cabozantinib, such as cholestagel or cholestyramine.

It is unknown whether cabozantinib is excreted in milk of lactating animals. It is not known whether cabozantinib and/or its metabolites are excreted in human milk. Because of the potential harm to the infant, mothers should discontinue breast-feeding during treatment with cabozantinib, and for at least 4 months after completing therapy (see SmPC section 4.6).

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows: In rat and dog repeat-dose toxicity studies up to 6 months duration, target organs for toxicity were GI tract, bone marrow, lymphoid tissues, kidney, adrenal and reproductive tract tissues. The no observed adverse effect level (NOAEL) for these findings were below human clinical exposure levels at intended therapeutic dose (see SmPC section 5.3).

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. Carcinogenicity studies have not been performed (see SmPC section 5.3). The lack of carcinogenicity studies is considered acceptable in this setting consistent with on ICH guidelines S1A and S9, in view of the absence of genotoxicity in both in vitro and in vivo bioassays, the lack of preneoplastic lesions in chronic repeat-dose toxicity studies in rats and dogs, the lack of demonstrated carcinogenic potential in the RTKi product class, and the intended treatment population of subjects with advanced, progressive medullary thyroid cancer with limited treatment options and a relatively short life expectancy.

Fertility studies in rats have shown reduced male and female fertility. Further, hypospermatogenesis was observed in male dogs at exposure levels below human clinical exposure levels at intended therapeutic dose (see SmPC section 5.3).

There are no data on human fertility. Both men and women should be advised to seek advice and consider fertility preservation before treatment (see SmPC sedction 4.6).

Embryo-foetal development studies were performed in rats and rabbits. In rats, cabozantinib caused postimplantation loss, foetal edema, cleft palate/lip, dermal aplasia and kinked or rudimentary tail. In rabbits, cabozantinib produced foetal soft tissue changes (reduced spleen size, small or missing intermediate lung lobe) and increased foetal incidence of total malformations. NOAEL for embryo-foetal toxicity and teratogenic findings were below human clinical exposure levels at intended therapeutic dose (see SmPC section 5.3). There are no studies in pregnant women using cabozantinib. The potential risk for humans is unknown. Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib (see SmPC sections 4.6).

Women of childbearing potential must be advised to avoid pregnancy while on cabozantinib. Female partners of male patients taking cabozantinib must also avoid pregnancy. Effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least 4 months after completing therapy. Because oral contraceptives might possibly not be

considered as “effective methods of contraception,” they should be used together with another method, such as a barrier method (see SmPC sections 4.6 and 4.5 and Discussion on clinical pharmacology).

Juvenile rats (comparable to a >2 year old pediatric population) administered cabozantinib showed increased WBC parameters, decreased haematopoiesis, pubescent/immature female reproductive system (without delayed vaginal opening), tooth abnormalities, reduced bone mineral content and density, liver pigmentation and bile duct hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Evaluations in juvenile rats (comparable to a <2 year old pediatric population) have not been performed (see SmPC section 5.3).

A pre-and postnatal development study of cabozantinib in rats is planned, and is scheduled to initiate dosing in 3Q13. This is covered in the RMP.

In order to evaluate potential effect in a paediatric population below 2 years of age, a further study with dosing from PND12 is planned, and will be submitted when finalised. This is included in the RMP.

In accordance with ICH S9, evaluation of metabolites is generally not warranted in patients with advanced cancer. However, metabolites M1, M2a (EXEL 1644), M4 and M8 are in much higher concentrations in humans than in the used animal models, especially M2a and M4 (about 39% and 13% of the total amount respectively). M1 and M8 are of low abundance in humans and are not expected to be genotoxic (M1 is not mutagenic in Ames test and M8 has no structural alert). M4 shows little pharmacodynamic activity and is not mutagenic in the Ames test. According to ICH S9 it is not necessary to test metabolites M1, M4 and M8 further for toxicity.

Metabolite EXEL 1644, which is of high abundance in humans, was not tested in animals. This metabolite was negative in the Ames test. In order to address the safety aspects of metabolite EXEL 1644, the applicant will perform a GLP-compliant 2-week toxicity study. This study is included in the RMP.

The applicant qualified the impurity ortho-fluoro cabozantinib in a 2 week rat study. It is not expected that ortho-fluoro cabozantinib will influence the safety of the product.

Potential genotoxic impurities in XL184 drug substance were identified and found positive in the Ames test. The specifications of the genotoxic impurities in the product are slightly higher than the threshold of toxicologic concern (TTC) value of 1.5 µg/day. However, it is agreed that specifications higher than the TTC may be acceptable under certain conditions, e.g. short-term exposure, for treatment of a life-threatening condition, or when life expectancy is less than 5 years (Guideline on the limits of genotox impurities), which is the case.

Based on the refined PECsw, no unacceptable risk for the environment is expected from cabozantinib. However, the CHMP recommended that the applicant should determine the log Kow according to OECD guidelines.

2.3.7. Conclusion on the non-clinical aspects

In general, the non-clinical data submitted were of good quality and meet the requirements to support this application. Remaining uncertainties from the non-clinical data are adequately addressed in the agreed RMP.

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

Table 10. Listing of clinical studies

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Safety, Efficacy	XL184-001	Establish MTD, preliminary efficacy in MTC MTD cohort	Non-randomized, dose escalation	Multiple doses of cabozantinib as powder in bottle and capsule formulations; once daily; oral	85	Patients with solid tumours, including MTC	Until progressive disease or toxicity
PD	XL184-001.CBM.001	Evaluate PD effects in biological samples	Non-randomized, dose escalation	Multiple doses of cabozantinib as powder in bottle and capsule formulations; once daily; oral	85	Patients with solid tumours, including MTC	Until progressive disease or toxicity
BA	XL184-004	Evaluate food effect on cabozantinib dosing	Open, randomized, two- period, two-sequence crossover	Cabozantinib 175 mg; once; oral	56	Healthy subjects	Two single doses separated by a washout period
PK	XL184-006	Drug-drug interaction with rifampicin (CYP3A4 inducer)	Open-label, two-treatment, single-sequence	Cabozantinib 175 mg and rifampicin 600 mg; oral	28	Healthy subjects	Period 1: Single cabozantinib dose Period 2: rifampicin qd Days 1-31; cabozantinib Day 11
PK	XL184-007	Drug-drug interaction with ketoconazole (CYP3A4 inhibitor)	Open-label, two-treatment, single-sequence	Cabozantinib 175 mg and ketoconazole 400 mg; oral	28	Healthy subjects	Period 1: Single cabozantinib dose Period 2: ketoconazole qd Days 1-27; cabozantinib Day 7
PK	XL184-008	Drug-drug interaction with rosiglitazone (CYP2C8)	Open-label, one sequence, cross-over	Cabozantinib 175 mg and rosiglitazone 4 mg; oral	40 (32 PK evaluable)	Patients with DTC, RCC	Rosiglitazone: Days 1 and 22 Cabozantinib: Day 2 onwards, until progressive disease or toxicity
PK	XL184-012	Mass balance	Open-label, single dose	Cabozantinib 175 mg [14C-labeled; 100µCi] solution formulation; oral	8	Healthy subjects	Single dose
BE	XL184-016	Evaluate PK of 2 capsules containing different amounts of 2 cabozantinib crystal forms	Open, randomized, two-period, two-sequence crossover	Cabozantinib 100 mg; once; oral	53	Healthy subjects	Two single doses separated by a washout period
Safety	XL184-201	Safety and preliminary efficacy	Non-randomized	Cabozantinib 175 mg capsules; once daily; oral	46	Patients with GBM	Until progressive disease or toxicity
Safety, Efficacy	XL184-301	Evaluate efficacy of cabozantinib vs. placebo	Randomized, controlled	Cabozantinib 175 mg or placebo capsules; once daily; oral	330	Patients with progressive MTC	Until progressive disease or toxicity
PK	XL184-301 PopPK	Evaluate PK	Randomized controlled	Cabozantinib 175 mg or placebo capsules; once daily; oral	330	Patients with progressive MTC	Until progressive disease or toxicity

PK-PD	XL184-301.ER.001	Evaluate exposure-response	Randomized controlled	Cabozantinib 175 mg or placebo capsules; once daily; oral	330	Patients with progressive MTC	Until progressive disease or toxicity
PD	XL184-301.CBM.001	Evaluate BM	Randomized controlled	Cabozantinib 175 mg or placebo capsules; once daily; oral	330	Patients with progressive MTC	Until progressive disease or toxicity

2.4.2. Pharmacokinetics

Absorption

Following a single oral dose, cabozantinib was absorbed with maximum plasma concentrations of cabozantinib achieved at median time of 2 to 5 hours post-dose across studies in healthy volunteers and cancer patients. Multiple peaks in the plasma concentration–time profile following a single oral dose suggest that cabozantinib is enterohepatically recirculated.

The absolute bioavailability of cabozantinib has not been determined. Based on the provided mass balance study, however, at least 27% of the administered cabozantinib is renally excreted, and thus at least this fraction of the administered dose was absorbed.

In current practice, the capsules contain mainly the N2 crystal form of cabozantinib. Based on the outcome of the provided bioequivalence study XL184-016, no relevant difference in bioavailability is to be expected in case different crystal forms, i.e., N1 or N2 are present.

A high-fat meal moderately increased cabozantinib C_{max} and AUC values by 41% and 57%, respectively, relative to fasted conditions in healthy volunteers. Based on this food-effect study, the Applicant decided to administer cabozantinib under fasted conditions, i.e., the patients are instructed not to eat for at least 2 hours before and 1 hour after taking cabozantinib. This posology was applied in all clinical studies.

Distribution

Cabozantinib was highly plasma protein bound at all concentration levels tested; the percentage bound was >99.9% for both the 0.2 and 1.0 µM levels, and 99.7% at 10 µM level. Cabozantinib does not extensively bind to erythrocytes. The popPK estimated volume of the central compartment (Vc/F) was approximately 350 l.

Metabolism

The following metabolites of cabozantinib were characterised in plasma: XL184-N-oxide, XL184-monohydroxysulphate, XL184 half dimer, half-dimer methyl ester, 6-demethyl half-dimer sulphate, 7-demethyl half-dimer sulphate, demethyl XL184 glucuronide A and B. The 6-demethyl half-dimer sulfate metabolite is the main circulating metabolite, and more abundant than cabozantinib in plasma. Based on LC-MS/MS analysis, mean exposure ratios for cabozantinib and metabolites XL184-half-dimer, XL184-N-oxide, XL184-sulfate and 6-demethyl half-dimer sulfate relative to total exposure (AUC0-t (each analyte)/AUC0-t (parent + 4 metabolites)) were 32.4%, 3.09%, 4.90%, 13.8% and 45.9%, respectively. The t1/2 of the major 6-demethyl half-dimer sulfate metabolite could not be determined, but is much longer than that of cabozantinib and the other characterised metabolites. In vitro data indicate that the formation of the XL184-N-oxide metabolite is dependent on CYP3A4, and to a lesser extent on CYP2C9. Formation of a number of other metabolites seems to be dependent on CYP3A4 as well, although only a limited number of CYPs were tested. It appears that non-conjugated

metabolites are present only at low levels, and are less active than cabozantinib (see Discussion on Clinical pharmacology).

Elimination

The plasma terminal half-life of cabozantinib in single dose studies was approximately 120 hours. Cabozantinib is eliminated both via the hepatic (at least 54% of the administered dose) and renal route (at least 27%). Cabozantinib is not directly excreted in urine, but is present to some extent in faeces. Both in urine and faeces, multiple metabolites are detected, with dequinolinyl XL184 glucuronide, dequinolinyl XL184 sulfate, and XL184 half dimer being the main metabolites in urine, while cabozantinib, M11 (minor metabolite, not identified), demethyl XL184, and XL184 oxidation B were the main metabolites in faeces.

Dose proportionality and time dependencies

Dose proportional cabozantinib pharmacokinetics was demonstrated for the powder-in-bottle suspension formulation up to a dose of approximately 1000 mg. For the capsule formulation dose-proportionality was assessed less extensively. In cancer patients, comparable –and thus not dose-proportional- exposures were observed for a 175 and 250 mg cabozantinib malate capsule dose, both after a single dose and under steady-state conditions. This may point at limited absorption at this dose, potentially caused by limited solubility of cabozantinib. At lower doses in healthy volunteers, the dose-normalised exposure upon administration of 100 mg or 175 mg cabozantinib malate (78 mg and 138 mg cabozantinib freebase, respectively) appears comparable, indicating dose-proportional behaviour between these two doses.

Accumulation of cabozantinib upon multiple dosing (AUC and C_{max} increase 4.6 and 3.9-fold, respectively) is reasonably in line with expected, based on a $t_{1/2}$ of approximately 120 hours. Steady state appears to be reached after 15 days of OD dosing. No major differences are apparent in cabozantinib PK between healthy volunteers and cancer patients, with C_{max}, AUC and t_{max}, as well as interindividual variability being comparable.

Special populations

Renal impairment.

Cabozantinib pharmacokinetics has not been investigated in patients with renal impairment (see Discussion on clinical pharmacology).

Hepatic impairment.

The PK of cabozantinib in hepatically impaired subjects is being evaluated in an ongoing dedicated study (see Discussion on clinical pharmacology).

Gender, weight, race and age.

Based on population PK studies there appears to be a difference in exposure between males and females, which is not expected to be clinically relevant. In the population PK analysis, there was no clear relationship between cabozantinib clearance and weight in the 40-135 kg range.

No data are available on the effect of race on cabozantinib pharmacokinetics.

The population PK analysis indicated that age did not affect cabozantinib PK to a clinically relevant extent. Cabozantinib has not yet been investigated in the paediatric population. The lack of data in the population <18 years is indicated in the SPC.

Pharmacokinetic interaction studies

Effect other drugs on cabozantinib pharmacokinetics.

Cabozantinib is a substrate for CYP3A4 and to a lesser extent CYP2C9.

Administration of the strong CYP3A4 inhibitor ketoconazole (400 mg daily for 27 days) to healthy volunteers decreased cabozantinib clearance (by 29%) and increased single-dose plasma cabozantinib exposure (AUC) by 38%. Administration of the strong CYP3A4 inducer rifampicin (600 mg daily for 31 days) to healthy volunteers increased cabozantinib clearance (4.3-fold) and decreased single-dose plasma cabozantinib exposure (AUC) by 77% (see Discussion on clinical pharmacology).

The solubility of cabozantinib is pH dependent, with very low solubility observed at a pH >3. Therefore, absorption of cabozantinib may be reduced in patients taking gastric pH modifying agents like proton pump inhibitors of H2 antagonists (see Discussion on clinical pharmacology).

Effect cabozantinib on PK of other drugs.

Based on the *in vitro* inhibition assays, cabozantinib is not expected to inhibit CYPs *in vivo* to a significant extent. Cabozantinib did not significantly inhibit CYP2C8 *in vivo* in a rosiglitazone drug-drug interaction study.

With respect to induction by cabozantinib, no *in vivo* induction of CYP1A1, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP3A4 is suggested by *in vitro* studies.

Cabozantinib was an inhibitor (IC50 = 7.0 µM), but not a substrate, of P-glycoprotein (P-gp) transport activities in a bi-directional assay system using MDCK-MDR1 cells. Therefore, cabozantinib may have the potential to increase plasma concentrations of co-administered substrates of P-gp. Subjects should be cautioned regarding taking a P-gp substrate (e.g., fexofenadine, aliskiren, ambrisentan, dabigatran etexilate, digoxin, colchicine, maraviroc, posaconazole, ranolazine, saxagliptin, sitagliptin, talinolol, tolvaptan) while receiving cabozantinib (see SmPC sections 4.4 and 4.5).

Cabozantinib has not been evaluated for possible interactions (as inhibitor) with other transporter pathways than P-gp (see Discussion on clinical pharmacology).

Pharmacokinetics using human biomaterials

No pharmacokinetic studies using human biomaterials were submitted.

2.4.3. Pharmacodynamics

Mechanism of action

Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, and metastatic progression of cancer. Cabozantinib was evaluated in non-clinical studies for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF

(vascular endothelial growth factor) receptors, as well as other tyrosine kinases including RET (glial cell derived neurotrophic factor receptor rearranged during transfection), AXL (GAS6 receptor), KIT (stem cell factor receptor), and FLT3 (Fms-like tyrosine kinase-3).

Primary pharmacology

Plasma markers of angiogenic pathways have been evaluated in previous clinical studies of anti-VEGFR2 tyrosine kinase inhibitors, e.g. for sunitinib. The common finding from trials of small molecule anti-VEGFR2 agents is an increase in the circulating levels of *VEGF* and *PlGF*, and a decrease in the level of soluble VEGFR2 (*sVEGFR2*) upon treatment. Therefore, in the Phase 1 dose finding Study XL184-001, these three plasma markers were investigated.

In addition to these three VEGFR2 pathway biomarkers, two additional plasma proteins were assessed on an exploratory basis in Study XL184-001. Soluble MET (*sMET*) was chosen due to the possible effects of MET or VEGFR2 inhibition on regulation of the MET receptor, and erythropoietin (*EPO*) was evaluated, as levels of EPO have been shown increase as a consequence of VEGF pathway inhibition in preclinical models ascribed to an upregulation of hepatic erythropoietin expression.

In the pivotal phase 3 study of cabozantinib XL184-301, changes in soluble KIT receptor (sKIT) were evaluated as a biomarker of KIT pathway inhibition as well.

In Study XL184-001, the change in plasma levels for VEGF, sVEGFR2, PlGF, EPO, and sMET were monitored. Three of the markers (sVEGFR2, PlGF, EPO) demonstrated statistically significant changes upon treatment when Day 29 pre-dose levels (175 mg daily cohort only) when compared to pre-treatment levels (Table 11).

Table 11. Summary of change in plasma biomarkers between day 1 and day 29 after O.D. treatment with 175 mg cabozantinib as capsule formulation (Study XL184-001)

Assay	Time Points	N	Relative Change (mean, SD)	P Value (2 sided t-test)	Significant ($p < 0.05$)
VEGF	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	3.660, 2.985	0.0900	no
PlGF	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	3.623, 2.578	< 0.0001	yes
EPO	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	2.059, 1.244	0.0007	yes
sVEGFR2	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	0.7115, 0.3180	< 0.0001	yes
sMET	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	1.126, 0.3235	0.0619	no
OPN	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	1.410, 1.838	0.1072	no
HGF	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	1.116, 0.5638	0.1799	no
ANG2	Day 29 Pre-dose vs. Day 1 Pre-dose	30 pairs	0.8611, 0.5004	0.1237	no

Relationship between plasma concentration and effect

In Study XL184-001, to understand whether there is a concentration dependency in the exposure/response relationship for XL184 plasma exposure and the biomarkers, the plasma levels for VEGF, sVEGFR2, PlGF, EPO, and sMET were plotted against the concurrent plasma concentration, the calculated plasma C_{max}, and the average plasma concentration (C_{ave}) of XL184. No statistically significant relationship exists between the C_{max} values of XL184 and the plasma biomarker concentrations (data not shown). Use of C_{ave} instead of XL184 concentrations led to a weaker relationship between exposure and response; only PlGF and sVEGFR2 maintained statistical significance. While there was clear evidence for a concentration dependence of the effect of XL184 on the four plasma biomarkers described above, the slopes of the effect curves were relatively flat, indicating that this pharmacodynamic effect is not highly dependent upon concurrent XL184 concentration and that the effect is measurable over a broad range of concentrations.

Genetic differences in PD response

RET mutations were investigated in Study XL184-301. DNA samples derived from blood and tumour tissue were analysed for alterations in the sequence of the gene encoding RET; subjects with a documented RET mutation were not required to provide a tumour sample for analysis. Genomic DNA was isolated from formalin-fixed paraffin-embedded biopsies. If necessary, tumour and adjacent normal tissue were separated by manual microdissection guided by a hematoxylin- and eosin-stained serial section. DNA extraction from blood was performed using the QIAamp DNA mini kit (Qiagen). Genomic DNA was amplified by polymerase chain reaction (PCR) and sequenced using the Sanger

method in most cases. Samples with low percentage tumour cell content were evaluated with a highly parallel sequencing method (454 Life Sciences, Branford, CT) to increase sensitivity to approximately 5% mutant allele burden.

Of the 330 subjects enrolled in the study, at least partial RET sequence data from one or both sample types was obtained for 319 subjects. For blood DNA samples, RET exons 5, 8, 10, 11, and 13-16 (which cover the vast majority of the characterized RET mutations) were analysed at a minimum. For tumour DNA samples, RET mutational hotspot exons 11 and 16 were analysed initially, with additional exons analysed subsequently if no mutations were identified in exons 11 and 16. For a sample to be considered negative for RET mutation, the complete DNA sequence for exons 10, 11, and 13-16 must have been obtained, and all RET sequence analysed must have been clearly free of alteration, with the exception of the single nucleotide polymorphisms (SNPs) G691S, L56M, or R982C. Blood or tumour samples that showed evidence for a RET sequence alteration were considered RET mutation positive if the identified mutation is listed as related to MTC or MEN 2 syndromes in the American Thyroid Association Medullary Thyroid Cancer Guideline publication. Note that RET sequence alterations not described in this publication were classified in the 'unknown' category, even though some of these are likely to be functional mutations. Also described as 'unknown' was any sample lacking sufficient sequence coverage of RET and without an identified qualifying RET mutation. In addition, a subject is classified as having sporadic MTC if his or her blood or tumour DNA sample qualified as RET mutation negative as described in Table . RET mutation status, subjects with the common RET M918T mutation, and MTC disease type (sporadic or hereditary) were evaluated in PFS and response rate subgroup analysis. Criteria used to define MTC disease type, and RET and RET M918T mutation status are listed in Table 12.

Table 12. RET genotyping subgroup definitions (Study XL184-301)

Genotyping Category	Definition
RET Mutation Status positive	*RET* mutation (as defined in Kloos et al. 2009) identified in blood or tumor DNA sample OR as documented by pathology report from a previous analysis
RET Mutation Status negative	DNA sequence available from exons 10-11, 13-16 of tumor sample (at a minimum) with no *RET* sequence alterations identified from any analyzed *RET* exon, aside from SNPs G691S, L56M, or R982C.
RET Mutation Status unknown	Either insufficient DNA sequence information to assign *RET* mutation negative status and no *RET* mutation is identified, OR subject harbors a *RET* alteration of unknown significance.
MTC Disease Type hereditary	*RET* mutation (as defined in Kloos et al. 2009) identified in blood DNA sample OR as documented by pathology report from a previous analysis
MTC Disease Type sporadic	DNA sequence available from exons 10-11, 13-16 of either tumor or blood sample (at a minimum) showing no *RET* sequence alterations identified from any analyzed *RET* exon, aside from SNPs G691S, L56M, or R982C.
MTC Disease Type unknown	Insufficient DNA sequence information from blood sample to assign *RET* mutation status and tumor sample can not be classified as *RET* mutation negative
RET M918T Mutation Status positive	*RET* M918T mutation identified in blood or tumor DNA sample OR as documented by pathology report from a previous analysis
RET M918T Mutation Status negative	DNA sequence available from exon 16 of the tumor sample with no evidence of *RET* M918T
RET M918T Mutation Status unknown	Subject lacks *RET* M918T mutation in the blood sample and lacks *RET* exon 16 data from the tumor sample

Overall, 48.2% of subjects showed evidence for a functional RET mutation in blood and/or tumour samples, while 12.4% are considered negative for RET mutation. An additional 39.4% are considered to be of unknown RET mutation status, due to missing sequence data or the presence of a RET mutation of unknown significance.

