SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Cabometyx® 20 mg
Cabometyx® 40 mg
Cabometyx® 60 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Cabometyx 20 mg
Each film-coated tablet contains cabozantinib (*S*)-malate equivalent to 20 mg cabozantinib.

Excipients with known effect
Each film-coated tablet contains 15.54 mg lactose.

Cabometyx 40 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 40 mg cabozantinib.

Excipients with known effect
Each film-coated tablet contains 31.07 mg lactose.

Cabometyx 60 mg
Each film-coated tablet contains cabozantinib (S)-malate equivalent to 60 mg cabozantinib.

Excipients with known effect
Each film-coated tablet contains 46.61 mg lactose

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

Cabometyx 20 mg
The tablets are yellow round with no score and debossed with “XL” on one side and “20” on the other side of the tablet.

Cabometyx 40 mg
The tablets are yellow triangle shaped with no score and debossed with “XL” on one side and “40” on the other side of the tablet.

Cabometyx 60 mg
The tablets are yellow oval shaped with no score and debossed with “XL” on one side and “60” on the other side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Renal cell carcinoma (RCC)
Cabometyx is indicated as monotherapy for advanced renal cell carcinoma
- as first-line treatment of adult patients with intermediate or poor risk, per IMDC criteria.
- in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy.

CABOMETYX, in combination with nivolumab, is indicated for the first-line treatment of advanced renal cell carcinoma in adults (see section 5.1).

Hepatocellular carcinoma (HCC)
Cabometyx is indicated as monotherapy for the treatment of hepatocellular carcinoma (HCC), in adults with Child-Pugh Class A hepatic impairment who have previously been treated with sorafenib.

Differentiated thyroid carcinoma (DTC)
CABOMETYX is indicated as monotherapy for the treatment of adult patients with locally advanced or metastatic differentiated thyroid carcinoma (DTC), refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy.

4.2 Posology and method of administration

Therapy with CABOMETYX should be initiated by a physician experienced in the administration of anticancer medicinal products.

Posology

CABOMETYX as monotherapy
For RCC, HCC and DTC, the recommended dose of CABOMETYX is 60 mg once daily.

Treatment should continue until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.

CABOMETYX in combination with nivolumab in first-line advanced RCC
The recommended dose of CABOMETYX is 40 mg once daily in combination with nivolumab administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks. The treatment should continue until disease progression or unacceptable toxicity. Nivolumab should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression (see the Summary of Product Characteristics (SmPC) for posology of nivolumab).

Treatment modification
Management of suspected adverse drug reactions may require temporary treatment interruption and/or dose reduction (see Table 1). When dose reduction is necessary in monotherapy, it is recommended to reduce to 40 mg daily, and then to 20 mg daily.

When CABOMETYX is administered in combination with nivolumab, it is recommended to reduce the dose to 20 mg of CABOMETYX once daily, and then to 20 mg every other day (refer to the nivolumab SmPC for recommended treatment modification for nivolumab).

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.

If a patient misses a dose, the missed dose should not be taken if it is less than 12 hours before the next dose.

Table 1: Recommended CABOMETYX dose modifications for adverse reactions

Adverse reaction and severity	**Treatment modification**
Grade 1 and grade 2 adverse reactions which are tolerable and easily managed	Dose adjustment is usually not required. Add supportive care as indicated.
Grade 2 adverse reactions which are intolerable and cannot be managed with a dose reduction or supportive care	Interrupt treatment until the adverse reaction resolves to grade ≤1. Add supportive care as indicated. Consider re-initiating at a reduced dose.
Grade 3 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment until the adverse reaction resolves to grade ≤1. Add supportive care as indicated. Re-initiate at a reduced dose.
Grade 4 adverse reactions (except clinically nonrelevant laboratory abnormalities)	Interrupt treatment. Institute appropriate medical care. If adverse reaction resolves to grade ≤1, re-initiate at a reduced dose. If adverse reaction does not resolve, permanently discontinue the treatment.
Liver enzymes elevations for RCC patients treated with CABOMETYX in combination with nivolumab	
ALT or AST > 3 times ULN but ≤10 times ULN without concurrent total bilirubin ≥ 2 times ULN	Interrupt CABOMETYX and nivolumab until these adverse reactions resolves to Grade≤1 Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC). Re-initiate with a single medicine or sequential re-initiating with both medicines after recovery may be considered. If re-initiating with nivolumab, refer to nivolumab SmPC.
ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN	Permanently discontinue CABOMETYX and nivolumab. Corticosteroid therapy may be considered if immune-mediated reaction is suspected (refer to nivolumab SmPC).

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (NCI-CTCAE v4)

Concomitant medicinal products

Concomitant medicinal products that are strong inhibitors of CYP3A4 should be used with caution, and chronic use of concomitant medicinal products that are strong inducers of CYP3A4 should be avoided (see sections 4.4 and 4.5).

Selection of an alternative concomitant medicinal product with no or minimal potential to induce or inhibit CYP3A4 should be considered.

Special populations

Elderly

No specific dose adjustment for the use of cabozantinib in elderly patients (≥ 65 years) is recommended.

Race
No dose adjustment is necessary based on ethnicity (see section 5.2).

Renal impairment
Cabozantinib should be used with caution in patients with mild or moderate renal impairment. Cabozantinib is not recommended for use in patients with severe renal impairment as safety and efficacy have not been established in this population.

Hepatic impairment
In patients with mild hepatic impairment no dose adjustment is required. Since only limited data are available for patients with moderate hepatic impairment (Child Pugh B), no dosing recommendation can be provided. Close monitoring of overall safety is recommended in these patients (see sections 4.4 and 5.2). There is no clinical experience in patients with severe hepatic impairment (Child Pugh C), so cabozantinib is not recommended for use in these patients (see section 5.2).

Cardiac impairment
There are limited data in patients with cardiac impairment. No specific dosing recommendations can be made.

Paediatric population
The safety and efficacy of cabozantinib in children and adolescents aged <18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration
CABOMETYX is for oral use. The tablets should be swallowed whole and not crushed. Patients should be instructed to not eat anything for at least 2 hours before through 1 hour after taking CABOMETYX.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As most adverse reactions 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. Adverse reactions that generally have early onset include hypocalcaemia, hypokalaemia, thrombocytopenia, hypertension, palmar-plantar erythrodysaesthesia syndrome (PPES), proteinuria, and gastrointestinal (GI) events (abdominal pain, mucosal inflammation, constipation, diarrhoea, vomiting).

Management of suspected adverse reactions may require temporary interruption or dose reduction of cabozantinib therapy (see section 4.2):
In renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy, dose reductions and dose interruptions due to an adverse event (AE) occurred in 59.8% and 70%, respectively, of cabozantinib-treated patients in the pivotal clinical