RET M918T, an activating mutation found in exon 16, is associated with the MEN 2B syndrome, development of MTC, and poor prognosis. This mutation was detected in 54.9% of subjects for whom the exon 16 sequence was assessable (118 of 215 subjects). M918T was the predominant mutation detected in XL184-301 subjects overall; 74.2% of subjects with confirmed RET mutations harbor M918T (118 of 159 subjects with mutations). Only a minority of subjects had evidence for hereditary disease, with 20 subjects demonstrating the presence of a functional RET mutation in their blood DNA sample.

Along with these typical MEN-associated mutations, three unusual germline RET alterations were also identified. RET I852M was detected in subject 1314-3007; this RET variant is thought to be weakly transforming (Machens et al. 2011) and may have cooperated with the somatic M918T mutation identified in the tumour of this subject. RET M1064T was identified in the blood DNA sample of subject 1418-3005. This mutation has been associated with Hirschsprung's disease, but its effect on RET function is unclear (Pelet et al. 1998). Subject 1418-3005 also had an M918T mutation in the tumour

sample, along with evidence of loss of the germline M1064 mutation in the tumour tissue. Finally, a novel sequence alteration was found in subject 4905-3001 (RET C478Y). This alteration is located in the fourth cadherin-like domain in the extracellular region of the receptor, but its significance is not known.

Two subjects showed discrepancy between their tumour and blood genotyping results (based on presence or absence of the G691S SNP). Accordingly they have been classified as 'unknown' for RET mutation state.

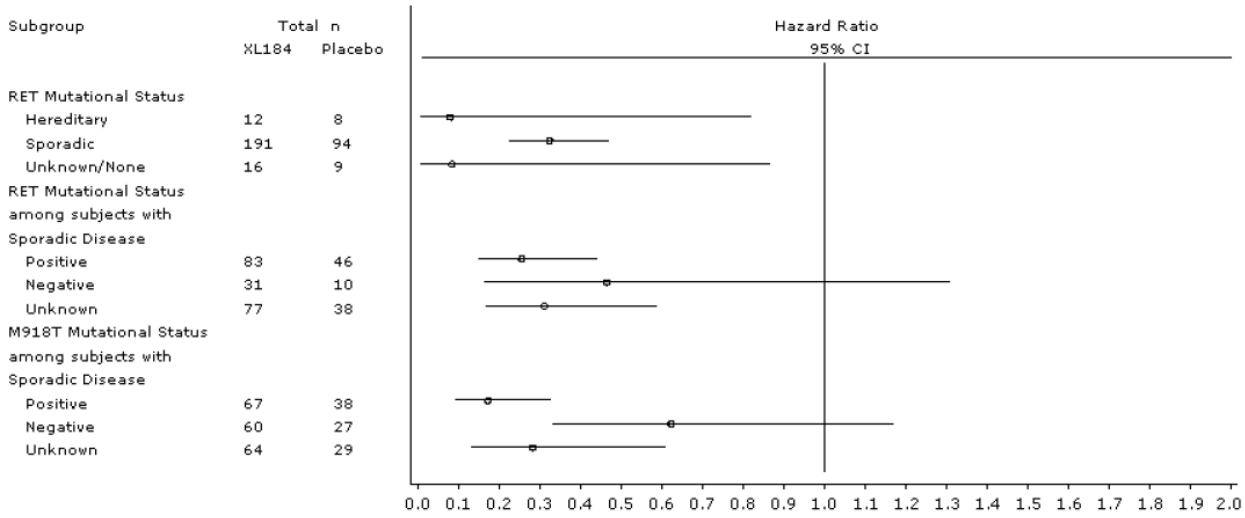
Table 13. Summary of RET Genotyping Results (Study XL184-301)

	Total, N=330 n (%)	XL184, N=219 n (%)	Placebo, N=111 n (%)
RET Mutation Status[a]			
RET Mutation Positive	159 (48.2)	101 (46.1)	58 (52.3)
RET Mutation Negative	41 (12.4)	31 (14.2)	10 (9.0)
RET Mutation Unknown	130 (39.4)	87 (39.7)	43 (38.7)
MTC Disease Type[b]			
Hereditary	20 (6.1)	12 (5.5)	8 (7.2)
Sporadic	285 (86.4)	191 (87.2)	94 (84.7)
Unknown	25 (7.6)	16 (7.3)	9 (8.1)
RET M918T Mutation Status[c]			
M918T Mutation Positive	118 (35.8)	75 (34.2)	43 (38.7)
M918T Mutation Negative	97 (29.4)	67 (30.6)	30 (27.0)
M918T Mutation Unknown	115 (34.8)	77 (35.2)	38 (34.2)

a *RET* Mutation Positive: evidence of functional *RET* mutation in either blood or tumor sample. *RET* Mutation Negative: adequate sequence of tumor sample without evidence of *RET* mutation.
b Hereditary: evidence of functional *RET* mutation in blood DNA sample. Sporadic: adequate sequence of blood or tumor sample with no evidence of *RET* mutation.
c M918T Mutation Positive: presence of a *RET* M918T mutation in either blood or tumor DNA sample. M918T Mutation Negative: adequate *RET* exon 16 sequence data from tumor DNA sample with no evidence of M918T mutation.

The effect of the RET mutational state on PFS and response rate is summarised in Figure 1. Overall, activity from XL184 treatment was observed for all three RET mutational subgroups; hazard ratios favouring the XL184-treatment group were 0.24 for the RET mutation-positive subgroup, 0.47 for the RET mutation-negative subgroup, and 0.30 for the RET mutation-unknown subgroup for PFS analysis.

Figure 1. Forest plot of RET mutation subgroup analyses for PFS (IRC-determined, ITT population) (Study XL184-301)



ITT=intent-to-treat; PFS=progression-free survival
Note: HR and 95% CI are unadjusted estimates from Cox Proportional-Hazards regression model with treatment group as the only effect. HR <1 indicates survival in favour of cabozantinib.

Further genetic analysis showed that a small proportion of patients harboured somatic tumour mutations in *HRAS*, *KRAS*, or *NRAS*. These patients (n=16) showed significant prolongation of PFS (HR of 0.15) and an objective response rate of 31%. *RET* mutation negative patients with no evidence of RAS mutation (n=33) showed a decreased PFS benefit on cabozantinib (HR of 0.87) and a lower response rate of 18% compared to other mutational subgroups.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 2 to 5 hours post-dose. Repeat daily dosing of cabozantinib at 140 mg for 19 days resulted in an approximately a 4- to 5-fold mean cabozantinib accumulation (based on AUC) compared to a single dose administration; steady state is achieved by approximately Day 15. A high-fat meal moderately increased Cmax and AUC values (41% and 57%, respectively) relative to fasted conditions in healthy volunteers administered a single 140 mg oral cabozantinib dose. There is no information on the precise food-effect when taken 1 hour after administration of cabozantinib (see SmPC section 5.2). Based on the population-pharmacokinetic (PK) model, the volume of distribution (V/F) is approximately 349 L (SE: ± 2.73%).

Cabozantinib is highly protein bound in vitro in human plasma (≥ 99.7%). Preliminary protein binding data obtained from the ongoing hepatic impairment study were provided, with albumin levels ranging from 2.7-4.3 g/dl. Based on the data provided, no effect of albumin level on plasma protein binding of cabozantinib was apparent down to albumin levels of 2.7 g/dl. This analysis may be supplemented later on upon completion of the hepatic impairment study, potentially extending the range of albumin levels investigated. This issue is covered in the RMP.

Cabozantinib was metabolized in vivo. Four metabolites were present in plasma at exposures (AUC) greater than 10% of parent: XL184-N-oxide, XL184 amide cleavage product, XL184 monohydroxy sulfate, and 6-desmethyl amide cleavage product sulfate. Two non-conjugated metabolites (XL184-N-oxide and XL184 amide cleavage product), which possess <1% of the on-target kinase inhibition potency of parent cabozantinib, each represent <10% of total drug-related plasma exposure.

Cabozantinib is a substrate for CYP3A4 metabolism in vitro, as a neutralizing antibody to CYP3A4 inhibited formation of metabolite XL184 N-oxide by >80% in a NADPH-catalyzed human liver microsomal (HLM) incubation; in contrast, neutralizing antibodies to CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP2E1 had no effect on cabozantinib metabolite formation. A neutralizing antibody to CYP2C9 showed a minimal effect on cabozantinib metabolite formation (i.e., a <20% reduction).

The plasma terminal half-life of cabozantinib in single dose studies in healthy volunteers is approximately 120 hours. Mean clearance (CL/F) at steady-state in cancer patients was estimated to be 4.4 L/hr in a population PK analysis. Within a 48-day collection period after a single dose of 14C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

Currently, the consequences of renal impairment have been investigated in the population PK study only. This study suggests no effect of mild renal impairment. However, the number and range of CrCl values in the moderate renally patient population is limited, and these data cannot be used to predict cabozantinib PK in this patient population. Cabozantinib should be used with caution in patients with renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment since there is limited data in patients with severe renal impairment, and safety and efficacy have not been established (see SmPC sections 4.2 and 5.2). A dedicated renal impairment study has been initiated and is included in the RMP.

Cabozantinib is not recommended for use in patients with hepatic impairment, since there are limited data in patients with hepatic impairment, and safety and efficacy have not been established (see SmPC sections 4.2 and 5.2). A hepatic impairment study has been initiated and is included in the RMP.

There is little experience with cabozantinib in non-White patients (see SmPC sections 4.2 and 5.2).

No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended. However, a trend in increased rate of SAEs has been observed in subjects aged 75 years and older (see SmPC section 4.2).

Cabozantinib has not yet been investigated in the paediatric population. The lack of data in the population <18 years is indicated in the SmPC (see section 4.2).

Cabozantinib is a substrate for CYP3A4 and to a lesser extent CYP2C9. Co-administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution. Chronic co-administration of strong CYP3A4 inducers (e.g., dexamethasone, phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John's Wort [*Hypericum perforatum*]) with cabozantinib should be avoided. Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered (see SmPC sections 4.2, 4.4 and 4.5).

Non-conjugated metabolites are present only at relatively low (total as well as unbound) levels, and are less active than cabozantinib. Low activity of the relatively abundant XL184 monohydroxysulphate and 6 demethyl half-dimer sulfate metabolite was observed. Therefore, cabozantinib parent is indicated to be pivotal for its cabozantinib's PD activity.

Considering the limited importance of a number of metabolites (<10% of parent cabozantinib) further data regarding into identification of UGT pathways (leading to M3 and M8) and carboxyamidases (leading to M7) are not considered necessary. However, considering the importance of the 6-demethyl half-dimer sulfate (M2a) and XL184 monohydroxy sulfate (M9), the applicant was recommended to perform further *in vitro* experiments on the identification of the sulphotransferases responsible for formation of 6-demethyl half-dimer sulfate (M2a) and XL184 monohydroxy sulfate (M9) metabolites.

The effect of proton pump inhibitors on the gastrointestinal absorption of cabozantinib has not been determined. Cabozantinib demonstrates pH dependent solubility; therefore the co-administration of cabozantinib with proton pump inhibitors may reduce a patient's exposure to cabozantinib. The concomitant use with this therapeutic class is therefore not recommended (see SmPC section 4.4). A clinical pharmacology study is currently ongoing to investigate the potential effect of gastric pH affecting drugs (esomeprazole and famotidine) on cabozantinib PK and is included in the RMP.

Cabozantinib has not been evaluated for possible interactions (as substrate) with other transporter pathways than P-gp. Therefore, studies to characterise whether cabozantinib may function as a substrate and/or inhibitor for a panel of individual drug transporters (ie, P-gp, BCRP, BSEP, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, MATE1 and MATE2k) will be conducted and are included in the RMP.

Cabozantinib is an inhibitor of P-gp *in vitro*. A warning against combination of cabozantinib and P-gp substrates has been included in the SmPC (see sections 4.4 and 4.5). At present, the outcome of different *in vitro* P-gp inhibition studies are not in agreement, precluding taking a decision on the need of an *in vivo* study. The Applicant will therefore conduct a follow-up experiment in Caco-2 cells. The need for conducting an *in vivo* P-gp inhibition study will be based on the outcome of that Caco-2 study. This issue is covered in the RMP.

The effect of cabozantinib on the pharmacokinetics of contraceptive steroids has not been investigated. As unchanged contraceptive effect may not be guaranteed, an additional contraceptive method, such as a barrier method, is recommended (see SmPC section 4.5).

Pharmacodynamics

Though cabozantinib is known to inhibit multiple RTKs involved in tumour growth and angiogenesis and metastatic progression of cancer, the precise mechanism of action of cabozantinib is not known. In line with the in vitro data regarding inhibition of multiple RTKs, certain pathways indeed appeared to be affected in vivo upon treatment with 175 mg cabozantinib (S)-malate (138 mg cabozantinib freebase), as shown by changes in biomarkers related to inhibition of VEGF, MET and KIT. Overall, the pattern of plasma marker modulation measured after cabozantinib exposure, with a significant increase in the circulating levels of VEGF and PlGF, and significant decreases in soluble forms of cabozantinib target receptors sVEGFR2 and sKIT after 29 days of treatment, is consistent with results reported for other inhibitors of the VEGFR2 signalling pathway, such as sunitinib and bevacizumab. Exposure to cabozantinib led to inhibition of the VEGFR2 and KIT receptors and downstream signalling pathways. The exposure-dependency of the VEGF, PlGF, VEGFR2 and KIT biomarkers to concurrent

cabozantinib concentration was statistically significant, though modest. Therefore, a target concentration for optimal PD effects cannot be derived from this analysis.

2.4.5. Conclusions on clinical pharmacology

In general, the Applicant has sufficiently described the clinical pharmacology of cabozantinib.

2.5. Clinical efficacy

The clinical development plan for this submission of cabozantinib (Cometriq™, XL184) 175 mg OD in patients with progressive, unresectable locally advanced or metastatic medullary thyroid cancer, is based on one pivotal Phase III XL184-301 study.

The results of the expansion cohort of the phase I XL184-001 study enrolling 25 patients with MTC were submitted as supportive information.

Table 14. Clinical development program of cabozantinib in MTC

			Number of patients		
Study	**Phase**	**Dosages**	**Cabozantinib**	**Control**	**Endpoints**
XL184-301	III	175 mg QD	219	111	**1°: PFS (IRC)** **2°: OS, ORR, DSR, PRO (MDASI THY), PK, Safety**
XL184-001 (expansion cohort)	I	175 mg QD	25 +12*	-	**1°: Safety (MTD, DLT), PK** **2°: PFS, ORR**
Total			256	111	

** Patients with MTC enrolled in the escalation phase of the study.*

2.5.1. Dose response study

The proposed cabozantinib dosing regimen of 140 mg orally once-daily (corresponding to about 177 mg L-malate salt) in patients with MTC has been selected on the results of the phase I dose escalation XL184-001 study.

Study XL184-001

In the phase I XL184-001 dose escalation trial conducted in patients with advanced solid tumors (N=85), with one expansion cohort (n=37) including 25 patients with MTC, cabozantinib was administered at doses ranging from 0.08 to 11.52 mg/kg on an intermittent 5 & 9 schedule using a powder-in-bottle (PIB) formulation, at 175 and 265 mg on a once-daily schedule using a PIB formulation, and at 175 and 250 mg on a once-daily schedule using a capsule formulation (see also Clinical Efficacy, Supportive studies).

The study used a conventional “3+3” design for dose escalation to determine the MTD. The maximum tolerated dose (MTD) of cabozantinib based on the first 28 days of continuous dosing was 175 mg (capsules) once daily. Dose-limiting toxicities included elevated aminotransferases, elevated lipase, mucosal inflammation, and palmar-plantar erythrodysesthesia (PPE).

In the dose-expansion cohort, Grade 3 or 4 frequently (⩾ 10% incidence) reported AEs were lipase increased, PPE, fatigue, weight decreased, blood amylase increased, diarrhea, abdominal pain, and pneumonia. Other than abdominal pain and pneumonia, the majority being judged by the investigator as drug-related. Of note, 31.4% of patients (n=11) had an AE leading to discontinuation of study treatment.

Study XL184-201

In the phase II XL184-201 study conducted in patients with glioblastoma multiforme, patients were treated with 175 mg OD cabozantinib dose. However, after enrollment of 46 patients the protocol was amended to explore efficacy and safety of a second cohort of patients receiving cabozantinib at 125 mg dose, due to the high rate of grade 3 and 4 adverse events (84.8%), serious adverse events (52%, of which 54% were considered potentially drug-related) and adverse events requiring dose interruption and/or reductions (84.8%). The scarce tolerability of cabozantinib was considered related to the patient population of the study XL184-201, consisting of heavily pre-treated patients with glioblastoma multiforme.

Based on these data, the proposed dose for further development in phase II and III studies as single agent given orally in patients with MTC is 175 mg OD (capsule formulation, as L-malate salt weight; 138 mg freebase equivalent weight). The proposed cabozantinib dose for registration is 140 mg freebase equivalent weight.

2.5.2. Main study

Study XL184-301

An International, randomized, double-blinded, Phase 3 Efficacy study of XL184 versus Placebo in Subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer.

Methods

Study Participants

Inclusion criteria

Patients had to fulfil all of the following criteria for inclusion in the study:

- Had a histologically confirmed diagnosis of MTC that was unresectable, locally advanced, or metastatic, and disease that was measurable or nonmeasurable per mRECIST.
- Was at least 18 years old.
- Had an ECOG performance status ≤ 2.
- Had documented PD on computerized tomography (CT), magnetic resonance imaging (MRI), bone scan, or X-ray using mRECIST at screening compared with a previous image done within 14 months of screening. Prior to Protocol Amendment 2, PD was determined by a radiologist at the IRC using these criteria. Following approval of Protocol Amendment 2, PD was determined by the investigator using these criteria. Modification of the RECIST consisted of further clarifications provided by the Independent Radiology Review Committee that further clarified the rules of the original RECIST 1.0.

- Had recovered to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v3.0 Grade ≤1 from clinically significant AEs due to antineoplastic agents, investigational drugs, or other medications that were administered prior to randomization.
- Had organ and marrow function as follows: absolute neutrophil count ≥1500/mm3, platelets ≥100,000/mm3, hemoglobin ≥9 g/dL, bilirubin ≤1.5 times the upper limit of normal (did not apply to subjects with Gilbert's syndrome), serum creatinine ≤1.5 mg/dL, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 times the upper limit of normal.
- Sexually active subjects must have agreed to use medically accepted methods of contraception during the course of the study and for 3 months following discontinuation of study treatments (excluding women who were not of childbearing potential and men who had been sterilized).
- Had no other diagnosis of malignancy (unless nonmelanoma skin cancer, carcinoma in situ of the cervix, or a malignancy diagnosed ≥2 years previously) and had no evidence of malignancy (unless nonmelanoma skin cancer or carcinoma in situ of the cervix).
- Female subjects of childbearing potential must have had a negative pregnancy test at screening. Females of childbearing potential were defined as sexually mature women without prior hysterectomy or who had any evidence of menses in the past 12 months. However, women who had been amenorrheic for at least 12 consecutive months were still considered to be of childbearing potential if the amenorrhea was possibly due to prior chemotherapy, antiestrogens, or ovarian suppression.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

- Received prior systemic anti-tumor therapy (eg, chemotherapy, biologic modifiers, or antiangiogenic therapy) within 4 weeks of randomization (6 weeks for nitrosoureas or mitomycin C).
- Received radiation to ≥25% of bone marrow.
- Received treatment with other investigational agents within 4 weeks of randomization.
- Received treatment with XL184.
- Had brain metastases or spinal cord compression, unless completed radiation therapy ≥4 weeks prior to randomization and stable without steroid and without anticonvulsant treatment for ≥10 days.
- Had a history of clinically significant hematemesis or a recent history of hemoptysis of >2.5 mL of red blood or other signs indicative of pulmonary hemorrhage or evidence of endobronchial lesion(s).
- Had a urine protein/creatinine ratio of ≥1 (reported in grams of protein divided by grams of creatinine).
- Had serious intercurrent illness, such as hypertension (two or more blood pressure [BP] readings performed at screening of >140 mm Hg systolic or >90 mm Hg diastolic) despite optimal treatment, unhealed wounds from recent surgery, or cardiac arrhythmias; or a recent history of serious disease such as either symptomatic congestive heart failure or unstable angina pectoris within the past 3 months, or myocardial infarction, stroke, or transient ischemic attack within the past 6 months.
- Was pregnant or breastfeeding.
- Had an active infection requiring systemic treatment.

- Had a known allergy or hypersensitivity to any of the components of the XL184 or placebo formulations.
- Was incapable of understanding and complying with the protocol or unable to provide informed consent.

Treatments

Pre-Treatment Period

Screening evaluations were completed within 28 days prior to randomization to determine the eligibility of subjects, including radiographically documented disease progression by mRECIST compared to a radiologic assessment performed no more than 14 months previously.

Eligibility tumor assessments were compared to historical assessments by a single reader at the IRC prior to randomization to determine if progression criteria per mRECIST were met. For subjects enrolled under Protocol Amendment 2, the investigator determined if progression criteria per mRECIST were met prior to randomization for the purpose of establishing eligibility

Treatment Period

Subjects were randomized 2:1 to receive either 140 mg (freebase equivalent) of cabozantinib or placebo capsules orally once per day until either intolerable toxicity or disease progression.

Radiologic tumor assessments were performed every 12 weeks (± 5 days) from randomization until PD as determined by the investigator using mRECIST. Tumour assessments were evaluated by the blinded IRC to determine response and/or progression. Haematology and serum chemistry laboratory evaluations and vital signs assessments were conducted every two weeks during Cycles 1 and 2, and every four weeks starting with Cycle 3. Blood and tissue samples for biomarker and blood samples for PK assessments were collected at specific protocol-defined visits. At each study visit, evaluations of adverse events (AEs) and concomitant medication use were performed.

Upon documented progression using mRECIST as determined by the investigator or unacceptable toxicity or other protocol-specified criteria, the subject discontinued study treatment and entered the post-treatment period. If study treatment was discontinued for reasons other than PD, the following efficacy and safety measures continued until documented tumour progression: tumour assessments; pharmacodynamic blood sampling; CTN, CEA, thyroid stimulating hormone (TSH), and free thyroxine (FT4) measurements; and MDASI Thyroid Module.

Post-Treatment Period

Thirty days (+7 days) after the last dose of study treatment, subjects returned to the study site for post-treatment assessments. The investigator obtained follow-up information, including survival status, every 12 weeks (± 15 days) after the last dose of study treatment. The study did not permit crossover from the placebo arm to the XL184 arm.

Objectives

Primary objective:

- To evaluate progression-free survival (PFS) with XL184 treatment as compared with placebo in subjects with unresectable, locally advanced, or metastatic medullary thyroid cancer (MTC).

Secondary objectives:

- To evaluate OS with XL184 treatment as compared with placebo.
- To evaluate the objective response rate (ORR) and duration of response in subjects with measurable disease treated with XL184 as compared with placebo per modified Response Evaluation Criteria in Solid Tumors 1.0 (mRECIST: defined in Appendix C of the protocol). The modifications, which comprised further definitions of rules, assumptions, and/or clarifications of the original RECIST 1.0 criteria, were provided by the Independent Radiology Review Committee (IRC).
- To evaluate changes in serum levels of calcitonin (CTN) and carcinoembryonic antigen (CEA) as prognostic biomarkers for XL184 treatment benefit as compared with placebo.
- To assess the potential relationship between *RET* germline and/or tumor DNA sequence alteration and the efficacy of XL184.
- To assess the pharmacodynamic effects of XL184.
- To evaluate the safety and tolerability of XL184 treatment.
- To assess the pharmacokinetics (PK) of XL184.

Outcomes/endpoints

Primary endpoint

- Progression-free survival (IRC determined) defined as the time from randomization to documented PD per mRECIST criteria or death due to any cause, whichever occurred first.

Secondary endpoints

- Overall survival (defined as the time from randomization to death due to any cause),
- Objective response rate (ORR, defined as the proportion of patients who had measurable disease at baseline for whom BOR at the time of data cut-off was complete response [CR] or partial response [PR] according to mRECIST criteria, and which was confirmed by a subsequent visit ≥28 days later)

- Disease stabilization rate (DSR, defined as the percentage of patients with CR, PR or stable disease [SD] for ≥24 weeks)
- Duration of response (defined as the time from first documentation of objective response [confirmed at a visit ≥28 days later] to PD by mRECIST or death due to any cause)
- Duration of stable disease (defined as the number of days between randomization and PD by mRECIST as determined by IRC or death for patients achieving SD as BOR).
- Evaluation of pharmacokinetics, pharmacodynamics, safety, changes of calcitonine and CEA serum levels, and assessment of biomarkers (VEGFR2, sKIT) and of the potential relationship between RET germline and/or tumor DNA sequence alteration and efficacy of cabozantinib.

Sample size

For the primary endpoint of PFS, assuming exponential PFS, proportional hazards, and a 2:1 (cabozantinib:placebo) treatment allocation ratio, 138 events were required to provide 90% power to detect a HR of 0.571 using the log-rank test and a 2-sided significance level of 5%. This corresponds to a 43% reduction in the risk of progression or death, or a 75% increase in median PFS from 8 months to 14 months. Under this design, the minimum observed effect that could have resulted in statistical significance for PFS was a 40.3% improvement (HR=0.713) in PFS from 8 to 11.2 months. If the true treatment effect was a 75% improvement in PFS, there was a 90% chance (power) of observing a 40.3% or greater improvement and a 50% chance of observing a 75% or greater improvement.

For the key secondary efficacy endpoint of OS, assuming a single interim analysis at the 31% information fraction at the time of the primary analysis of PFS and a subsequent primary analysis, 217 deaths were required to provide 80% power to detect an HR of 0.667 using the log-rank test and a 2-sided significance level of 4%. This corresponds to a 33.3% reduction in the risk of death, or a 50% increase in median survival from 22 to 33 months. Under this design, the minimum observed effect that would result in statistical significance for the primary analysis of OS is a 33.3% improvement (HR=0.75) in OS from 22 to 29.3 months. If the true treatment effect is a 50% improvement in OS, there is an 80% chance (power) of observing a 33.3% or greater improvement, and a 50% chance of observing a 50% or greater improvement.

A total of 315 eligible subjects (210 cabozantinib and 105 placebo) were planned to be randomized and followed to observe the required number of events within the planned study duration. With protocol Amendment 1, the number of subjects to be enrolled with nonmeasurable disease was capped at 10%.

A single planned interim analysis for OS was performed at the time of the primary PFS analysis at the 44% information fraction (i.e., 96 deaths events) using the data base cut-off date of 15 June 2011. Type I error was controlled by implementing a Lan-De Mets O'Brien-Fleming alpha-spending function to control the total alpha for OS at 0.04 level.

Randomisation

Eligible subjects were to be randomized strictly sequentially in a 2:1 ratio.

Stratification factors were age (≤ 65 years, > 65 years) and prior use of a TKI (yes, no) as determined at study entry.

Blinding (masking)

The study was double-blind.

Statistical methods

Primary endpoint analysis

Hypothesis testing to evaluate the duration of PFS between the two treatment arms was performed using the stratified log-rank test with a 2-sided 0.05 level of significance. The stratification factors were the same factors used to stratify the randomization: age (⩽65 years versus >65 years) and known prior receipt of a tyrosine kinase inhibitor (TKI) (Yes versus No).

The HR was estimated using a Cox regression model and included the treatment groups as the main effect and stratification factors, age, and prior TKI exposure.

Censoring rules

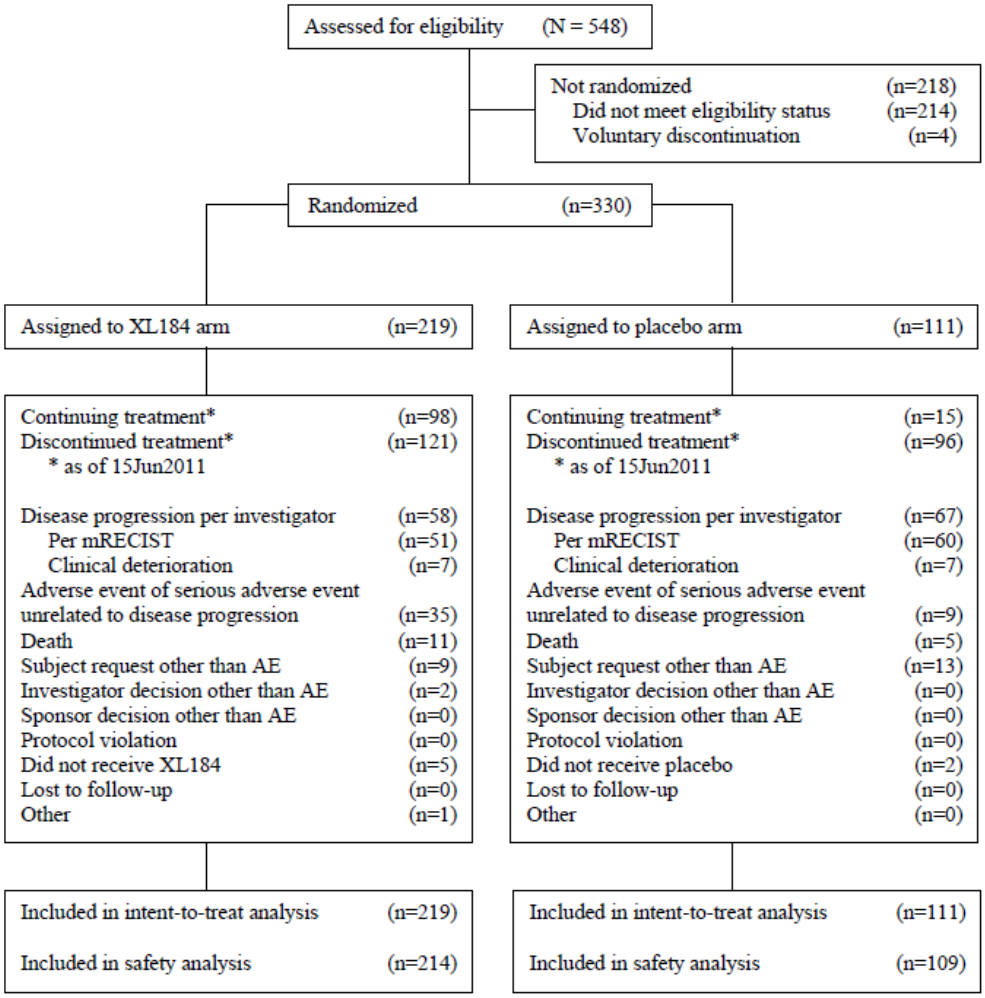
The following censoring rules were applied for the analyses of the primary endpoint (PFS):

1. Subjects who died more than 26 weeks after their last adequate tumor assessment were right censored to the date of their last adequate tumor assessment; 2. Subjects who did not have any post-baseline adequate tumor assessment and did not die within 26 weeks of randomization were right censored on the date of randomization; 3. Subjects with no adequate tumor assessment for more than 26 weeks were right censored at their last adequate tumor assessment before the missing tumor assessments; 4. Subjects who received subsequent anticancer therapy (including palliative radiation to nontarget lesions or other local therapies) before experiencing an event were censored at the date of the most recent adequate tumor assessment prior to receipt of such treatment; 5. Subjects who did not progress or die (and were not otherwise censored) at the time of data cut-off were right censored on the date of their last adequate tumor assessment.

Results

Participant flow

Figure 2. Participant flow of the pivotal XL184-301 study



Recruitment

The study (period from 10 September 2008 to 15 June 2011) was conducted at 90 centers across 23 countries, randomized across Europe (184 pts: 124 treated with cabozantinib and 60 with placebo), North America (99 pts: 69 treated with cabozantinib and 33 with placebo), and rest of the World (44 pts: 26 treated with cabozantinib and 18 with placebo).

Conduct of the study

The original study protocol (dated 21 April 2008) was subsequently amended twice. No patients were enrolled under the original protocol, 295 under protocol amendment 1 and 35 under protocol amendment 2.

Amendment 1 (dated 11 June 2008, implemented after comments received from FDA during a SPA) essentially modified ECG and PK time points in order to match them, introduced the possibility to re-escalate the dose of study drug no sooner than two weeks beyond resolution to Grade ≤1 or to the baseline value of symptoms, modified stratification factors, and capped enrollment of patients with only non measurable disease to 31 (10% of the total planned number).

Amendment 2 (dated 24 September 2010) essentially changed determination of eligibility due to radiologic disease progression from a blinded radiologist of the IRC to the investigator.

Furthermore, Country-specific protocol amendments were created for the United Kingdom, France, India and Germany, in order to meet specific country-requirements. They essentially concern inclusion/exclusion criterion of patients sexually active and women with childbearing potential, and they did not change the study population and planned analyses. However, a specific amendment was made in Germany in order to accept radiographic documentation of disease progression at study entry within 3 months instead of 28 days, as requested in the other countries.

The SAP was modified 3 times:

- on 22 July 2008, to revise stratification factors to match Protocol Amendment 1.0;
- on 07 February 2011, in order to clarify the methods used to address missing or inadequate tumor assessments for PFS or ORR, refine details of planned supportive analyses, include an additional sensitivity analysis of PFS based on investigator assessment of radiographic progression, match the inclusion criterion related to assessment of disease progression at baseline with protocol amendment 2;
- on 29 August 2011 (before unblinding), in order to establish an imputation rule for partial start dates of subsequent anticancer therapy and for partial start and stop dates for dose interruption.

Protocol Deviations

There were 33 protocol deviations reported in 28 patients treated with cabozantinib and 12 protocol deviations reported in 11 patients treated with placebo.

Twenty-six deviations (18 in the cabozantinib and 8 in the placebo arm) concerned inclusion/exclusion criteria, whereas 15 deviations (11 in the cabozantinib and 4 in the placebo arm) concerned continuation of treatment after determination of disease progression per mRECIST by the investigator. A total of four deviations regarded incorrect dosing of study drug. All these deviations were determined to be major deviations.

Other minor protocol deviations were reported, essentially regarding missed or out of window laboratory procedures or visits.

Baseline data

The great majority of patients were males (66.9%), white (89.4%), with a median age of 55 years (range, 20-86 yr), an ECOG PS 0 (54.2%) and stadium IVc of disease (95%) according to AJCC cancer staging at enrollment. Median time since initial diagnosis was 3.59 years in the cabozantinib arm and 4.41 years in the placebo arm, and median time since development of metastasis was 1.94 years in the cabozantinib arm and 2.04 years in the placebo arm. The majority of patients had RET mutation positive status (48.1%). The great majority of patients had at least two metastatic sites (87%).

No obvious imbalances between the cabozantinib and placebo arms were observed in several demographic and baseline characteristics evaluated, in particular no significant differences were found in terms of age, race, median weight, presence of measurable disease, AJCC stadium at time of enrollment, median number of prior anticancer therapy regimens received, previous treatment with radiotherapy, tyrosine kinase inhibitors and thyroidectomy.

However, slightly more patients in the cabozantinib group were males (68.9% vs 63.1%, respectively), former (38.8% vs 30.6%) or current (10% vs 2.7%) smokers, had ECOG PS 0 (56.2% vs 50.5%), greater median of the sum of the longest diameter for target lesions at baseline (106.15 vs 88.8 mm), and shorter median time since initial diagnosis of MTC (3.59 vs 4.41 years), since metastasis (3.64 vs 4.64 years), and liver (69.4% vs 60.4%) and mediastinum (59.4% vs 54.1%) as tumor localization. In contrast, more patients in the placebo arm were females (36.9% vs 31.1%), had age ≤45 years (29.7% vs 24.7%), never smoked (66.7% vs 51.1%), had ECOG PS 2 (9.9% vs 4.1%), RET positive tumors (52.3% vs 46.1%), and lung metastases (57.7% vs 53%).

Regarding the use of selected medications before start of the study, slightly more patients in the placebo arm used antidiarrhoeals (30.3% vs 25.2%) and antiemetics (7.3% vs 4.7%), whereas a slightly higher number of patients in the cabozantinib arm used antihypertensive drugs (26.6% vs 21.1%) and bisphosphonates (10.3% vs 6.4%).

Table 15. Baseline and Demographic Characteristics in XL184-301 study (ITT population)

	Cabozantinib (N=219)	Placebo (N=111)
Age (years)		
Mean (SD)	54.4 (13.33)	53.8 (13.39)
Min, Max	20, 86	21, 79
≥65-74, n (%)	35 (16.0%)	26 (23.4%)
75-84, n (%)	12 (5.5%)	2 (1.8%)
≥85, n (%)	1 (0.5%)	0
Male, n (%)	151 (68.9%)	70 (63.1%)
Female, n (%)	68 (31.1%)	41 (36.9%)
White, n (%)	196 (89.5%)	99 (89.2%)
Asian, n (%)	9 (4.1%)	6 (5.4%)
Black, n (%)	2 (0.9%)	1 (0.9%)
Other, n (%)	5 (2.3%)	1 (0.9%)
Not Reported, n (%)	7 (3.2%)	4 (3.6%)
Europe	124 (56.6%)	60 (54.1%)
North America	69 (31.5%)	33 (29.7%)
Rest of World	26 (11.9%)	18 (16.2%)
AJCC Stage IVc (metastatic) disease at enrolment	210 (95.9%)	105 (94.6%)
Common sites of metastatic disease at enrolment, n (%)		
Lymph nodes	175 (79.9%)	86 (77.5%)
Liver	152 (69.4%)	67 (60.4%)
Lung	116 (53.0%)	64 (57.7%)
Bone	112 (51.1%)	56 (50.5%)
≥2 sites	191 (87.2%)	96 (86.5%)
ECOG performance status, n (%)		
0 (normal activity, asymptomatic)	123 (56.2%)	56 (50.5%)
1 (symptomatic, fully ambulatory)	86 (39.3%)	44 (39.6%)
2 (symptomatic, in bed <50% of the time)	9 (4.1%)	11 (9.9%)
Measurable Disease per mRECIST, IRC determination, n (%)	208 (95.0%)	104 (93.7%)
Median baseline sum of the longest diameter of target lesion, IRC determination (mm)	106.15	88.80
Number of prior anticancer therapies, median (range)	1.0 (1-6)	1.0 (1-7)
Prior systemic therapy for MTC, n (%)	81 (37.0%)	47 (42.3%)
Prior tyrosine kinase inhibitor use, n (%)	44 (20.1%)	24 (21.6%)
MTC Disease Type, n (%)[a]		
Hereditary	12 (5.5%)	8 (7.2%)
Sporadic	191 (87.2%)	94 (84.7%)
Unknown	16 (7.3%)	9 (8.1%)
Tumour's *RET* mutational status, n (%)[b]		
Positive	101 (46.1%)	58 (52.3%)
Negative	31 (14.2%)	10 (9.0%)
Unknown	87 (39.7%)	43 (38.7%)

AJCC = American Joint Committee on Cancer (version 6), ECOG=Eastern Cooperative Oncology Group, IRC = Independent Radiology Review Committee; mRECIST = modified RECIST

[a] Hereditary: evidence of functional *RET* mutation in blood DNA sample. Sporadic: adequate sequence of blood or tumour DNA with no evidence of *RET* mutation.

Table 16. Study XL184-301: Cancer History (ITT Population)

	Cabozantinib (N = 219)	Placebo (N = 111)
Years since Initial Diagnosis of MTC		
N	219	111
Mean (SD)	5.88 (6.370)	7.27 (7.942)
Median (25%, 75%)	3.59 (1.47, 7.60)	4.41 (1.65, 10.08)
Years since Initial Diagnosis of Metastasis		
N	218	110
Mean (SD)	3.64 (4.740)	4.64 (5.867)
Median (25%, 75%)	1.94 (0.79, 4.66)	2.04 (0.91, 5.91)
Cancer Staging at Enrolment[a]		
III	0	1 (0.9%)
IVa	4 (1.8%)	1 (0.9%)
IVb	2 (0.9%)	1 (0.9%)
IVc	210 (95.9%)	105 (94.6%)
Unknown	3 (1.4%)	3 (2.7%)
Extent of Metastatic Disease at Enrolment		
Bone	112 (51.1%)	56 (50.5%)
Lymph nodes	175 (79.9%)	86 (77.5%)
Liver	152 (69.4%)	67 (60.4%)
Brain	5 (2.3%)	2 (1.8%)
Neck	37 (16.9%)	12 (10.8%)
Lung	116 (53.0%)	64 (57.7%)
Pelvis	5 (2.3%)	5 (4.5%)
Other	24 (11.0%)	20 (18.0%)
Prior Thyroidectomy	201 (91.8%)	104 (93.7%)

[a] Staging is defined according to the American Joint Committee on Cancer (AJCC) guidelines

Table 17. Study XL184-301: Prior Cancer and Radiation Therapy for MTC (ITT Population)

	Cabozantinib (N = 219)	Placebo (N = 111)
Number of subjects with prior therapy for MTC (%)		
Prior cancer therapy only[a]	37 (16.9%)	23 (20.7%)
Prior radiation therapy only	56 (25.6%)	27 (24.3%)
Prior cancer therapy and radiation[a]	48 (21.9%)	25 (22.5%)
No prior therapy reported	78 (35.6%)	36 (32.4%)
Number of Prior Cancer Therapy Regimens per Subject		
n	85	48
Mean (SD)	1.7 (1.07)	1.9 (1.24)
Prior systemic therapy for MTC	81 (37.0%)	47 (42.3%)
Prior tyrosine kinase inhibitor use, n (%)	44 (20.1%)	24 (21.6%)

[a] Prior cancer therapy includes systemic treatment and chemoembolization but not radiation therapy

Systemic therapies prior study entry

Overall, the treatment groups were generally balanced with respect to prior cancer therapy. Over 90% of subjects in each treatment group had a prior thyroidectomy (91.8% in cabozantinib arm and 93.7% in the placebo arm). The proportions of patients who received prior anticancer therapy, prior radiation therapy, or both, were similar between the treatment groups. The median (range) number of prior MTC therapy regimens per subject was 1.0 (1-6) in the cabozantinib arm and 1.0 (1-7) in the placebo arm.

A total of 37.0% of subjects in the cabozantinib arm and 42.3% of subjects in the placebo arm received prior systemic therapy for MTC; prior use of a TKI was similar in each treatment group

(20.1% vs 21.6%, respectively). The most common prior anticancer therapies were vandetanib (11.4% vs 8.1%), doxorubicin (5.9% vs 6.3%), dacarbazine (5.0% vs 0.9%), sorafenib (5.0% vs 7.2%), cisplatin (4.1% vs 3.6%), fluorouracil (4.1% vs 2.7%), therapeutic radiopharmaceuticals (3.2% vs 7.2%) and octreotide (0.5% vs 5.4%). Alongs with vandetanib and sorafenib, the most common TKI received by the patients were motesanib (3.2% vs 1.8%), sunitinib (2.7% vs 2.7%), axitinib (1.4% vs 0%), pazopanib (0.5% vs 1.8%), and imatinib (0% vs 1.8%).

Numbers analysed

Table 18. Patient disposition XL184-301 study

	XL184 N (%)	Placebo N (%)
Total number of randomized subjects (ITT population)[a]	219	111
Safety population[b]	214 (97.7)	109 (98.2)
Per-Protocol population[c]	198 (90.4)	102 (91.9)

[a] Percentages for the populations are based on all randomized subjects.
[b] Safety population includes all subjects who received any amount of treatment.

The primary population for the efficacy analysis was the intent-to-treat (ITT) population, which was defined as all randomized patients, independently on whether they received or not study medication (N= 330)

The Safety population was defined as all patients who received any amount of treatment with XL184 or placebo, according to the actual treatment received and comprised all patients who received at least 1 dose of study medication (N=323)

The Per-protocol (PP, N=300) population was defined as all patients included in the safety population who:

- Had a baseline and at least one adequate post-randomization scheduled tumor assessment (or tumor assessment of PD at any time), or failed to have post-randomization tumor assessment ≤182 days after randomization due to either death or clinical deterioration,
- Received randomized treatment,
- Met specific inclusion (presence of histologically confirmed MTC unresectable, locally advanced or metastatic pneumomediastinum, ECOG PS≤2, documented PD determined by blinded IRC or by investigator [after amendment 2], adequate organ function) and exclusion (previous treatment with XL-184, presence of asymptomatic brain metastases or spinal cord compression at least 4 weeks after and without steroid and anticonvulsant for at least 10 days, presence of serious intercurrent illness, such as uncontrolled hypertension, unhealed wounds from recent surgery or cardiac arrhythmias or recent serious cardiovascular disease) criteria.

Outcomes and estimation

Primary objective: Progression Free Survival (IRC-determined according to mRECIST, ITT population)

A total of 139 PFS events (42.1%) were included in the analysis (cut-off 06 April 2011), 79 (36.1%) events in the cabozantinib arm (58 [26.5%] as disease progression and 21 [9.6%] as deaths events) and 60 events (54.1%) in the placebo arm (50 [45%] as disease progression and 10 [9%] as death events).

In the ITT population there was a statistically significant difference in PFS between treatment arms (HR=0.28, 95% CI 0.19-0.40, p<0.0001) at the stratified analysis. The estimated median PFS was 48.6 weeks (11.2 months) in the cabozantinib arm and 17.4 weeks (4.0 months) in the placebo arm. The Kaplan-Meier PFS rates at 3, 6, 9 and 12 months were 86% vs 57%, 70.1% vs 26.4%, 58.7% vs 14.4%, 47.3% vs 7.2%, in the cabozantinib and placebo arm, respectively.

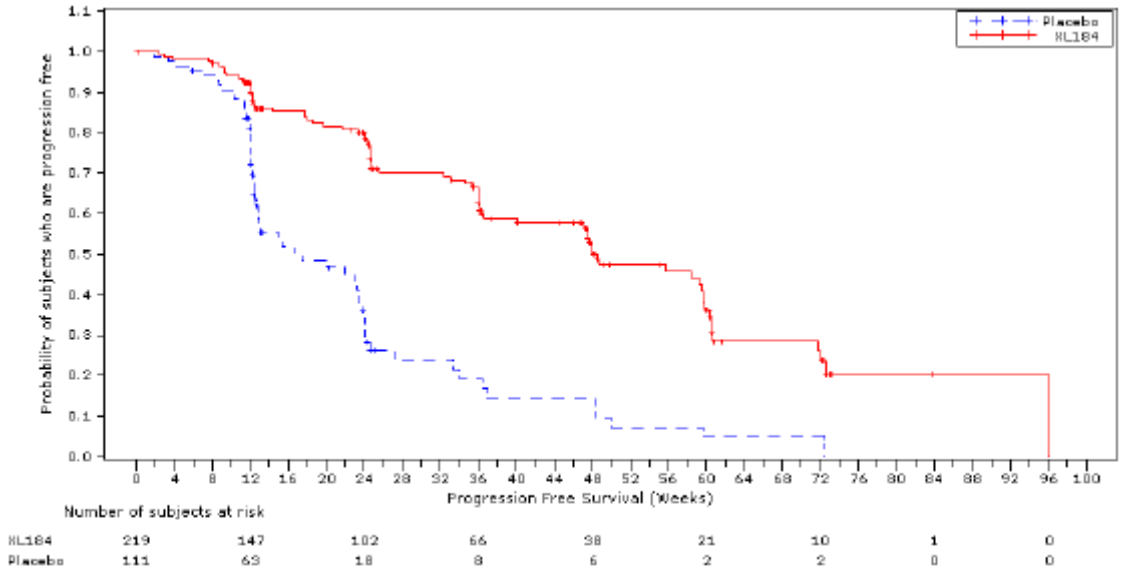
In sensitivity analyses, the IRC and investigator agreed on subjects' PD status 77.9% of the time, and the IRC and investigator agreed on PD dates 74.4% of the time.

Table 19. PFS in XL184-301 Study (IRC-determined, ITT population)

	XL184 N=219	Placebo N=111
Number (%) of Subjects		
Censored	140 (63.9)	51 (45.9)
Event	79 (36.1)	60 (54.1)
Death	21 (9.6)	10 (9.0)
Progressive disease	58 (26.5)	50 (45.0)
Duration of progression free survival (weeks)		
Median (95% CI)	48.6 (40.14, 59.71)	17.4 (12.86, 23.57)
25th percentile, 75th percentile[a]	24.6, 71.9	12.1, 27.1
Range	0.1+ - 96.0	0.1+ - 72.4
p-value (stratified log-rank test)[b]	<0.0001	
Hazard ratio (95% CI; stratified)[c]	0.28 (0.19, 0.40)	

Note: 139 events occurred by the date of the 138th event.
+ indicates a censored observation; CI=confidence interval; IRC=Independent Radiology Review Committee; ITT=intent-to-treat
[a] Median and percentiles are based on Kaplan-Meier survival estimates.
[b] Stratification factors include age at randomization (≤65, >65) and prior tyrosine kinase inhibitor status (yes, no).
[c] Estimated using the Cox proportional hazard model adjusted for stratification factors. HR <1 indicates PFS in favor of XL184.

Figure 3. Kaplan-Meier Plot of PFS in XL-184-301 Study (IRC-determined, ITT population)



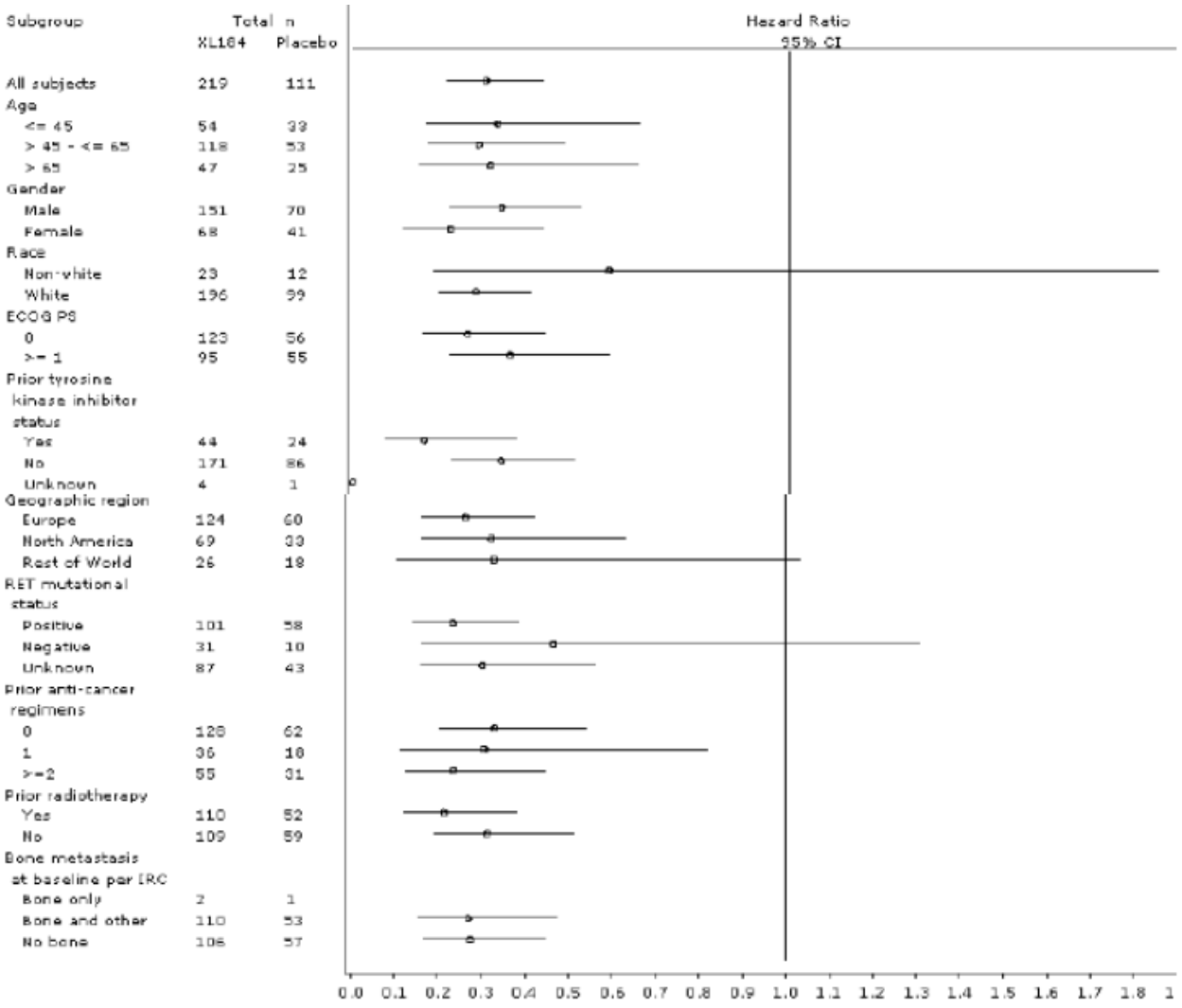
IRC=Independent Radiology Review Committee; ITT=intent-to-treat

Table 20. Event and Censoring Status in the Primary PFS Analysis

	Cabozantinib (n, %)	Placebo (n, %)
Randomized	219 (100)	111 (100)
Event	79 (36)	60 (54)
Radiographic PD	58 (26)	50 (45)
Death	21 (10)	10 (9)
Censored	140 (64)	51 (46)
No event observed by data cutoff	80 (37)	12 (11)
Received subsequent anticancer therapy	21 (10)	19 (17)
No postbaseline tumor assessments	37 (17)	20 (18)
Missed assessments before event	2 (1)	0 (0)

Abbreviations: PD, progressive disease; PFS, progression-free survival.

Figure 4. Forest Plot for PFS by subgroup (Study XL184-301, IRC-Determined, ITT population)



Secondary endpoint: Overall Survival (OS)

An interim analysis of OS was conducted at the time of the primary analyses of PFS (cut-off date 15 June 2011). A total of 96 deaths were reported, representing 44% (96/217) of the total required for the pre-specified primary analysis of OS. The median time of follow-up (from randomization through 15 June 2011) was 13.9 months (range 3.6 - 32.5 months).
In the ITT population, the proportion of deaths was similar in both treatment groups (30.1% vs 27% in the cabozantinib and placebo arm, respectively); median duration of OS was 21 months in the cabozantinib arm and could not be estimated in the placebo arm (HR 0.98, 95% CI 0.63-1.52, p=0.9304). Kaplan-Meier estimates of OS were similar among all subjects at all time points.

An updated (not pre-specified) OS analysis has been conducted with a cut-off date of 15 June 2012. The analysis is based on 162 (75%) of the 217 death events required for the final analysis (103 in the cabozantinib arm and 59 in the placebo arm). The HR was 0.83 (95% CI 0.60-1.14), median OS was 26 months with cabozantinib compared with 20.3 months with placebo.

Table 21. OS in XL184-301 Study (15 June 2012 cut-off - ITT)

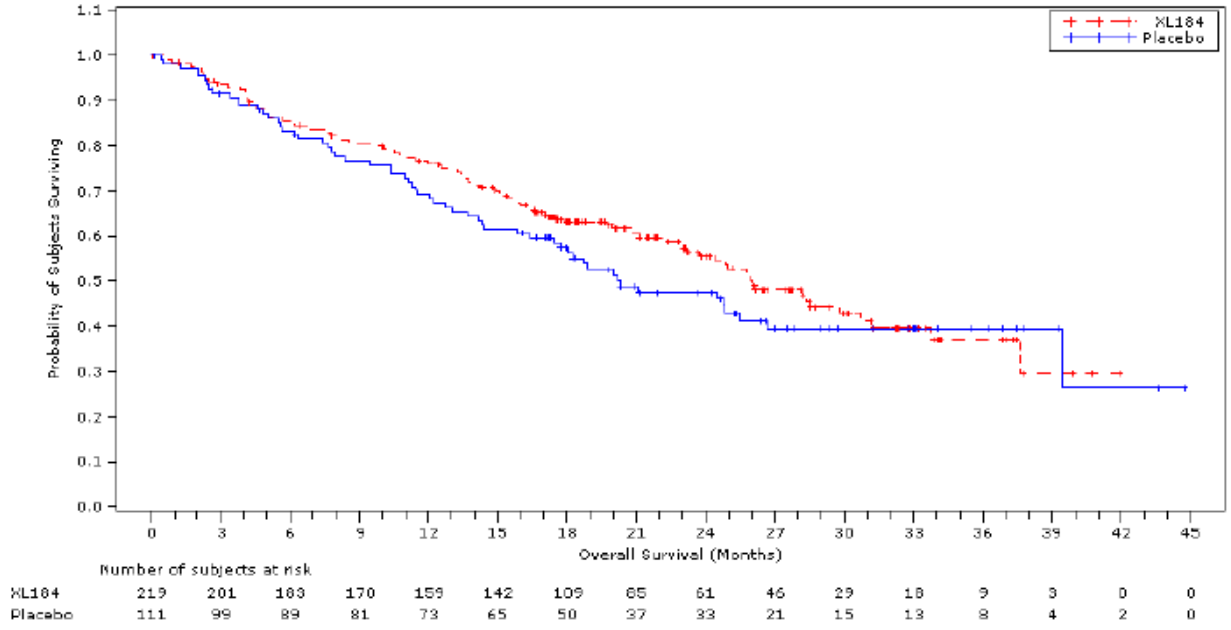
	Cabozantinib N=219	Placebo N=111
Number (%) of Subjects		
Censored	116 (53.0)	52 (46.8)
Death	103 (47.0)	59 (53.2)
Duration of Overall Survival (months)		
Median (95% CI)	26.0 (23.20, 31.18)	20.3 (17.41, 39.46)
25th percentile, 75th percentile[a]	12.8, NA	10.4, NA
Range	0.1+, 42.0+	0.1+, 44.7+
Hazard ratio (95% CI; stratified)[b]	0.83 (0.60, 1.14)	

+ indicates a censored observation; CI=confidence interval; NA=Not available

[a] Medians and percentiles are based on Kaplan-Meier estimates

[b] Estimated using the Cox proportional hazard model adjusted for stratification factors of age at randomisation (≤65, >65) and prior TKI status (yes, no). A HR <1 favours cabozantinib.

Figure 5. Kaplan-Meier Plot of OS data through at least 15 June 2012 (Administrative Analysis; ITT Population)



Post study Therapies

Table 22. Subsequent Anti-cancer Therapy Classification (Study XL184-301, cut-off "at least" 15 June 2012)

	Cabozantinib (n=219)	Placebo (n=111)
Any subsequent Anticancer Therapy	72 (32.9%)	58 (52.3%)
Local Therapy	29 (13.2%)	21 (18.9%)
Systemic Therapy	48 (21.9%)	50 (45.0%)
Vandetanib	21 (9.6%)	18 (16.2%)
TKIs excluding Vandetanib	21 (9.6%)	26 (23.4%)
Other Targeted Therapy	6 (2.7%)	6 (5.4%)
Cytotoxic	5 (2.3%)	9 (8.1%)
Other/Unknown	3 (1.4%)	8 (7.2%)

Note: subjects may have received more than one type of systemic therapy and are counted in each individual group
TKI: Targeted Kinase Inhibitor.
TKI (excluding vandetanib) included: cediranib, investigational TKIs including E7080, pazopanib, sorafenib, sunitinib.
Targeted - Other included: everolimus, notch inhibitor labelled PJC-004, sirolimus.
Other Systemic Therapy included: interferon, PEG interferon alpha-2b, investigational drug OSI-027, pasireotide, therapeutic radiopharmaceutical.

Secondary objective: Objective Response Rate (ORR) and Disease Stabilization rate (DSR)

Table 23. Tumor Response in Subjects with Measurable Disease at Baseline (IRC-Determined, ITT Population)

Subjects in ITT Population	XL184 N=219	Placebo N=111
Subjects with Measurable Disease	**208**	**104**
Best Overall Response (n, %)[a,b]		
Confirmed complete response (CR)	0	0
Confirmed partial response (PR)	58 (27.9)	0
Stable disease (SD)	100 (48.1)	52 (50.0)
Progressive disease	18 (8.7)	35 (33.7)
Unable to evaluate	5 (2.4)	1 (1.0)
Missing[c]	27 (13.0)	16 (15.4)
Objective Response Rate (ORR=CR+PR)[b,d]		
n (%)	58 (27.9)	0
95% confidence interval	21.9%, 34.5%	NA
99% confidence interval	20.2%, 36.6%	NA
p-value (stratified Cochran-Mantel-Haenszel test)[e]	<0.0001	
Disease Stabilization Rate (DSR=ORR+SD)[b,f]		
n (%)	115 (55.3)	14 (13.5)
95% CI	48.3%, 62.2%	7.6%, 21.6%
p-value (stratified Cochran-Mantel-Haenszel test)	<0.0001	

IRC=Independent Radiology Review Committee; ITT=intent-to-treat; NA=not available

[a] Best overall response determined by Independent Radiology Review Committee using mRECIST criteria.

[b] Percentages are based on the number of subjects with measurable disease.

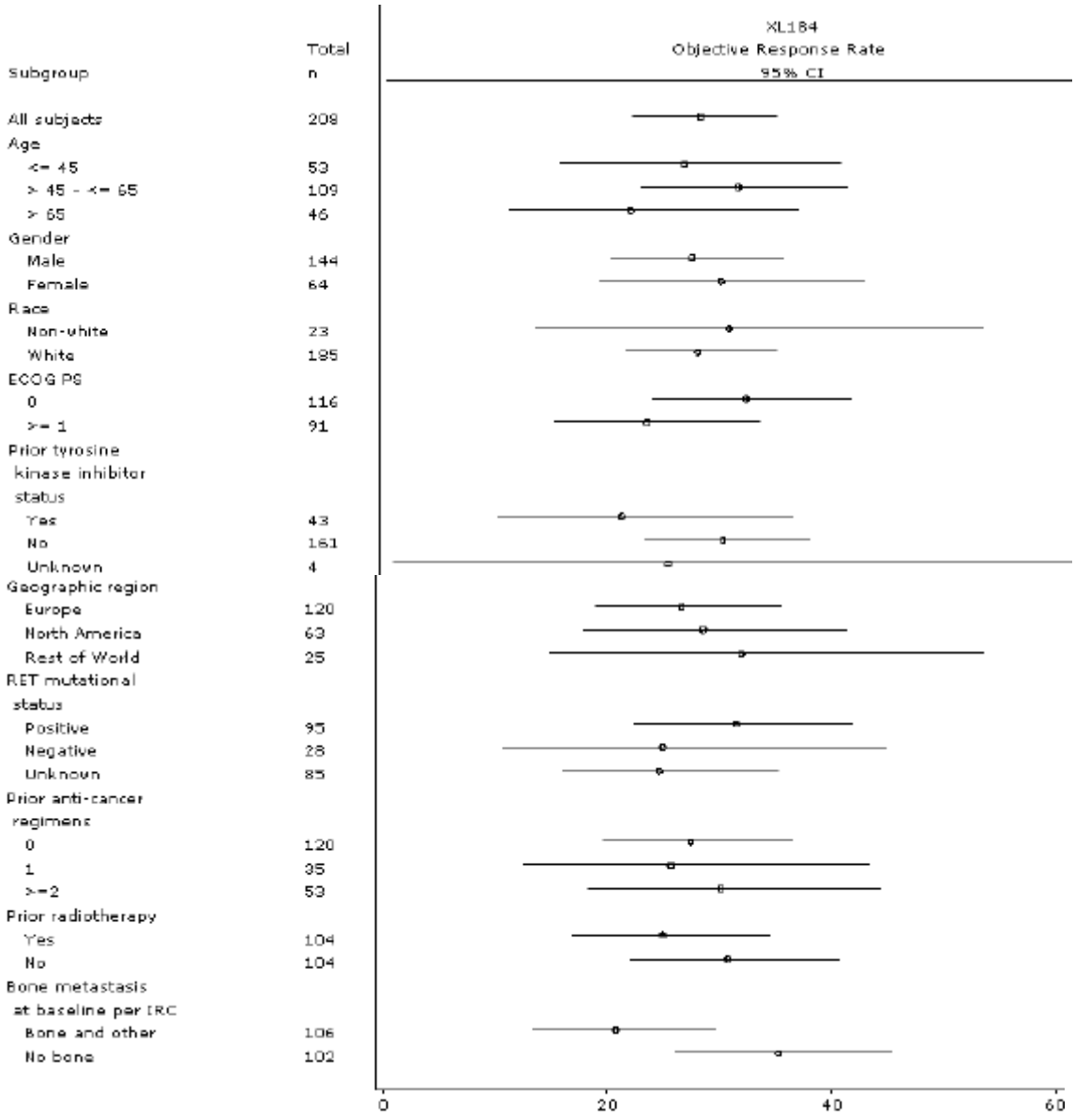
[c] Missing=no qualifying post-baseline assessment for overall response.

[d] ORR is defined as the proportion of subjects with measurable disease achieving best overall response of confirmed CR or confirmed PR.

[e] p-value from Cochran-Mantel-Haenszel test with stratification factors age and prior tyrosine kinase inhibitor status.

[f] DSR is defined as the proportion of subjects with measurable disease achieving best overall response of confirmed CR, confirmed PR, or SD on or after the Week 24 tumor assessment without prior PD or receipt of subsequent therapy.

Figure 6. ORR by different subgroups



Exploratory objective: Patient-Reported Outcomes – MDASI Thyroid Module (MDASI THY)

MDASI Thyroid Module was evaluated at screening and every 12 weeks (± 5 days) from randomization until disease progression, in order to evaluate the most frequently reported and most serious symptoms in patients with MTC. MDASI THY consists of 2 parts: 1) a part (Question 1-9) covering 13 core cancer and treatment related symptoms with severity scored from 0 (not present) to 10 (symptom as bad as you can imagine it could be); 2) a part (Questions 20-25) evaluating how symptoms have interfered with patient's life in the previous 24 hours scored from 0 (no interference) to 10 (interfered completely).

A Primary Symptom Severity Score included diarrhea, fatigue, sleep disturbance, distress, and difficulty remembering. An Overall Mean Symptom Severity Score included the 13 “core” and six thyroid-specific items. A Mean Symptoms Interference Subscale was defined as the subject’s six interference items. Mean scores were calculated for all the composite scores when patients answered more than half of the items for that score. A high MDASI score indicates the presence of more symptoms. In the evaluation of difference in mean symptoms and interference change over time between treatment groups, an effect size of 0.5 (half of a SD of baseline values) was deemed clinically meaningful.

At baseline, percentages of subjects in the combined cabozantinib and placebo groups rating MDASI-THY symptom scores as of moderate or greater severity were: fatigue (38%), diarrhoea (35%), sleep disturbance (29%), hoarseness (28%) and emotional distress (27%).

Approximately 75% of patients in each treatment group contributed to the MDASI-THY data at Week 12. By Week 24, the percentage of patients completing the MDASI-THY assessment declined to 55% and 28% in the cabozantinib and placebo groups, respectively. At subsequent visits the number of patients further declined, therefore scores were not examined.

At week 12 nausea, lack of appetite, dry mouth and feeling cold were clinically-meaningfully more severe in the cabozantinib arm compared to the placebo arm, as well as nausea, feeling cold and diarrhoea at week 24. Only shortness of breath was more severe in the placebo arm. However, at week 24 only 31 patients were included in the analysis. Interference with quality of life got worse in both arms but was not different between treatment arms at week 24.

Exploratory endpoints

For a summary of RET Genotyping Results in XL184-301 study see above (Clinical pharmacology, Pharmacodynamics).

Summary of main study

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 24. Summary of efficacy for trial XL 184-301

Title: An International, Randomised, Double-Blinded, Phase III Efficacy Study of XL184 in Patients with Unresectable, Locally Advanced or Metastatic Medullary Thyroid Cancer			
Study identifier	XL184-301		
Design	A Phase III, international, randomised, double-blinded efficacy study of XL184 in patients with unresectable, locally advanced or metastatic medullary thyroid cancer		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Patients remained in the Treatment Period until PD per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria. N/A N/A
Hypothesis	Superiority		
Treatments groups	175mg XL184 (L-malate saltweight)		**Treatment**: once per day (qd) oral administration **Duration**: On-going. Patients remained in the Treatment Period until PD per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria. **Number randomized**: 219
	Placebo		**Treatment**: once per day oral administration **Duration**: On-going. Patients remained in the Treatment Period until PD per mRECIST as determined by the investigator, as long as they did not experience unacceptable toxicity or did not meet other protocol-specified criteria **Number randomized**: 111
Endpoints and definitions	Primary endpoint	PFS	Progression Free survival
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	ORR	Objective response rate
Database lock	On-going (data in report up until 15 June 2011)		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat All patients who were randomized, regardless of whether any study treatment or the correct study treatment was administered. The analysis was conducted after at least 315 patients had been randomised and at least 138 progression events (non-censored radiographic progression per mRECIST as assessed by the IRC, or death) had occurred		
Descriptive statistics and estimate	Treatment group	XL184	Placebo
	Number of patients	219	111

variability	PFS (Weeks)	48.6	17.4
	(95% CI) p-value	(40.14, 59.71) <0.0001	(12.86, 23.57)
	OS* Median (Months)	26.0	20.3
	(95% CI) p-value	(23.20, 31.18) 0.2432	(17.41, 39.46)
	ORR (ORR=CR+PR) (n (Percentage)) 95% CI 99% CI p-value	58 (27.9%) 21.9%, 34.5% 20.2%, 36.6% <0.0001	0 N/A N/A
Notes	This study is currently ongoing. Data up to 15 June 2011 are contained in this clinical study report. As of the 15 June 2011 database cut-off date, 44.7% (98/219) of patients in the XL184 arm and 13.5% (15/111) of patients in the placebo arm were still receiving study treatment. Additional data collected from these patients will be presented after final analysis of overall survival (OS) for the study.		

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

The most relevant findings from the pivotal trial and the expansion cohort of the phase I XL184-001 trial conducted in patients with MTC are shown in the table below:

Table 25. Summary of Efficacy from clinical trials performed with cabozantinib and supporting this submission for MAA

	XL-184-301		XL-184-001[&]
	Cabozantinib	Placebo	Cabozantinib
Pts enrolled, n	219	111	25
RESULTS			
PFS*			
Pts with event	79 (36.1%)	60 (54.1%)	-
Median PFS (weeks)	48.6	17.4	-
	HR 0.28 (0.19-0.49) p<0.0001		-
6 months PFS rate#	70.1%	26.4%	-
OS[1]			
Pts with event	66 (30.1%)	30 (27%)	-
Median (months)	21.1	NA	-
	HR 0.98 (0.63-1.52) p=0.9304		
OS[2]			
Pts with event	103 (47%)	59 (53.2%)	-
Median (months)	26	20.3	-
	HR 0.83 (0.60-1.14) p= NS		-
12 months OS rate#			-
ORR (CR+PR)*			
Pts evaluable	208	104	25
ORR (CR+PR)	58 (27.9%)	0	7 (28%)
CR	0	0	0
PR	58 (27.9%)	0	7 (28%)
SD	100 (48.1%)	52 (50%)	17 (68%)
PD	18 (8.7%)	35 (33.7%)	1 (0.4%)
NE	32 (15.4%)	17 (16.4%)	0
DSR[$]	115 (55.3%)	14 (13.5%)	-

Pts: patients; PFS: Progression Free Survival; OS: Overall Survival; ORR: Objective Response Rate; CR: Complete Remission; PR: Partial Remission; SD: Stable Disease; DSR: Disease Stabilization Rate (CR+ PR); 95% CI: 95% Confidence Interval; *: assessed by IRC; [&]: data from patients with MTC enrolled in the expansion cohort at the MTD (175 mg/day capsule), cut-off date 19 April 2010; [1]: cut-off 15 June 2011; [2]: cut-off at least 15 June 2012; NS: Not significant; #: estimated by Kaplan-Meier plot; NE: Not evaluable due to not measurable disease or missing assessment; $: DSR is defined as the proportion of patients with measurable disease achieving confirmed CR, PR or SD on or after Week 24 tumor assessment without prior PD or receipt of subsequent therapy.

Clinical studies in special populations

Cabozantinib has not been studied in children (< 18 years) or in pregnant or lactating women. Cabozantinib has been given to patients ≥75 years of age, but experience is very limited. Moreover the great majority of patients enrolled in the studies performed with cabozantinib to date were whites, with data essentially lacking in patients with other races (e.g., blacks, etc.).

Hepatic and renal impairment

To date, the effect of hepatic or renal impairment on cabozantinib pharmacokinetics, disposition and safety has not been studied in patients, therefore it is not known whether dose adjustment is appropriate. A phase I clinical pharmacology study evaluating the effect of hepatic impairment on cabozantinib PK is ongoing. A phase I study in patients with renal impairment is planned.

Supportive study

Study XL184-001

Study XL184-001 was an open-label, non-randomized, single-agent, dose escalation study to determine safety, tolerability and maximum tolerated dose (MTD), pharmacokinetics, and biomarker status of cabozantinib. After a dose escalation phase to determine the MTD including doses ranging from 0.08 to 11.52 mg/kg on an Intermittent 5&9 schedule using a powder-in-bottle (PIB) formulation, at 175 and 265 mg on a once-daily schedule using a PIB formulation, and at 175 and 250 mg on a once-daily schedule using a capsule formulation, an expansion cohort in patients with MTC was conducted at dose level 175 mg OD cabozantinib. Overall, 37 patients with MTC were enrolled in Study XL184-001, of which 25 patients were enrolled in the expansion cohort. First signs of clinical activity were observed at dose levels ≥ 5.12 mg/kg PIB. Of the 25 patients, 21 (84%) were male, 16 (64%) had an ECOG PS of 0 (36% had ECOG PS 1), and 24 (96%) were white. The mean time (SD) since initial diagnosis was 4.9 (± 4.471) years and the mean time since initial diagnosis of metastasis was 3.31 (± 3.067) years. Prior anticancer therapy (chemotherapy or radiotherapy) was received by 9 (36%) patients (2 had received vandetanib and 2 sorafenib) and 16 (64%) patients had received no prior anticancer therapy.

Of the 25 patients treated, 18 patients had discontinued study treatment at the time of cut off (19 April 2010). Of note primary reason for discontinuation in the majority of patients was adverse event or SAE (not including death) (9 pts [36%]), objective radiological disease progression (3 pts [12%]), subject withdrew consent (not including AE) (3 pts [12%]), death (1 pt [4%]) and other reason (2 pts [8%]).

All 25 patients were evaluable for response: partial response (PR) was reported in 7 patients (28%) and stable disease (SD) in 17 patients (68%), whereas disease progression was documented in 1 patient (4%). The median time to response for 7 pts experiencing a PR was 28 days (range 21-118 days). Median duration of treatment was 429 days in the 7 patients with PR (range 159-708+), but 3 of them were still on treatment at time of cut off. Duration of treatment in 8 out 17 patients experiencing SD was more than 6 months.

Three (25%) out of the 12 patients with MTC treated during the dose escalation phase of the study at dose levels other than 175 mg capsules or with PIB formulation had a best overall response of PR: 2 patients treated at 5.12 mg/kg intermittent dosing, PIB formulation, and 1 patient treated with 265 mg qd, PIB formulation.

PFS was not assessed due to the high number of patients discontinuing study treatment without progression who did not undergo tumor assessment after stop of treatment. OS was not evaluated. According to the Applicant the majority of the patients had a RET mutation. Three patients were RET negative: 1 achieved confirmed PR, 1 not confirmed PR and 1 PD.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The proposed cabozantinib dose is 140 mg (free base) QD, administered orally. From a methodological point of view the dose selection is considered acceptable as based on the results of the phase I XL184-001 study, employing a classical dose finding approach. However, by analysis of the results of the

phase III pivotal XL184-301 trial where 75% of patients required at least one dose reduction after steady-state concentrations were reached (median time to dose reduction: 43 days) and 41% of patients needed two dose reductions due to persistent toxicity, serious concerns were raised regarding the appropriateness of the dose proposed for registration. From the data presented to date, it is not possible to correlate efficacy and dose. Based on efficacy data alone, it is not clear whether a lower dose than the MTD could be equally effective.

Study XL184-301 is a pivotal, phase III, multicenter, multinational, randomized, double blind, placebo-controlled study. The two arms design of the study with placebo as comparator is considered acceptable, as at the time the study was performed no other standard treatment options were available. The population enrolled in the pivotal study reflects the target population as mentioned by the wording of the proposed indication. Minor imbalances between demographic and baseline characteristics are observed, but it is not expected that such differences could affect study results. PFS (IRC-determined according to modified RECIST criteria) was the primary study endpoint.

Efficacy data and additional analyses

The choice of PFS as primary endpoint is considered acceptable. The results show a statistically significant improvement in PFS for cabozantinib compared with placebo (HR 0.28, 95% CI 0.19-0.40, p=0.0001), with a gain in median PFS of 7.2 months in favour of cabozantinib (median PFS 48.6 vs 17.4 weeks, respectively). Results are consistent with several sensitivity analyses, performed to evaluate robustness of the results and minimize the effect of potential informative censoring. The PFS effect appears to be maintained in all subgroups of the population treated, with the exception of patients with RET negative tumours where no statistical significance was achieved. The interim OS analysis, performed at the time of the primary PFS analysis and including 96 (44%) of death events did not show any significant difference between the two study arms (HR 0.98, 95% CI 0.63-1.52, p=0.9304, median OS 21.1 months vs NA with cabozantinib and placebo, respectively). A higher percentage of patients randomized to placebo received post-study local (18.9% vs 13.2%) and systemic (45% vs 21.9%) anticancer therapy, including vandetanib (16.2% vs 9.6%) and other TKIs (23.4% vs 9.6%).
Objective response rate (ORR: CR+PR, IRC assessed) was significantly higher with cabozantinib (27.9%) compared with placebo (0%). Disease stabilization rate was also significantly higher in the cabozantinib arm compared with the placebo arm (55.3% vs 13.5%, respectively).

In the evaluation of patient reported outcome according to the MDASI THY score, several cancer related symptoms (like gastrointestinal symptoms and feeling cold), were significantly more frequently observed and with greater severity in the cabozantinib versus the placebo arm at weeks 12 after start of treatment, possibly related to the toxicity of the drug.

Some evidence of activity appears to be observed in patients pre-treated with vandetanib (ORR: 7/25 (28%), median PFS 12.8 vs 2.8 months with vandetanib and placebo, respectively), as it is clear that 6 of 7 patients reporting tumor response after treatment with vandetanib actually stopped vandetanib treatment due to disease progression (data not shown).

Impact of RET status and Dose

Only a minority of patients had RET status determined on metastatic sites of disease. This raises concerns over the reliability of the RET mutation analysis procedures, in particular in patients reported

as RET mutation negative. In effect, in 2 out of the 14 patients where primary tumour as well as metastatic tumour tissues were available, a discrepancy was observed in RET mutational status, being negative in the primary tumour and positive in the metastatic tissue. This supports the hypothesis that several patients classified as RET mutation negative actually could have acquired RET mutations in the course of disease as the result of further tissue dedifferentiation. Otherwise, the different RET status determination within one patient could also point toward a validation-problem of the RET mutation procedure. As the precise mechanism of action of cabozantinib on RET remains unclear, the impact of RET mutation status on the efficacy of cabozantinib needs to be further ascertained in a dose comparative study (XL-184-401). In addition to this, the same study will address possibility of giving effective lower dosages with less toxicity.

Therefore, a conditional marketing authorisation was recommended to gather the missing information, taking into consideration that the risk-benefit balance of cabozantinib, as defined in Article 1(28a) of Directive 2001/83/EC, is positive (see Discussion on the benefit-risk balance.

In the framework of the conditional marketing authorisation, given the need to confirm the benefit risk balance in RET mutation negative or unknown MTC patients, the following statements were included in the Product Information:

Cometriq is indicated for the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma.

For patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in SmPC sections 4.4 and 5.1).

A relationship between prolonged PFS and significant improvement in OS (HR 0.53, p=0.0179) has been demonstrated only in the subgroup of RET M918T mutation positive patients (n=81/219 cabozantinib arm). OS has not yet been analysed in other RET and/or RAS mutation subgroups.

2.5.4. Conclusions on the clinical efficacy

A statistically significant improvement in PFS with cabozantinib compared with placebo has been observed in the pivotal XL184-301 study in patients with locally advanced or metastatic MTC, experiencing radiologic disease progression within 14 months before start of treatment. The 7 months improvement in median PFS is considered of clinical relevance and is supported by a statistically significant improvement in tumour response and duration of response associated with treatment with cabozantinib.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in patients with hereditary or sporadic medullary thyroid cancer.

Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumor tissue samples will be required from all enrolled subjects, and guidelines will be provided to maximize tissue quality. Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification

test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes).

PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolites in this population.

The CHMP considers the following measures necessary to address issues related to efficacy:

- A mature OS analysis including subgroup analyses on relevant demographic and baseline tumour characteristics and potential confounding effect of post-study therapies.

2.6. Clinical safety

Analysis of safety of cabozantinib has been based on the Safety Analysis Set, comprising of three clinical studies performed in cancer patients receiving at least one dose of 175 mg cabozantinib qd (n=295) or placebo (n=109), including a total of 348 (cabozantinib+placebo) subjects with MTC :

Table 26. Clinical Studies included in the cabozantinib's Safety Analysis Set

Study	Phase	Number of Subjects Treated	
		Cabozantinib 175 mg (138 mg freebase equivalent weight)	Placebo
Total (Safety Analysis Set)		295 (239 MTC, 56 non-MTC)	109 (109 MTC)
XL184-301	Phase 3	214 (MTC)	109 (MTC)
XL184-001	Phase 1	35 (25 MTC, 10 other solid tumours)	—
XL184-201 (Group A)	Phase 2	46 (GB)	—

—, not applicable; GB, glioblastoma multiforme; MTC, medullary thyroid cancer.

Patient exposure

Across all subjects included in the Safety Analysis Set, 295 subjects were treated with cabozantinib and 109 subjects were treated with placebo. In the pivotal XL184-301 phase III study, 330 patients with MTC were included, of which 323 were included in the safety population: 214 were treated with cabozantinib 175 mg qd and 109 with placebo. In Study XL184-301, the median duration of exposure was longer, approximately twice as long, for the cabozantinib arm compared with placebo (203.5 days [6.7 months] vs 105.0 days [3.4 months]), corresponding to a mean number of cycles received per subject of 9.4 and 5.6 in the cabozantinib arm and placebo arm, respectively. As of the clinical cut-off date of 15 June 2011 for the pivotal phase III XL184-301 study, about half of the subjects in the cabozantinib arm and most of the subjects in the placebo arm had discontinued study treatment (54.2% vs 86.2%). 23.8% and 55.0% of patients in the cabozantinib and placebo arm, respectively discontinued study drug due to disease progression. Discontinuation due to AEs or SAEs unrelated to disease progression occurred in 16.4% and 8.3% of patients, respectively.

Seventy-two percent of subjects treated with cabozantinib vs 28% of patients treated with placebo experienced dose interruptions. At least one dose reduction was needed in 79% of cabozantinib

treated patients. Two or more dose reductions occurred in 41.% of patients treated with cabozantinib, which implies that the majority of subjects did not tolerate the initial dose, i.e. the dose intended for marketing.

As a result of the frequent dose reductions only 54 subjects (25.2%) in the phase III XL184-301 study received cabozantinib at 175 mg daily as their final dose at the cut-off date, whereas 33.3% and 41.6% of subjects received 125 mg and 75 mg of cabozantinib as the final dose, respectively. The overall median dose intensity was lower in the cabozantinib arm compared with placebo (125.31 mg/day vs 175 mg/day), corresponding to a mean relative dose intensity of 71.60% vs 100.00% respectively.

Moreover, median duration of treatment for the 175 mg, 125 mg and 75 mg dose levels were 39, 52.5 and 91 days, respectively. The short duration of treatment with 175 mg indicates also that this dose was not tolerated by the patients. Relative dose intensity in the cabozantinib group decreased quickly over the first four 4-week cycles in this study, whereas in the placebo group, relative dose intensity was generally more stable over time. The median time to first dose reduction in the cabozantinib arm was only 43 days.

High inter-subject variability in exposure has been demonstrated with PopPK analysis Subjects with higher model-predicted oral clearance (ie, those with low predicted steady state cabozantinib AUC values) tended to dose reduce later in the course of treatment.

Adverse events

Adverse events were coded according to MedDRA system. All AEs were graded by the investigators per Common Terminology Criteria for Adverse Events (CTCAE) v3.0. A treatment-emergent adverse event (TEAE) was any AE or laboratory abnormality that started or worsened after the first dose of study treatment.

In the pivotal phase III XL184-301 study 100% of patients in the cabozantinib arm versus 94.5% of patients in the placebo arm experienced a TEAE, of which 98.6% vs 74.3%, respectively, were assessed as drug related. Treatment related grade 3 or 4 TEAEs occurred more frequently in the cabozantinib group (64.0%) vs placebo group (19.3%) (Table 14). The level of AEs in the placebo arm of Study XL184-301 indicate that the underlying disease generate numerous disease related AEs. However, Grade 3 or 4 TEAEs, SAEs and deaths due to other causes than PD were all experienced approximately more than twice as often in the cabozantinib arm as in the placebo arm, indicating that cabozantinib treatment is accompanied by numerous important AEs.

Table 27. Overview of Treatment Emergent Adverse Events (Safety Analysis Set)

	XL184-001 Cabozantinib (175 mg) (N = 35)	XL184-301 Cabozantinib (175 mg) (N = 214)	XL184-301 Placebo (N = 109)	XL184-201 Cabozantinib (175 mg) (N = 46)
TEAEs	35 (100.0%)	214 (100.0%)	103 (94.5%)	46 (100.0%)
Treatment-related TEAEs	34 (97.1%)	211 (98.6%)	81 (74.3%)	45 (97.8%)
Grade 3 or 4 TEAEs	28 (80.0%)	148 (69.2%)	36 (33.0%)	39 (84.8%)
Treatment-related Grade 3 or 4 TEAEs	22 (62.9%)	137 (64.0%)	21 (19.3%)	34 (73.9%)
Grade 5 TEAEs	2 (5.7%)	17 (7.9%)	8 (7.3%)	0
Treatment-related Grade 5 TEAEs	0	9 (4.2%)	2 (1.8%)	0
SAEs	22 (62.9%)	90 (42.1%)	25 (22.9%)	24 (52.2%)
Treatment-related SAEs	6 (17.1%)	71 (33.2%)	7 (6.4%)	13 (28.3%)
TEAEs leading to dose modification[a]	29 (82.9%)[b]	185 (86.4%)	24 (22.0%)	37 (80.4%)[c]
TEAEs leading to discontinuation of study drug	11 (31.4%)	35 (16.4%)	9 (8.3%)	10 (21.7%)
Total deaths	12 (34.3%)	65 (30.4%)	30 (27.5%)	38 (82.6%)
Deaths through 30 days of last dose of study drug	2 (5.7%)	22 (10.3%)	8 (7.3%)	6 (13.0%)
Deaths due to causes other than PD	2 (5.7%)	12 (5.6%)	3 (2.8%)	0

AE, adverse event; CRF, case report form; CSR, clinical study report; PD, progressive disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
Adverse events were graded per NCI-CTCAE V3.0.
At each level of summarization, a subject is counted only once if the subject reported one or more events.
[a] Dose modifications included dose reduction or treatment interruption reported either as 'Drug interrupted' or 'Dose decreased' on the CRF for adverse events. For a given AE, both a reduction and interruption could have occurred but only one action could be recorded on the AE CRF.
[b] Five additional subjects are included here but are not included in the XL184-001 CSR (XL184-001 CSR Section 12.1.2.2). Three subjects (001-01-99-085, 001-02-99-062, 001-01-12-048) have errors in the adverse event data (XL184-001 CSR Listing 16.2.4.1.1). Two subjects (001-05-99-080, 001-05-99-088) discontinued study treatment while experiencing a dose interruption. In the XL184-001 CSR, study drug interruptions after the last dose were not included in the analysis of dose modifications.
[c] Two additional subjects had a study drug interruption reported as due to an AE, but "drug interrupted" was not reported as the action taken for an AE (XL184-201 CSR Section 12.4.3.1).
Source: Table 16, Table 17, SCS Table 2.1, SCS Table 2.18.

TEAEs (any grade, by preferred term) more frequently observed (≥20% difference) with cabozantinib compared with placebo were palmar plantar erythrodysesthaesia syndrome (=hand-foot syndrome, PPE) (50.0 % vs 1,8%), weight loss (47.7% vs 10.1%), hair colour changes (33.6% vs 0.9%), decreases appetite (45.8% vs 15.6%), diarrhea (63.1% vs 33.0%), dysgeusia (34.1% vs 5.5%), stomatitis (29.0% vs 2.8%), hypertension (29.4% vs 3.7%), vomiting (24.3% vs 1.8%), and nausea (43.0 vs. 21.1). All these AEs were judged by the investigator as at least possibly drug related.

Regarding grade 3 or 4 TEAEs a similar pattern was observed: 64.0% of patients receiving cabozantinib experienced a grade 3 or 4 treatment related TEAEs versus 19.3% of patients receiving placebo.

The most common grade ≥3 AEs more frequently seen in the cabozantinib arm compared to the pacebo arm were: diarrhoea (15.9% cabozantinib arm, 1.8% placebo arm), PPE (12.6% vs 0%),

weight loss (4.7% vs 0%), decreased appetite (4.7% vs 0.9%), nausea (1.4% vs 0%), and fatigue (9.3% 2.8%). In contrast, there was a higher incidence of Grade ≥3 dyspnoea in the placebo arm (2.3% vs 10.1%).

Grade 4 AEs occurred in 14.5% of subjects in the cabozantinib arm vs 10.1% in the placebo arm; the most frequently reported were hypocalcaemia (3.3% in the cabozantinib arm versus 0% in the placebo arm) and pulmonary embolism (2.3% vs 0.9%).

Several of the most common Grade 3 or higher TEAEs (e.g. diarrhoea and PPE) were not among the most frequently reported SAE, indicating that the majority of the Grade 3 or higher TEAEs may not be life-threatening. However, in a palliative setting numerous Grade 3 or higher TEAEs is of concern.

Moreover, It is evident that most grade 3 or higher AEs occurred with 175 mg of cabozantinib and within the first cycles of treatment. Although many AEs tend to be reversible over time with the appropriate dose reductions applied, some AEs like PPE and diarrhea only resolve slowly over time and tend to persist, which will likely negatively influence quality of life over a longer period of time. These results further underscore the importance an appropriate dose finding to prevent patients receiving a too high starting dose of 175 mg of cabozantinib.

Table 28. Summary of Frequent adverse events sorted by preferred terms in decreasing order of the difference (≥10%) in percentage between cabozantinib and placebo arms in study XL184-301

MedDRA Preferred Term	XL184-001 Cabozantinib (175 mg) (N = 35)	XL184-301 Cabozantinib (175 mg) (N = 214)	XL184-301 Placebo (N = 109)	XL184-201 Cabozantinib (175 mg) (N = 46)
Subjects with a TEAE	35 (100.0%)	214 (100.0%)	103 (94.5%)	46 (100.0%)
Palmar-plantar erythrodysaesthesia syndrome	22 (62.9%)	107 (50.0%)	2 (1.8%)	17 (37.0%)
Weight decreased	16 (45.7%)	102 (47.7%)	11 (10.1%)	13 (28.3%)
Hair colour changes	12 (34.3%)	72 (33.6%)	1 (0.9%)	10 (21.7%)
Decreased appetite	26 (74.3%)	98 (45.8%)	17 (15.6%)	22 (47.8%)
Diarrhoea	29 (82.9%)	135 (63.1%)	36 (33.0%)	31 (67.4%)
Dysgeusia	12 (34.3%)	73 (34.1%)	6 (5.5%)	7 (15.2%)
Stomatitis	3 (8.6%)	62 (29.0%)	3 (2.8%)	17 (37.0%)
Hypertension	12 (34.3%)	63 (29.4%)	4 (3.7%)	18 (39.1%)
Vomiting	22 (62.9%)	52 (24.3%)	2 (1.8%)	13 (28.3%)
Nausea	25 (71.4%)	92 (43.0%)	23 (21.1%)	17 (37.0%)
Constipation	17 (48.6%)	57 (26.6%)	6 (5.5%)	22 (47.8%)
Mucosal inflammation	8 (22.9%)	50 (23.4%)	4 (3.7%)	3 (6.5%)
Dry skin	8 (22.9%)	41 (19.2%)	3 (2.8%)	14 (30.4%)
Hypocalcaemia	6 (17.1%)	45 (21.0%)	5 (4.6%)	4 (8.7%)
Alanine aminotransferase increased	13 (37.1%)	46 (21.5%)	6 (5.5%)	15 (32.6%)
Aspartate aminotransferase increased	12 (34.3%)	46 (21.5%)	6 (5.5%)	16 (34.8%)
Blood lactate dehydrogenase increased	1 (2.9%)	40 (18.7%)	3 (2.8%)	11 (23.9%)
Alopecia	4 (11.4%)	35 (16.4%)	2 (1.8%)	2 (4.3%)
Oropharyngeal pain	6 (17.1%)	38 (17.8%)	5 (4.6%)	12 (26.1%)
Oral pain	11 (31.4%)	29 (13.6%)	1 (0.9%)	5 (10.9%)
Fatigue	28 (80.0%)	87 (40.7%)	31 (28.4%)	35 (76.1%)
Dyspepsia	4 (11.4%)	24 (11.2%)	0	6 (13.0%)
Dysphonia	7 (20.0%)	43 (20.1%)	10 (9.2%)	18 (39.1%)
Abdominal pain	10 (28.6%)	36 (16.8%)	7 (6.4%)	12 (26.1%)
Blood thyroid stimulating hormone increased[a]	NA	28 (13.1%)	3 (2.8%)	NA
Glossodynia	5 (14.3%)	22 (10.3%)	0	4 (8.7%)

MedDRA, Medical Dictionary for Regulatory Activities; NA, not applicable; PT, preferred term; TEAE, treatment-emergent adverse event.
Reported adverse events were coded using MedDRA V14.0.
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.
[a] Blood thyroid stimulating hormone was not collected in Studies XL184-001 and XL184-201.
Source: SCS Table 2.15.

Adverse reactions are listed in Table 29 according to MedDRA system organ class and frequency categories. Frequencies are based on all grades and defined as: very common (≥1/10), common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 29. Adverse reactions reported with cabozantinib

System Organ Class	Very Common	Common	Uncommon
Infections and infestations		abscess (including visceral, skin, tooth), pneumonia, folliculitis, fungal infection (including skin, oral, genital)	aspergilloma
Endocrine disorders		hypothyroidism	
Metabolism and nutrition disorders	decreased appetite, hypocalcaemia, hypophosphataemia, hyperbilirubinemia, hypoalbumenia	dehydration	
Psychiatric disorders		anxiety, depression, confusional state	abnormal dreams, delirium
Nervous system disorders	dysgeusia, headache, dizziness	peripheral neuropathy, paraesthesia, ageusia, tremor	ataxia, disturbance in attention, hepatic encephalopathy, loss of consciousness, speech disorder, transient ischaemic attack, posterior reversible encephalopathy syndrome
Eye disorders		vision blurred	cataract, conjunctivitis
Ear and labyrinth disorders		ear pain, tinnitus	hypoacusis
Cardiac disorders		atrial fibrillation	angina pectoris, supraventricular tachycardia
Vascular disorders	hypertension	hypotension, venous thrombosis, pallor, peripheral coldness	arterial thrombosis
Respiratory, thoracic, and mediastinal disorders	dysphonia, oropharyngeal pain	non-gastrointestinal fistula (including tracheal, pneumomediastinum, tracheo-oesophageal), pulmonary embolism, respiratory tract haemorrhage (including pulmonary, bronchial, tracheal), pneumonia aspiration	atelectasis, pharyngeal oedema, pneumonitis

System Organ Class	Very Common	Common	Uncommon
Gastrointestinal disorders	diarrhoea, nausea, stomatitis, constipation, vomiting, abdominal pain, dysphagia, dyspepsia, glossodynia	gastrointestinal perforation, gastrointestinal haemorrhage, pancreatitis, haemorrhoids, anal fissure, anal inflammation, cheilitis	gastrointestinal fistula, oesophagitis
Hepatobiliary disorders		cholelithiasis	
Skin and subcutaneous tissue disorders	palmar-plantar erythrodysaesthesia syndrome, hair colour changes, rash, dry skin, alopecia, erythema	hyperkeratosis, acne, blister, hair growth abnormal, skin exfolation, skin hypopigmentation	skin ulcer, telangiectasia
Musculoskeletal and connective tissue disorders	arthralgia, muscle spasms	musculoskeletal chest pain, osteonecrosis of jaw	Rhabdomyolysis
Renal and urinary disorders		proteinuria, dysuria, haematuria	renal failure acute
Reproductive system and breast disorders			amenorrhoea, vaginal haemorrhage
General disorders and administration site conditions	fatigue, mucosal inflammation, asthenia	impaired wound healing, chills, face oedema	cyst, facial pain, localised oedema
Investigations	weight decreased, serum ALT, AST, and ALP increased, blood LDH increased, blood TSH increased, lymphopenia, neutropenia, thrombocytopenia	blood creatinine phosphokinase increased, neutrophil count decreased	activated partial thromboplastin time shortened, eosinophil count increased, platelet count increased

Adverse Events of special interest (AESI)

Consistent with the expected pharmacology, the pre-clinical toxicology profile and the mechanism of action of cabozantinib including VEGF inhibition and the population treated, AEs of special interest (AESI) included gastrointestinal perforation, gastrointestinal fistula, intra-abdominal and pelvic abcess, non-gastrointestinal fistula, hemorrhage (CNS and non-CNS), osteonecrosis, thromboembolism (venous and arterial), hepatocellular toxicity, and pancreatitis.

Gastrointestinal (GI) Perforation

In the pivotal study XL184-301, GI perforation occurred in 7 (3.3%, all grade 3 or 4) patients treated with cabozantinib vs 0 percent in the placebo group. No grade 5 perforation was seen. No GI perforation occurred in studies XL184-001 and XL184-201. Three of 7 patients with GI perforation had

underlying GI disorders prior to study entry, including Crohn's disease, chronic pancolitis, irritable bowel disease and diverticulosis.

Gastrointestinal fistula

Two patients treated with cabozantinib in the X184-301 experienced GI fistula: one patient developed a grade II anal fistula resulting from an anal abcess, and one patient with metastases to the neck, lung, and pre-tracheal and para-tracheal lymph nodes, prior radiation therapy to the neck and an extensive surgical history, developed a grade 5 (fatal) oesophageal fistula. No events of gastro-intestinal fistula occurred in the placebo group.

There was one event of grade 3 gastric fistula observed in Study XL184-001.

Abcesses

In the cabozantinib arm abcess AEs were reported more frequently than in the placebo arm in Study XL184-301 (7.9% vs 0%). In the cabozantinib arm, the median time to first incidence was 17 weeks; the most frequently reported in the cabozantinib arm were tooth abscess (3.3% vs 0%), anal abscess (1.4% vs 0%), and lung abscess (1.4% vs 0%).

Five patients (2.3%) treated with cabozantinib in study XL184-301 experienced intra-abdominal or pelvic abscesses. There were three Grade 2 anal abcesses and two Grade 3 events (peridiverticular abcess and peritoneal abcess). There were no Grade 4 or 5 events of intra-abdominal and pelvic abscesses. The incidence of events of intra-abdominal and pelvic abscess was higher in phase I Study XL184-001 and similar in Study XL184-201 compared with the cabozantinib arm of Study XL184-301 (5.7% and 2.2%, respectively vs 2.3%). Of the five subjects who experienced events of intra-abdominal or pelvic abscess in Study XL184-301, one event was associated with a Grade 3 event of large intestine perforation and one event was associated with a Grade 2 anal fistula.

Non-gastrointestinal perforation and fistulas

In the pivotal XL184-301 study, non-gastrointestinal perforation occurred in 8 patients (3.7%), including 3 patients with a trachea-oesophageal fistula, 2 patients with a tracheal fistula, 1 patient with a sinus fistula, 1 patient with a nasal septum perforation and 1 patient with a pneumomediastinum. One patient with an extensive prior history of neck surgery and radiation therapy died due to the trachea-oesophageal fistula. Median time to development of a clinical fistula was 11.5 weeks in patients treated with cabozantinib. No non-gastro-intestinal fistulas occurred in the placebo group and in studies XL184-001 and XL184-201.

Five out of 6 subjects who experienced tracheal fistula, acquired trachea-oesophageal fistula, or pneumomediastinum had lung metastasis at baseline. One of these subjects also had metastasis to the bronchus and four of these subjects also had mediastinal metastasis at baseline. One subject had metastasis to the mediastinum and partial infiltration of the trachea. Only one of these subjects had received prior radiotherapy to the mediastinum. Therefore, tumour infiltration in the trachea and prior radiotherapy might be risk factors for development of trachea(-oesophageal) fistulas.

Non-CNS haemorrhage

Non-CNS haemorrhage occurred more frequently in the cabozantinib arm compared to the placebo arm in Study XL184-301 (3.3% vs 0.9%). In the cabozantinib arm of Study XL184-301, the median time to first occurence of non-CNS haemorrhage AE was 13 weeks. Grade 3 events consisted of haemorrhoidal haemorrhage, colonic haematoma, duodenal ulcer haemorrhage, and intestinal haemorrhage. There was one grade 4 hemoptysis in a patient with a medical history of hemoptysis. There were 2 grade 5 events which consisted of one event of haemorrhage and one event of haemoptysis.

Non-CNS haemorrhage occurred at similar rates in Studies XL184-001 and XL184-201 compared with the cabozantinib arm of Study XL184-301 (2.9% and 6.5%, respectively vs 3.3%).

CNS haemorrhage

Only in study XL-184201 where patients with GB were treated with cabozantinib, CNS haemorrhage occurred in 2 (4.3%) patients. No CNS haemorrhages were reported in Study XL184-301 within 30 days after the last study drug administration, whereas one patients reported a grade 2 intracranial haemorrhage more than 30 days after the last administered dose of cabozantinib.

Osteonecrosis

Osteonecrosis occurred in 1.4% of patients treated with cabozantinib in study XL-184-301 versus 0% in patients treated with placebo. In the cabozantinib arm, the median time to first incidence of osteonecrosis was 21 weeks. The incidence of Grade 3 osteonecrosis of the jaw was 0.5%, which was reported as a SAEs as well. In these patients, 2 out of 3 had a history of osteonecrosis of the jaw or tooth infection prior to the event of osteonecrosis.

Arterial and venous thromboembolism

Five (2.3%) patients receiving cabozantinib in the XL-184-301 study experienced arterial thromboembolism, all of except one were SAEs. No arterial thromboembolism occurred in the placebo group. Mean time to occurrence was 19.0 weeks. Events included transient ischemic attack, arterial thrombosis of the limb, cerebral infarction, and thrombosis. There were no grade 4 or 5 AEs of arterial thromboembolism in study XL 184-301. One patient who experienced a TIA had cardiovascular risk factors. Two other patients in which arterial thromboembolism occurred underwent procedures that increased the risk for such event.

The incidence of venous thromboembolism was higher in the cabozantinib arm versus the placebo arm in Study XL184-301 (5.6%; (grade 3 or 4: 4.2%) vs 2.8%). In the cabozantinib arm in Study XL184-301, the median time to first incidence was 13 weeks. The incidence of events of venous thromboembolism was slightly higher in Study XL184-001 compared to study XL184-201 and to the cabozantinib arm in Study XL184-301 (8.6% and 4.3%, respectively vs 5.6%).

Hepatotoxicity

Hepatocellular toxicity (including hepatic failure, hepatotoxicity, toxic hepatitis) occurred more often in the cabozantinib group versus the placebo arm in Study XL184-301 (2.8% vs 0.9%). There was one event of Grade 5 hepatic failure in the cabozantinib arm: the subject had liver metastases and had discontinued cabozantinib due to progressive disease. There was one event of Grade 5 hepatic failure

in the placebo group as well. Four out of the 6 cabozantinib-treated subjects who experienced hepatocellular toxicity had liver metastases. There were no events of hepatocellular toxicity reported in studies XL184-001 and -201.

Four cabozantinib-treated and 3 placebo-treated subjects had drug-induced liver injury based on laboratory findings. Three of the cabozantinib-treated subjects had liver metastases at baseline and one patient had a history of Gilbert's disease.

Pancreatitis

Pancreatitis was more frequently reported in the cabozantinib arm versus the placebo arm in Study XL184-301 (5 patients: 2.3% vs 1 patient: 0.9%). In the cabozantinib arm in Study XL184-301 median time to first incidence was 36 weeks. All grade 3 events (1.4%) in the cabozantinib arm were reported as SAE. There were no Grade 4 or 5 events of pancreatitis.

Palmar-plantar erythrodysesthesia syndrome (PPE)

Palmar-plantar erythrodysesthesia syndrome (PPE) was very common (50.0%; 12.6% Grade 3, 21.5% Grade 2, and 15.4% Grade 1) in the cabozantinib arm compared to placebo (1.8%) in study XL184-301. There were no grade 4 or 5 PPE events.

In study XL184-001 PPE occurred even more frequently: 62.9% of patients experienced PPE, in 20% was of grade 3 severity.

Weight loss

In study XL184-301 weight loss was more frequently reported in the cabozantinib arm compared with the placebo arm (47.7% vs. 10.1%; grade 3 4.7% vs 0%). No SAEs of weight decreased were reported. The incidence of subjects with a >10% weight loss from baseline was 43.0% in the cabozantinib arm and 16.5% in the placebo arm. Concomitant symptoms in this group were diarrhoea (80.4%), anorexia (62.0%), mucositis (57.6%), nausea/vomiting (60.9%), dysgeusia/ageusia, and abdominal pain (34.8%). Weight loss AEs resulted in dose modification in 12.6% of cabozantinib treated subjects and in 0% of placebo treated subjects.

Mucositis

Mucositis-related AEs were more frequently reported in the cabozantinib (58%) arm of Study XL184-301 compared with placebo (6.5%). The most frequently reported Preferred Terms (PT) in the cabozantinib arm were stomatitis (29.0%; 1.9% Grade 3) and mucosal inflammation (23.4%; 3.3% Grade 3). Events were generally manageable with dose reductions. Only few patients discontinued treatment with cabozantinib because of diarrhea or mucositis.

Pneumonia

Pneumonia occurred at similar rates in both groups of study XL184-301: 3,7% in the cabozantinib arm vs 3.7% in the placebo arm. Pneumonia aspiration (2.8% vs. 0.9%), bronchopneumonia (0.9% vs. 0%), pneumonitis (0.9% vs 0%), lung infiltration (0.5% vs 0%), and bacterial pneumonia (0.5% vs. 0%) occurred more often in the cabozantinib arm compared with the placebo arm.

There was 1 grade 5 aspiration, 1 grade 5 bronchopneumonia and 1 grade 5 pneumosepsis reported in the cabozantinib arm, whereas 2 subjects in the placebo arm died of pneumonia.

Wound complication

A 1.9% rate of wound complications was reported in the cabozantinib arm versus 0.9% in the placebo arm of study XL184-301. There were no grade 4 or 5 events.

Reversible posterior leuco-encephalopathy (RPLS)

One patient experienced grade 4 RPLS in the cabozantinib arm of study XL184-301, which AE was reported as a SAE as well.

Hypertension

Hypertension occurred frequently in the cabozantinib arm of Study XL184-301 compared with placebo (29.4% vs 3.7%). Five events (2.3%) in the cabozantinib arm of Study XL184-301 were reported as SAEs. Grade 3 hypertension was reported in 7.9% of subjects treated with cabozantinib and in 0% of patients treated with placebo. There were no Grade 4 or 5 events of hypertension and nearly all of these events were reported to be related to study medication (26.2% with cabozantinib, 3.7% with placebo). The incidence of hypertension was similar in Studies XL184-001 and XL184-201 compared with the cabozantinib arm in Study XL184-301 (34.3% and 39.1%, respectively vs 29.4%).

Hypocalcemia

In Study XL184-301, there was a higher incidence of hypocalcaemia in the cabozantinib arm compared with placebo (21.0% [grade 3 9.3%] vs 4.6% [grade 3:0%]). Six events (2.8%) in the cabozantinib arm of Study XL184-301 were reported as SAEs.

Elevated TSH

In Study XL184-301, there was a higher incidence of serum TSH increase in the cabozantinib arm compared with the placebo arm (13.1% vs 2.8%, respectively). The events were of Grade 1 intensity (8.9% cabozantinib arm, 1.8% placebo arm) or Grade 2 (4.2%, 0.9%).

A thyroid stimulating hormone (TSH) value above normal after first dose was observed in 57% of patients on cabozantinib versus 19% of patients on placebo (regardless of baseline values). Ninety-two percent of patients on the cabozantinib arm had a prior thyroidectomy, and 89% were taking thyroid hormones prior to first dose.

QT prolongation

The effect of cabozantinib on QT interval prolongation was evaluated in study XL184-301. Electrocardiograms were obtained in triplicate at screening, at pre-dose and 2, 4 and 6 hours post-dose during Day 1 (C1D1), and Day 29 (C2D1), and centrally read by a cardiologist blinded to study treatment. All scheduled ECG assessments on Days 1 and 29 were time matched with PK samples.

No ECG's were performed in healthy subjects for ethical reasons.

No increase in QTcF change from baseline (ie, delta-QTcF) for cabozantinib-treated subjects was seen on Day 1, but a significant increase was seen on Day 29 for the cabozantinib arm versus placebo:

+11.5 ms in the cabozantinib group vs. 1.7 ms in the placebo group 2 hours post-dose, 8.4 ms vs -0.8 ms 4 hours post-dose and 7.9 vs -2.3 ms 6 hours post-dose.

Although data in the high range cabozantinib concentrations are limited, delta QtcF seems to increase with higher cabozantinib concentrations.

Overall, these results suggest a mild to moderate increase of mean QTcF at day 29 (where steady state plasma concentrations of cabozantinib have been reached) of 10 ms (upper bound of one-sided 95% CI <15 ms) from baseline. A total of 5 patients treated with cabozantinib in the XL184-301 study experienced QT prolongations (3 of grade 1; 1 of grade 2). This effect was not associated with a change in cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects had a QTcF >500 ms (see SmPC section 4.8).

No other cardiac arrhythmias including Torsade de pointes have been reported. The PR interval and QRS interval did not show changes considered clinically relevant.

Cardiac related events

There were two patients with cardiopulmonary failure in study XL184-301: one (0.9%) in the cabozantinib and one in the placebo group (0.9%). The patient in the cabozantinib arm with a medical history of dysphagia experienced grade 4 cardiac arrest and subsequently grade 5 cardiopulmonary failure, possibly related to aspiration of study medication.

Serious adverse event / deaths / other significant events

In the XL184-301 study SAEs occurred more frequently in the cabozantinib arm compared with the placebo arm (42.1% vs 22.9%). The incidence of SAEs in Studies XL184-001 and XL184-201 were similar to XL184-301. SAEs that occurred more frequently in the cabozantinib arm compared with the placebo arm were hypocalcaemia (2.8% vs 0%), mucosal inflammation (2.8% vs 0%), hypertension (2.3% vs 0%), and pulmonary embolism (2.3% vs 0%), all of which were regarded as treatment related. Overall, the incidence of SAEs considered by the investigator to be treatment-related was 33.2% in the cabozantinib arm and 6.4% in the placebo arm (Table 30).

Table 30. Summary of Serious Adverse Events (Preferred Terms with ≥1%Incidence in the Study XL184-301 Cabozantinib Arm) (Safety Analysis Set)

Preferred Term	XL184-001 Cabozantinib (175 mg) (N = 35)	XL184-301 Cabozantinib (175 mg) (N = 214)	XL184-301 Placebo (N = 109)	XL184-201 Cabozantinib (175 mg) (N = 46)
Subjects with a serious TEAE	22 (62.9%)	90 (42.1%)	25 (22.9%)	24 (52.2%)
Pneumonia	2 (5.7%)	7 (3.3%)	3 (2.8%)	0
Hypocalcaemia	0	6 (2.8%)	0	0
Mucosal inflammation	0	6 (2.8%)	0	0
Dehydration	1 (2.9%)	5 (2.3%)	1 (0.9%)	1 (2.2%)
Dysphagia	0	5 (2.3%)	2 (1.8%)	0
Hypertension	0	5 (2.3%)	0	0
Pulmonary embolism	1 (2.9%)	5 (2.3%)	0	2 (4.3%)
Fatigue	0	4 (1.9%)	1 (0.9%)	1 (2.2%)
Pneumonia aspiration	1 (2.9%)	4 (1.9%)	1 (0.9%)	1 (2.2%)
Vomiting	1 (2.9%)	4 (1.9%)	1 (0.9%)	1 (2.2%)
Abdominal pain	3 (8.6%)	3 (1.4%)	0	1 (2.2%)
Acquired tracheo-oesophageal fistula	0	3 (1.4%)	0	0
Diarrhoea	0	3 (1.4%)	1 (0.9%)	2 (4.3%)
Hypokalaemia	0	3 (1.4%)	0	0
Hypotension	0	3 (1.4%)	0	0
Lipase increased	0	3 (1.4%)	1 (0.9%)	1 (2.2%)
Lung abscess	1 (2.9%)	3 (1.4%)	0	0
Multi-organ failure	0	3 (1.4%)	0	0
Palmar-plantar erythrodysaesthesia syndrome	1 (2.9%)	3 (1.4%)	0	0
Pancreatitis	0	3 (1.4%)	0	1 (2.2%)
Sepsis	1 (2.9%)	3 (1.4%)	0	0
Thrombocytopenia	0	3 (1.4%)	0	0

TEAE, treatment-emergent adverse event.
Reported adverse events were coded using MedDRA V14.0.
At each level of summarization, a subject was counted once for the most severe event if the subject reported one or more events.
Source: SCS Table 2.10.

The SAEs with a median onset within the first 30 days of study treatment included abdominal pain, hypocalcemia, thrombocytopenia, hypertension, vomiting, PPE, and hypokalaemia. Median time to first toxicity for GI perforation, GI fistula and Intra-abdominal/Pelvic Abscess was 7, 29 and 2 weeks, respectively. Although there are few observations, it appears as if at least half of such events occurred during the first two months of treatment, adding additional uncertainty to whether dose reductions is a suitable strategy to avoid SAEs.Overall, in study XL184-301, the incidence of deaths in the cabozantinib arm was slightly higher than in the placebo arm (30.4% vs 27.5%). There was a higher incidence of deaths in the cabozantinib arm within 30 days of last dose (10.3% vs 7.3%). Of note, in spite of the high frequencies of dose reductions and the short median time interval patients received

175 mg dose, half (11/22) of deaths through 30 days after the last dose in the cabozantinib arm occurred at the highest dose level.

The number of subjects experiencing an SAE decreases with lower doses: 29%, 22% and 17% of subjects experienced an SAE among those who received the 175, 125 and 75 mg dose levels

respectively

Most frequent occuring SAEs had a lower frequency during the period after the final dose reduction, with the exception of dysphagia (rates are similar before and after last dosereduction but equivalent to rates in the placebo arm) and pulmonary embolism (2 events[0.002 per person month] before final dose reduction vs. 3 events [0.003 per person month]after final dose reduction).

The incidence of deaths after 30 days of last dose was similar in both arms (20.1% vs 20.2%).

Almost 80% of patients in the pivotal phase III study were younger than 65 years, not fully representing the clinical population with MTC. Although SAES in patients aged 74 years and younger did not differ from SAEs in the 75+ group and data were very limited, a trend in increased rate of SAEs in the 75+ group of patients treated with cabozantinib have been observed compared to patients aged 74 years and younger (61.5% vs. 40.1%).

Deaths

Overall, in study XL184-301, the incidence of deaths in the cabozantinib arm was slightly higher than in the placebo arm (30.4% vs 27.5%). There was a higher incidence of deaths in the cabozantinib arm within 30 days of last dose (10.3% vs 7.3%). The incidence of deaths after 30 days of last dose was similar in both arms (20.1% vs 20.2%).

The incidence of death through 30 days of last dose due to disease progression was similar between the cabozantinib and the placebo arm (4.7% vs 4.6%). However, death due to other causes occurred more frequently in the cabozantinib arm than in the placebo arm (5.6% vs 2.8%). These included infections (3 cases; 1.4%), fistula (3 cases;1,4%) respiratory failure (2 cases; 0.9%), haemorrhage (1 case; 0.4%). In three patients, the cause of death was listed as sudden death, death, cause not otherwise specified (NOS), cardiopulmonary failure, or cardiac arrest (multiple causes specified for one case).

Review of the case narratives suggests no potential association of these death events to Torsades de Pointes (related to QTc prolongation). When analysing, causes of death appear to be heterogeneous and might be confounded by underlying disease factor. However, the more frequent occurrence of fatal fistulas and hemorrhage have been observed with other VEGF inhibitors.

For all grade 5 SAEs combined, the rate was the same before and after the last dose reduction of cabozantinib (9 events [0.009 per person-month] in each period) and the overall rate per person-month of Grade 5 SAEs in the cabozantinib arm was lower than in the placebo arm

The reasons for death in the placebo arm were progressive disease (5 subjects); shock (1 case; 0.9%), acute respiratory distress (1 case; 0.9%), and general deterioration (1 case; 0.9%).

The incidence of deaths in Study XL184-001 was similar to that in the cabozantinib arm in Study XL184-301 (34.3% vs 30.4%). The overall incidence of deaths in cabozantinib-treated subjects in Study XL184-201 was higher than in the cabozantinib arm of Study XL184-301 (82.6% vs 30.4%),

probably due to the higher mortality rate in patients with glioblastoma compared to patients with progressive MTC.

Laboratory findings

In study XL184-301 the most common hematological abnormalities were: lymphopenia (53.3% vs 47.7% in the cabozantinib vs placebo arm, respectively, with 15,4 % and 9.2 % being grade 3 AEs), neutropenia (35.0% vs 12.8% in the cabozantinib vs placebo arm, respectively, with 2.8 % and 1.8 % being grade 3 AEs), and decreased platelets (34.6% vs 3.7%, respectively, with 0% and 2.8% being grade 3 AEs). Decreased haemoglobin was equally reported in the cabozantinib (39.3%; grade 3 or 4 AEs 1.9%) and placebo (40.4%; grade 3 or 4 AEs 3.7%) arms.

The most common biochemical abnormalities were liver chemistry abnormalities: AST increase (86.4% vs 30.3% in the cabozantinib and placebo arms, respectively, with 3.3% vs 1.8% being grade 3 or 4 AEs), ALT increase (85.5% vs 39.4%, respectively, with 6.1% vs 1.8% being grade 3 or 4 AEs), ALP increased (51.4% vs 32.1%, respectively, with 1.9% vs 2.8% being grade 3 or 4 AEs), decreased albumin (43.0% vs 15.6%, respectively, with 1.9% vs 0% being grade 3 or 4 AEs), total bilirubin increased (24.8% vs 13.8%, respectively, with 1.4% vs 4.6% being grade 3 or 4 AEs).

The most common grade 3 or 4 other biochemical abnormalities were decreased calcium (12.1% in the cabozantinib arm vs. 2.8% in the placebo arm), increased lactate dehydrogenase (35.0% vs 3.7%), increased lipase (11.2% vs. 9.2%), increased amylase (4.7 vs 7.3%), decreased potassium (3.7 vs. 2.8%), decreased phosphorus (3.3% vs 0.9%), and proteinuria (1.4% vs 0%).

Grade 3 events of activated PTT increased occurred in 7 (3.3%) subjects in the cabozantinib arm and no placebo subject.

Regarding thyroid function, hypothyroidism was reported as an AE in 9.3% of cabozantinib subjects and 0.9% of placebo subjects. Serum TSH increase occurred in 13.1% of cabozantinib subjects versus 2.8% of placebo subjects. Of note, at enrolment, most subjects in each treatment group had prior thyroidectomy (91.8% in the cabozantinib group and 93.7% in the placebo group), and 89.3% of cabozantinib treated subjects and 91.7% of placebo-treated subjects were taken thyroid hormone replacement therapy.

Safety in special populations

A population PK analysis was performed based on a pooled analysis of cabozantinib plasma concentrations from Studies XL184-001 (capsule cohorts: 175 mg/day and 250 mg/day, N = 40), XL184-201 (Group A, N = 39), and XL184-301 (N = 210). The dose was 175 mg/day of the L-malate salt form of cabozantinib, except for five subjects in Study XL184-001 who were dosed at 250 mg/day.

Grade > 3 liver biochemistry abnormality appears to correlate with AUC steady state levels of cabozantinib, where for weight loss and diarrhea, correlations were not that clear. Of note, AE of palmar-plantar erythrodysesthesia (PPE (Grade >1) in cabozantinib-treated subjects did not show a correlation with AUC, although results were difficult to interpret because many subjects experienced dose reductions or interruptions.

Hepatic impairment

No studies specifically in patients with hepatic impairment have been conducted. All patients included in the studies performed with cabozantinib were required to have bilirubin ≤ 1.5x ULN and ASAT/ALAT ≤ 2.5. No treatment related AEs were sorted out by severity of liver dysfunction.

Renal impairment

No studies in patients with renal impairment have been conducted. All patients included in the studies performed with cabozantinib to date were required to have serum creatinine ≤ 1.5x ULN.
Based on baseline calculated creatinine clearance, no effect of mild renal impairment on clearance of cabozantinib was detected.

Paediatric population

No studies in paediatric populations have been performed to date with cabozantinib, therefore no data over safety of cabozantinib in paediatric patients are available.

Age

In the three clinical studies included in the Safety set, the overall incidence of the treatment related common AEs was similar between age groups (<65 years, 65-75, and ⩾ 75 years). In the pivotal XL184-301 study, patients treated with cabozantinib <65 years reported higher incidence of palmar plantar erythrodysethesia compared to patients 65-75, and ⩾ 75 years (51.8% vs 42.9 and 46.2%). Constipation, hypocalcemia and decreased appetite were more often seen in patients treated with cabozantinib aged ⩾75 years compared to patients in the other age categories.

Gender

In study XL184-301, the incidence of AEs was similar in female and male patients in the cabozantinib group (100.0% vs 100.0%) and in the placebo group (92.8% vs 97.5%). In the cabozantinib group, there was a higher incidence of nausea (56.9% females, 36.9% males), and vomiting (35.4% females, 19.5% males) in females, whereas males and females who received placebo reported nausea and vomiting at a similar, lower frequency (20.5 vs 22% and 0 and 5% respectively).

In XL184-001 and XL184-201 studies, a similar trend was observed.

Race

In study XL184-301 study, 89.6% of subjects that were treated with cabozantinib were whites. The overall incidence of grade 3 or 4 events was similar among race groups (63.5% white vs 66.7% non-white). No data were provided regarding type of AEs among different races.

Safety related to drug-drug interactions and other interactions

In vitro studies indicate that cabozantinib is a substrate for CYP3A4 and to a lesser extent for CYP2C9.

In the clinical XL184-006 study cabozantinib AUCs were decreased by 76% - 77% following co-administration with the strong CYP3A inducer rifampin compared to cabozantinib alone. When co-administered with rifampin, the apparent oral clearance of cabozantinib was 4.3-fold higher than for cabozantinib alone. These results confirm that rifampin affects the PK of cabozantinib leading to significantly lower plasma cabozantinib exposure levels. Other strong inducers of CYP3A4 activity (eg. phenytoin, carbamazepine, and phenobarbital) may also increase metabolism of cabozantinib and reduce cabozantinib plasma concentrations potentially leading to decreased efficacy.

When cabozantinib was co-administered with ketoconazole in another clinical study, the mean plasma t½ of cabozantinib increased from 122 hours to 144 hours. Together with the lower apparent oral clearance of cabozantinib of 29%, these results confirm that ketoconazole affects the PK of cabozantinib leading to significantly higher plasma cabozantinib exposure levels. Other strong inhibitors of CYP3A4 activity (e.g. itraconazole, erythromycin) may also decrease metabolism of cabozantinib and might increase cabozantinib plasma concentrations potentially leading to increased toxicity.

No effect of mild renal impairment on clearance of cabozantinib was observed by PK analysis. Patients with moderate and severe renal impairment were excluded from clinical studies performed with cabozantinib to date, therefore no conclusion can be drawn over the PK of cabozantinib in patients with moderate or severe renal impairment.

Discontinuation due to adverse events

In the pivotal study XL184-301, 16.4% of patients discontinued study treatment. Adverse events that frequently led to discontinuation of cabozantinib were hypocalcaemia (1.4%) and PPE syndrome (1.4%). Overall, 79.0% and 72.0% of patients required dose reductions and interruptions, respectively, due to TEAEs. Forty-one percent (41%) of patients required two dose reductions due to toxicity. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days. Close monitoring of patients is therefore recommended during the first eight weeks of therapy (see SmPC section 4.2 and 4.4).

AEs that led to dose modification occurring at 10% higher frequency in the cabozantinib arm compared with the placebo arm were PPE syndrome (28.0% vs 0%); diarrhea (19.2% vs 1.8); fatigue (13.1%,2.8%); weight decreased (12.6% vs 0%); decreased appetite, nausea (11.7% vs 0.9% each), stomatitis (10.7% vs 0%), and asthenia (10.3% vs 0%). The median time to first dose reduction or interruption in the cabozantinib arm was 43 days and occurred after achievement of steady-state concentrations (i.e., by about Day 15). Subjects with higher individual-predicted steady-state AUC of cabozantinib experienced earlier dose modifications. However, Although PPE was a frequent reason for cabozantinib dose modification, PPE in cabozantinib-treated subjects did not show a marked correlation with individual predicted steady-state AUC of cabozantinib. Most grade 3 or higher AEs occur with 175 mg of cabozantinib and within the first cycles of treatment. Although many AEs tend to be reversible over time with the appropriate dose reductions applied, some AEs like PPE and diarrhea only resolve slowly over time and tend to persist, which will likely negatively influence quality of life over a longer period of time. These results further underscore the importance an appropriate dose finding to prevent patients receiving a too high starting dose of 175 mg of cabozantinib.

Post marketing experience

Due to the recent first in the world US approval of cabozantinib, no post-marketing data for cabozantinib have been made available or submitted.

2.6.1. Discussion on clinical safety

Overall, the safety profile of cabozantinib (Cometriq) was consistent across studies and is typical for a small molecule with targeted inhibition of the VEGFR and other tyrosine kinase-mediated pathways: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhea, mucositis,

fistulas, abcesses) were prominent, whereas hematologic toxicities were limited. The most common serious adverse reactions associated with cabozantinib are pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism, and hypertension. The most frequent adverse reactions of any grade (experienced by at least 20% of patients) included diarrhoea, PPES, weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair colour changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, asthenia, hypocalcaemia, and dysphonia.

A concern was raised regarding the risk for medication errors given the available tablet strengths of 20 mg and 80 mg on the one hand and the recommended dose and adjustments (140 mg to be adjusted to 100 mg and 60 mg) on the other hand. Additionally, the safety of cabozantinib could be improved in case a dose lower than the MTD was considered more clinically appropriate. Depending on the results of study XL-184-401, expected to inform on the dose-exposure relationship and the clinically recommended dose, more appropriate tablet strengths, if necessary, should be developed by the applicant. This was included in the agreed RMP.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system (see SmPC section 4.8).

Dose reductions and dose interruptions occurred in 79% and 72%, respectively, of cabozantinib-treated patients in the pivotal clinical trial. Two dose reductions were required in 41% of patients. The median time to first dose reduction was 43 days, and to first dose interruption was 33 days. Close monitoring of patients is therefore recommended during the first eight weeks of therapy (see section 4.2).

The available analysis of the safety profile of cabozantinib did not include patients with a history of hepatic or renal impairment or with ongoing or recent cardiovascular diseases. Moreover, almost 80% of patients in the pivotal phase III study was younger than 65 years. This is adequately reflected in the SmPC (see section 4.2 and discussion on Clinical pharmacology).

In the pivotal XL184-301 study, AEs more frequently observed (⩾20% difference) with cabozantinib compared with placebo were palmar plantar erythrodusesthaesia syndrome (50.0 % vs 1,8%), weight loss (47.7% vs 10.1%), hair colour changes (33.6% vs 0.9%), decreases appetite (45.8% vs 15.6%), diarrhea (63.1% vs 33.0%), dysgeusia (34.1% vs 5.5%), stomatitis (29.0% vs 2.8%), hypertension (29.4% vs 3.7%), vomiting (24.3% vs 1.8%), and nausea (43.0 vs. 21.1). All these AEs were judged by the investigator as possibly drug-related. The increased incidence was mainly due to grade 1 and 2 adverse events.

Palmar-plantar erythrodysesthesia syndrome (PPE; hand foot syndrome) was very common (50.0%; 12.6% Grade 3, 21.5% Grade 2, and 15.4% Grade 1) in the cabozantinib arm compared to placebo (1.8%) in study XL184-301 and led to dose modification in 28% and to drug discontinuation in 1.4% of patients. Hypertension occurred more frequently in the cabozantinib arm of Study XL184-301 compared with placebo (29.4% overall, 7.9% grade 3 or 4), consistent with VEGF inhibition by cabozantinib. Five events (2.3%) in the cabozantinib arm of Study XL184-301 were reported as SAEs. Hypertension led to dose modification and to drug discontinuation in 7.0% and 0.9% of patients, respectively.

Most deaths in the pivotal study were due to disease progression. When analysing, causes of death seem to be heterogeneous, and not related to cardiac arrhythmias. However, in spite of the high frequencies of dose reductions and the short median time interval patients received 175 mg dose, half (11/22) of deaths through 30 days after the last dose in the cabozantinib arm occurred at the highest dose level.

Although the majority of AEs were reported as of grade 1-2 in severity, almost 80% of patients required a 1-level dose reduction (from 175 mg qd to 125 mg cabozantinib qd), whereas in 41% of patients a 2-level dose reduction (to 75 mg) was necessary to manage AEs. PPE was the most frequent reason for dose reductions, a clinical syndrome which highly impacts patient's quality of life, even at low grades of severity. Consistent with these large amounts of dose reductions, the mean level of exposure was 125 mg in the pivotal XL184-301 study.

Serious GI perforations and fistulas, sometimes fatal, and intra-abdominal abscesses have been observed with cabozantinib. Patients who have had recent radiotherapy, have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, or diverticulitis), have tumour infiltration of trachea, bronchi, or oesophagus, have complications from prior GI surgery (particularly when associated with delayed or incomplete healing), or have complications from prior radiation therapy to the thoracic cavity (including mediastinum) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas. Non-GI fistula should be ruled out as appropriate in cases of onset of mucositis after start of therapy. Cabozantinib should be discontinued in patients who experience a GI perforation or a GI or non-GI fistula (see SmPC section 4.4).

Events of venous thromboembolism and events of arterial thromboembolism have been observed with cabozantinib. Cabozantinib should be used with caution in patients who are at risk for, or who have a history of, these events. Cabozantinib should be discontinued in subjects who develop an acute myocardial infarction or any other clinically significant arterial thromboembolic complication (see SmPC section 4.4).

Hemorrhage has been observed with cabozantinib. Patients who have evidence of involvement of the trachea or bronchi by tumour or a history of haemoptysis prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients with serious haemorrhage or recent haemoptysis (see SmPC section 4.4).

Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, if possible. The decision to resume cabozantinib therapy after surgery should be based on clinical judgment of adequate wound healing. Cabozantinib should be discontinued in patients with wound healing complications requiring medical intervention (see SmPC section 4.4).

Hypertension has been observed with cabozantinib. All patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib dose should be reduced. Cabozantinib should be discontinued if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. In case of hypertensive crisis, cabozantinib should be discontinued (see SmPC section 4.4).

Events of osteonecrosis of the jaw (ONJ) have been observed with cabozantinib. An oral examination should be performed prior to initiation of cabozantinib and periodically during cabozantinib therapy. Patients should be advised regarding oral hygiene practice. For invasive dental procedures, cabozantinib treatment should be held at least 28 days prior to scheduled surgery, if possible. Caution should be used in patients receiving agents associated with ONJ, such as bisphosphonates. Cabozantinib should be discontinued in patients who experience ONJ (see SmPC section 4.4).

Proteinuria has been observed with cabozantinib. Urine protein should be monitored regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome (see SmPC section 4.4).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS), also known as Posterior Reversible Encephalopathy Syndrome (PRES) has been observed with cabozantinib. Cabozantinib treatment should be discontinued in patients with RPLS (see SmPC section 4.4).

Cabozantinib should be used with caution in patients with a history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be used with caution (see SmPC section 4.4).

No specific dose adjustment for the use of cabozantinib in older people (≥ 65 years) is recommended. However, a trend in increased rate of SAEs has been observed in subjects aged 75 years and older (see SmPC section 4.2).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

Management of suspected adverse drug reactions may require temporary interruption and/or dose reduction of Cometriq therapy. Dose reductions are adequately described in the SmPC (see section 4.2). When dose reduction is necessary, it is recommended to reduce to 100 mg daily, taken as one 80 mg orange capsule and one 20 mg grey capsule, and then to 60 mg daily, taken as three 20 mg grey capsules. Dose interruptions are recommended for management of CTCAE grade 3 or greater toxicities or intolerable grade 2 toxicities. Dose reductions are recommended for events that, if persistent, could become serious or intolerable. As most events can occur early in the course of treatment, the physician should evaluate the patient closely during the first eight weeks of treatment to determine if dose modifications are warranted. Events that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), and gastrointestinal (GI) events (abdominal or mouth pain, mucosal inflammation, constipation, diarrhoea, vomiting. The occurrence of some serious adverse events (like GI fistula) might be dependent on the cumulative dose and might present in a later stage of treatment. If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose. There is limited data in patients with cardiac impairment. No specific dosing recommendations can be made (see SmPC section 4.2).

There is no specific treatment for cabozantinib overdose and possible symptoms of overdose have not been established. In the event of suspected overdose, cabozantinib should be withheld and supportive care instituted. Metabolic clinical laboratory parameters should be monitored at least weekly or as

deemed clinically appropriate to assess any possible changing trends. Adverse reactions associated with overdose are to be treated symptomatically (see SmPC section 4.9).

Cabozantinib has a minor influence on the ability to drive and use machines. Adverse reactions such as fatigue and weakness have been associated with cabozantinib. Therefore, caution should be recommended when driving or operating machines (see SmPC section 4.7).

2.6.2. Conclusions on the clinical safety

The toxicity profile was considered acceptable. Overall, the safety profile of cabozantinib (Cometriq) was consistent across studies and typical for a small molecule with targeted inhibition of the VEGFR and other (MET, RET) tyrosine kinase-mediated pathways: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhea, mucositis, fistulas, abcesses) were prominent, whereas hematologic toxicities were limited.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in patients with hereditary or sporadic medullary thyroid cancer.

Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumor tissue samples will be required from all enrolled subjects, and guidelines will be provided to maximize tissue quality. Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes).

PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolites in this population.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The PRAC agreed to the safety concerns identified in the submitted RMP. Moreover, the PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

Finally, the PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice with changes. More specifically, a study to address interactions with individual drug transporters (XL184-NC-043) and dose-exposure relationship information from the Specific Obligation XL184-NC-401 study to address the potential for medication errors were added to the RMP. Moreover, amendments to milestones of studies included in the RMP, based on more accurate estimation of expected results, were proposed by the applicant after the final PRAC advice and considered acceptable by the CHMP.

The finally agreed content of the Risk Management Plan is as follows:

- **Safety concerns**

Table 31. Summary of the Safety Concerns

Important identified risks	• GI Perforation • GI and non-GI Fistula • Intra-Abdominal and Pelvic Abscess • Thromboembolic events • Haemorrhage • Wound complications • Hypertension • Osteonecrosis • RPLS • Diarrhoea • Palmar-plantar erythrodysaethesia syndrome • Proteinuria
Important potential risks	• QT Prolongation • Renal failure • Hepatotoxicity • High-dose toxicity • Fertility impairment • Embryotoxicity • Medication errors • Drug-drug interactions • Food-drug interactions
Important missing information	• Use in Paediatric population • Use in Patients with ethnicity other than White

	• Use in Patients with hepatic impairment • Use in Patients with renal impairment • Use in Patients with cardiac impairment • Use in pregnant or lactating women • Drug-drug interactions o Individual drug transporters including P-glycoprotein substrates o Drugs affecting gastric pH o Drugs affecting enterohepatic recirculation • Toxicity of metabolite EXEL-1644 • Carcinogenicity studies

- **Pharmacovigilance plans**

Table 32. Ongoing and planned studies in the PhV development plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
XL184-003, A Phase 1, Open-Label, Parallel-Group, Single-Dose Study to Assess the Pharmacokinetics of XL184 (Cabozantinib) Capsules in Hepatic Impaired Adult Subjects (category 3)	Safety and tolerability in hepatic impaired patients	Safety and tolerability in hepatic impaired patients	Ongoing	December 2014 (planned)
XL184-011, A Phase 1 Study of XL184 (Cabozantinib) in Children and Adolescents with Recurrent or Refractory Solid Tumors, including CNS Tumors (category 3)	PK, safety and tolerability in paediatric patients	Safety and tolerability in paediatric patients	Ongoing	December 2016 (planned per the PIP)

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
XL184-017, A Phase 1, Open-Label, Parallel-Cohort, Single-Dose Study to Assess the Pharmacokinetics of Cabozantinib (XL184) Capsules in Subjects with Impaired Renal Function (category 3)	Safety and tolerability in patients with renal impairment	Safety and tolerability in patients with renal impairment	Ongoing	December 2014 (planned)
XL184-NC-039 (category 3)	Assess interactions with P-gp substrates and other individual drug transporters	P-gp substrate and other drug interactions (PK and safety)	Completed	June 2014 (planned)
XL184-NC-043 (category 3)	Assess interactions with individual drug transporters	Other drug interactions (PK and safety)	Completed	June 2014 (planned)
XL184-018 (category 3)	Assess interactions with drugs affecting gastric pH	Interactions with drugs affecting gastric pH (PK and safety)	Ongoing	December 2014 (planned)
XL184-NC-036 (category 3)	Assess carcinogenicity potential (rat)	Carcinogenic potential	Initiated	October 2016 (planned)
XL184-NC-042 (category 3)	Assess carcinogenicity potential (mouse)	Carcinogenic potential	Planned	October 2014 (planned)
Nonclinical toxicity study XL184-NC-040 (category 3)	Toxicity study of cabozantinib in younger juveniles	Potential risks in paediatric patients (≤2 years)	Initiated	December 2014 (planned)

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Nonclinical toxicity study EXEL1644-NC-004 (category 3)	Characterisation of specific metabolite toxicity	Potential risks resulting from metabolite not previously characterized in parent (cabozantinib)	Completed	June 2014 (planned)
XL184-NC-034 (category 3)	Bacterial mutagenicity study of metabolites EXEL-1644 and EXEL-1646	Potential risk of mutagenicity by metaboilites	Completed	June 2014 (planned)
Millipore EXL084 (category 3)	Kinase panel IC50 determinations for metabolites EXEL-1644 and EXEL-1646	Potential risks resulting from metabolite not previously characterized in parent (cabozantinib)	Completed	June 2014 (planned)
Enterohepatic recirculation evaluation in dogs XL184-NC-045 (category 3)	Evaluation of potential enterohepatic recirculation of cabozantinib in dogs	Potential risks of drugs affecting cabozantinib enterohepatic recirculation and PK	Initiated	December 2014 (planned)
Enterohepatic recirculation evaluation in rats XL184-NC-046 (category 3)	Evaluation of potential enterohepatic recirculation of cabozantinib in rats	Potential risks of drugs affecting cabozantinib enterohepatic recirculation and PK	Initiated	December 2014 (planned)
XL184-401 (category 2)	Safety, PK, and efficacy at 2 doses, evaluated via a non-inferiority design Guide the development of tablet strengths	Safety of 2 different doses Medication errors	Planned	March 2019 (planned)

- **Risk minimisation measures**

Table 33. Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
GI Perforation	SPC section 4.4 Patients at a higher risk for the event, and recommendation for careful assessment before initiating therapy, and close monitoring after initiating therapy; and to discontinue cabozantinib in patients who present with the event. SPC section 4.8 Described the frequency of the event as common	None
GI and non-GI fistulae	SPC section 4.4 Describes patients at a higher risk for the event, and recommendation for careful assessment before initiating therapy, and close monitoring after initiating therapy; and to discontinue cabozantinib in patients who present with the event. SPC section 4.8 Described the frequency of the event as common to uncommon	None
Intra-abdominal and pelvic abscess	SPC section 4.4 Describes patients at a higher risk for the event, and recommendation to discontinue cabozantinib in patients who present with the event or are at a higher risk for the event. SPC section 4.8 Describes the frequency of the event as common	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Thromboembolic events	SPC section 4.4 and 4.8 Describes patients at a higher risk for the event, and recommendation to discontinue cabozantinib in patients who present with acute myocardial infarction or any other clinically significant arterial thromboembolic complication. SPC section 4.8 Describes the frequency of the event as common to uncommon	None
Haemorrhage	SPC section 4.4 and 4.8 Describes patients at a higher risk for the event and recommendation to carefully evaluate patients where the tumor may be involving the trachea, bronchi or history of hemoptysis and to not administer cabozantinib in patients who present with serious haemorrhage or recent haemoptysis. SPC section 4.8 Describes the frequency of the event as common to uncommon	None
Wound complications	SPC section 4.4 Describes criteria to resume cabozantinib treatment after surgery. Describes the need to stop cabozantinib at least 28 days prior to scheduled surgery and the need to discontinue cabozantinib in patients with wound healing complications requiring medical intervention. SPC section 4.8 Describes the frequency of the event as common	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypertension	SPC section 4.4 Describes the need for monitoring of all patients, the reduction of cabozantinib dose in the case of persistent hypertension and the need to discontinue cabozantinib if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of cabozantinib. SPC section 4.8 Describes the frequency of the event as very common	None
Osteonecrosis	SPC section 4.4 Describes patients at a higher risk for the event. Provides a recommendation to discontinue cabozantinib in patients who present with osteonecrosis. Provides the recommendation for oral examination prior to initiation of cabozantinib and periodically during cabozantinib therapy and the need for holding treatment in case of dental surgery. SPC section 4.8 Describes the frequency of the event as common	None
Reversible Posterior Leukoencephalopathy Syndrome (RPLS)	SPC section 4.4 Describes the need to discontinue cabozantinib treatment if the event occurs SPC section 4.8 Describes the frequency of the event as uncommon	None
Diarrhoea	SPC section 4.8 Describes the frequency of the event as very common	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
PPES	SPC section 4.4 Describes dose modification guidance for when PPES occurs. SPC section 4.8 Describes the frequency of the event as very common	None
Proteinuria	SPC section 4.4 Describes the need for urine protein monitoring regularly during cabozantinib treatment. Cabozantinib should be discontinued in patients who develop nephrotic syndrome SPC section 4.8 Describes the frequency of the event as common	None
QTc Prolongation	SPC section 4.4 Describes caution in use with patients of history of QT interval prolongation, patients who are taking antiarrhythmics, or patients with relevant pre-existing cardiac disease, bradycardia, or electrolyte disturbances. When using cabozantinib, periodic monitoring with on-treatment ECGs and electrolytes (serum calcium, potassium, and magnesium) should be considered. Concomitant treatment with strong CYP3A4 inhibitors, which may increase cabozantinib plasma concentrations, should be used with caution	None
Renal failure	SPC section 4.8 Describes the frequency of the risk as uncommon	None
Hepatotoxicity	SPC section 4.8 Describes the frequency of hepatobiliary disorders as common	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in patients with cardiac impairment	SPC Section 4.2: There is limited data in patients with cardiac impairment. No specific dosing recommendations can be made.	None
High-dose toxicity	SPC section 4.2 and 4.4 Provides dosing recommendation and criteria for dose reduction. Provides the frequency and timing of dose modifications in the clinical study. Instructs the health care provider to closely monitor patients for the first 8 weeks of treatment.	None
Fertility impairment	SPC section 4.6 and 5.3 Describes the lack of human data and the potential risk in patients taking cabozantinib based on findings in animal experiments.	None
Embryotoxicity	SPC section 4.6 and 5.3 Describes the potential risk for humans is unknown. Cabozantinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with cabozantinib.	None
Medication errors	SPC section 4.2 Describes how to take cabozantinib and proper dosing identification	None
Drug-drug interactions: • CYP3A4 • Individual drug transporters including P-gp substrates • Drugs affecting gastric pH	SPC section 4.2 and 4.4 Provides a recommendation to use caution for concomitant medicinal products that are strong inhibitors of CYP3A4 and avoidance of chronic use of strong inducers of CYP3A4. Describes the potential to increase plasma concentrations of co-administered substrates of P-gp. Describes the potential to reduce a patient's exposure to cabozantinib if dosed with proton pump inhibitors. Describes the potential for oral contraceptives being ineffective and advices the use of barrier methods as additional contraceptive method.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Food-drug interactions	SPC section 4.2 and 5.2 Describes that a high-fat meal can increase the exposure of cabozantinib. Provides dosing recommendations (patients should fast for at least 2 hours before through 1 hour after taking cabozantinib capsules).	None
Use in paediatric population	SPC section 4.2 Describes the lack of data in children <18 years of age.	None
Use in Patients with ethnicity other than White	SPC Section 4.2 Describes the lack of data in non-White patients	None
Use in patients with hepatic impairment	SPC section 4.2 and 5.2 Describes that cabozantinib is not recommended for use in patients with hepatic impairment and the absence of information in this population	None
Use in patients with renal impairment	SPC section 4.2 and 5.2 Describes that cabozantinib should be used with caution in patients with renal impairment and not recommended in patients with severe renal impairment. Describes the absence of information in this population	None
Pregnant and lactating women	SPC section 4.6 Describes the potential risk for embryotoxicity if taken by pregnant women and the need for proper contraception while being treated with cabozantinib through 4 months after treatment. Describes the risk of potential harm to infants if the mother breastfeeds while taking cabozantinib and up to 4 months after treatment.	None
Toxicity of metabolite EXEL-1644	SPC Section 5.3: Studies assessing the toxicity of metabolites have not been concluded.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Carcinogenicity	SPC section 5.3 Describes a potential carcinogenicity risk in the absence of completed carcinogenicity studies.	None

2.9. 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

The evidence of efficacy of cabozantinib in patients with MTC is based on the results of one pivotal study (XL184-301), supported by the data of the expansion cohort of the phase I XL184-001 study, enrolling 25 patients with MTC.

Study XL184-301 was a pivotal, phase III, multicenter, multinational, randomized, double blind, placebo-controlled study. A total of 330 patients with unresectable locally advanced or metastatic MTC, experiencing disease progression within 14 months from previous radiological assessment, were randomized (2:1) to receive oral cabozantinib 175 mg qd (as L-malate salt weight; 138 mg freebase equivalent weight) or matching placebo. The population enrolled in the pivotal study reflects the target population as mentioned by the wording of the proposed indication. However, patients with locally advanced MTC represented < 5% of patients enrolled in the pivotal study.

The results, based on the final PFS analysis (IRC determined, according to modified RECIST criteria) as performed after 139 (42.1%) events, show a statistically significant improvement in the primary endpoint of PFS for cabozantinib compared with placebo (HR 0.29, 95% CI 0.19-0.49, p<0.0001), with a gain in median PFS of 31.2 weeks (7.2 months) in favour of cabozantinib (median PFS 48.6 weeks vs 17.4 weeks, respectively). The PFS effect was maintained in several subgroups of the population, with the exception of patients with RET negative tumors, where the effect did not reach statistical significance.

Objective response rate (ORR: CR+PR, IRC assessed) was significantly higher with cabozantinib (27.9%) compared with placebo (0%). Disease stabilization rate was also significantly higher in the cabozantinib arm compared with the placebo arm (55.3% vs 13.5%, respectively).

Uncertainty in the knowledge about the beneficial effects

A trend toward PFS benefit was observed in the RET negative group, but results were not statistically significant and therefore the magnitude of clinical benefit should be further confirmed. Study XL-184-401 will be conducted to address this issue. Fresh tumor tissue samples will be required from all enrolled subjects, and guidelines will be provided to maximize tissue quality (see discussion on Clinical Efficacy and Discussion on the benefit-risk balance).

The interim OS analysis, performed at the time of the primary PFS analysis and including 96 (29%) of death events did not show any significant difference between the two study arms (HR 0.98, 95% CI 0.63-1.52, p=0.9304, median OS 21.1 months vs NA with cabozantinib and placebo, respectively). The updated OS analysis also showed no significant difference between the two study arms. This should be confirmed in a more mature dataset and increased power to detect any differences. Final OS results will be provided according to agreed timelines (see discussion on Clinical Efficacy and Discussion on the benefit-risk balance).

Risks

Unfavourable effects

Overall, the safety profile of cabozantinib (Cometriq) was consistent across studies and is typical for a small molecule with targeted inhibition of the VEGFR and other (MET, RET) tyrosine kinase-mediated pathways: hypertension, skin (hand-foot syndrome, rash) and gastrointestinal toxicities (diarrhea, mucositis, fistulas, abcesses) were prominent, whereas hematologic toxicities were limited.

In the pivotal XL184-301 study, AEs more frequently observed (⩾20% difference) with cabozantinib compared with placebo were palmar plantar erythrodysesthaesia (PPE) syndrome (50.0 % vs. 1,8%), weight loss (47.7% vs. 10.1%), hair colour changes (33.6% vs. 0.9%), decreased appetite (45.8% vs. 15.6%), diarrhoea (63.1% vs. 33.0%), dysgeusia (34.1% vs. 5.5%), stomatitis (29.0% vs. 2.8%), hypertension (29.4% vs. 3.7%), vomiting (24.3% vs. 1.8%), and nausea (43.0 vs. 21.1).

The most common serious adverse reactions associated with cabozantinib were pneumonia, mucosal inflammation, hypocalcaemia, dysphagia, dehydration, pulmonary embolism, and hypertension. The most frequent adverse reactions of any grade (experienced by at least 20% of patients) included diarrhoea, PPES, weight decreased, decreased appetite, nausea, fatigue, dysgeusia, hair colour changes, hypertension, stomatitis, constipation, vomiting, mucosal inflammation, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, asthenia, hypocalcaemia, and dysphonia.

A thyroid stimulating hormone (TSH) value above normal after first dose was observed in 57% of patients on cabozantinib versus 19% of patients on placebo (regardless of baseline values). Ninety-two percent of patients on the cabozantinib arm had a prior thyroidectomy, and 89% were taking thyroid hormones prior to first dose.

The cardiac toxicity of cabozantinib was mild. A mild to moderate increase of mean QTcF at day 29 (where steady state plasma concentrations of cabozantinib have been reached) of 10 msec from baseline was observed at a dose of 140 mg qd, which was considered not clinically relevant. ECG assessments in the pivotal study indicated that cabozantinib can cause QT prolongation, with a mean QTcF change from baseline of 9.7 ms on Day 29 of treatment. One patient had a QTcF prolongation

of >60ms, and 2 patients were identified with a new QTcF >480 ms. This effect was not associated with a change in cardiac wave form morphology or new rhythms.

According to the MDASI THY score, several cancer related symptoms (like gastrointestinal symptoms), were significantly more frequently observed and with greater severity in the cabozantinib versus the placebo arm, indicating a detrimental effect of cabozantinib compared with placebo in terms of quality of life, possibly related to the toxicity of the drug.

Overall, almost 80% of cabozantinib-treated patients needed one and 41% required two dose reductions due to toxicity. The main AEs leading to dose reductions were PPE, weight decrease, decreased appetite, fatigue, diarrhea, stomatitis, asthenia and nausea. Discontinuation occurred in 16.4% of patients. Due to the dose reductions, the median overall exposure in the pivotal XL184-301 study was 100 mg instead of the proposed 140 mg.

Uncertainty in the knowledge about the unfavourable effects

From a methodological point of view the dose selection is considered acceptable as based on the results of the phase I XL184-001 study, employing a classical dose finding approach. However, only two dose levels (175 mg and 250 mg OD) have been evaluated with the capsule formulation. In view of such findings, further data should confirm if the benefit-risk balance cannot be improved using a lower dose. The XL-184-401 study, is expected to further clarify the safety-exposure relationship (see Discussion on Clinical efficacy and Clinical safety).

Benefit-risk balance

Importance of favourable and unfavourable effects

Metastatic MTC is a highly invalidating and life threatening condition. Despite the possibility of protracted course of disease, patients with metastatic MTC will invariably experience disease progression and the great majority die from the disease: median overall survival in patients with metastatic and progressive disease is about 2-3 years.

In the metastatic setting patients may be affected by several symptoms related to local disease (dysphagia, neck pain, swallowing problems) and to systemic release of calcitonin or other factors (diarrhoea, flushing, fatigue, Cushing syndrome) or to metastatic localization (e.g., pain related to bone metastases, fistulas forming, etc.). Treatments goals in the metastatic setting essentially aim to improve survival and/or delay disease progression when associated with reduction of disease related symptoms and/or improvement in quality of life.

There are limited treatment options available for patients with metastatic MTC: cytotoxic chemotherapy (as monotherapy or as combination regimens) has been administered in the past decades with disappointing results, consisting of low rate of tumour response and remarkable toxicity.

In 2012, vandetanib, an orally available tyrosine kinase inhibitor of RET, EGFR and VEGFR, has been approved in the EU for the treatment of patients with locally advanced or metastatic MTC. Approval has been limited to patients with aggressive and symptomatic disease. Treatment with vandetanib was associated in particular with significant QT prolongation with related risk of torsade de pointes and other arrhythmias.

In this context the results of the pivotal XL184-301 study, showing a high level of efficacy in terms of PFS and an acceptable toxicity profile, without significant QT prolongation, are considered of clinical relevance.

Benefit-risk balance

From a regulatory perspective (CPMP/EWP/2330/99), licensing based on the results of one single pivotal study is acceptable if the study is particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. The efficacy results of the XL184-301 study show a robust and statistically significant improvement in PFS associated with treatment with cabozantinib (median gain 7.2 months), which is considered of clinical relevance. The toxicity profile is considered acceptable and the benefit-risk balance is considered to be positive.

Discussion on the benefit-risk balance

As the precise mechanism of action of cabozantinib on the RET tyrosine kinase remains unclear, the impact of RET mutation status on the efficacy of cabozantinib needs to be further ascertained in a dose comparative study (XL-184-401). In addition to this, the same study will address possibility of giving effective lower dosages with less toxicity.

Following consultation with the applicant, the CHMP considered the granting of a conditional marketing authorisation for cabozantinib in accordance with Article 4 of Commission Regulation (EC) No 507/2006.

Cabozantinib aims at the treatment of seriously debilitating diseases or life-threatening diseases and therefore falls within the scope of Commission Regulation (EC) No 507/2006. In addition, Cometriq was designated as an orphan medicinal product.

The Committee found that although comprehensive clinical data referring to the efficacy of the medicinal product had not been supplied, all of the following requirements were met:

- The risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive

In the randomized, double-blind, placebo-controlled study presented in patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma (XL184-301), a statistically significant improvement in the primary endpoint of PFS was shown for cabozantinib compared with placebo (HR 0.29, 95% CI 0.19-0.49, $p<0.0001$), with a gain in median PFS of 31.2 weeks (7.2 months) in favour of cabozantinib (median PFS 48.6 weeks vs 17.4 weeks, respectively).

From a quantitative point of view, the specific benefit in patients with RET negative tumours or tumours with unknown RET mutation status was less as compared with what was observed in patients with RET+ tumours. The possible lower beneficial effects of cabozantinib in patients in whom RET mutation are not known or is negative has been included in the indication and further information is warranted to clarify this further.

The toxicity profile was considered acceptable. However, in view of the frequent dose reductions due to toxicity, the benefit-risk balance might be further improved by studying the efficacy and safety of a lower starting dose.

In summary, the benefit/ risk is considered positive. The possibility of giving effective lower dosages with less toxicity needs to be explored further. Also, the impact of the RET status on the efficacy needs to be further ascertained in the dose comparative study XL-184-401 by establishing the RET status in the patients enrolled.

- It is likely that the applicant will be in a position to provide comprehensive clinical data

The applicant has provided an outline of the proposed dose-comparison study (XL-184-401) (140 mg vs 60 mg) in patients with hereditary or sporadic medullary thyroid cancer. Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumor tissue samples will be required from all enrolled subjects, and guidelines will be provided to maximize tissue quality. Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes).

PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolite(s) in this population. The general features of the study design are considered acceptable and feasible; applicant has provided significant assurance that the trial will be conducted according to agreed timelines. Therefore is likely that the applicant will be in a position to provide comprehensive clinical data.

- Unmet medical needs to be fulfilled

There is only one approved medicinal product (vandetanib) for MTC patients with aggressive progressive disease. Although a direct efficacy comparison is not available, the effect on PFS associated with cabozantinib was broadly comparable to the effect observed with vandetanib.

However, vandetanib is associated with a clinical relevant QTc prolongation. Cabozantinib was associated with clinically relevant efficacy in terms of PFS and an acceptable toxicity profile, without significant QTc prolongation. In the subset of patients with aggressive progressive disease, in view of the improved safety profile as regards QTc prolongation, cabozantinib is considered to fulfil an unmet need by providing an alternative treatment with a different safety profile.

There are no medicinal products approved for treatment of MTC in patients with less symptomatic disease (i.e., in the absence of “aggressive” progressive disease).

Therefore, the CHMP concluded that cabozantinib will fulfil unmet needs.

- The benefits to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required

The CHMP considered that the potential risks inherent in marketing cabozantinib for the specific indication, while additional, more comprehensive data becomes available in the future, is offset by the potential benefit to the patients whose only treatment options currently available are surgery

and vandetanib. The RMP for cabozantinib is considered adequate to address any identified and unknown risks.

The CHMP concluded that all the requirements for the granting of a conditional marketing authorisation had been met.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Cometriq in the treatment of adult patients with progressive, unresectable locally advanced or metastatic medullary thyroid carcinoma [for patients in whom Rearranged during Transfection (RET) mutation status is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision (see important information in sections 4.4 and 5.1)] is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being

reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
A mature OS analysis of study XL184-301 including subgroup analyses on relevant demographic and baseline tumour characteristics and potential confounding effect of post-study therapies.	30 April 2015

- ***Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation***

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
A dose-comparison study (XL-184-401) (140 mg vs 60 mg) in 112 patients with hereditary or sporadic medullary thyroid cancer. Patients with both sporadic and hereditary forms of MTC will be eligible for the study. Fresh tumour samples for tumour genetic analysis from the most recent metastatic site in patients enrolled in the dose-comparison study should be collected. Samples will undergo thorough evaluation for RET and RAS mutations. Tumor tissue samples initially will undergo histological evaluation, manual tumor enrichment, and DNA isolation. The resulting DNA samples will be evaluated for quality by a PCR-based amplification test, and by Sanger sequencing for RET M918T. A replacement sample will be requested if an original sample fails during the PCR quality or the Sanger sequencing tests. Next generation sequencing of RET exons 10, 11, and 13-16 will be performed, which covers the vast majority of known RET mutations. In addition, samples will be evaluated for mutations in RAS gene hotspots (HRAS, KRAS, and NRAS genes). PK assessments will be required for all subjects (both dose groups). Results will be used to evaluate the exposure to cabozantinib at the 60 and 140 mg dose levels and to further characterize the population PK models and exposure response relationships of cabozantinib and possible metabolites in this population.	31 March 2019

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that cabozantinib (as S-malate) is qualified as a new active substance.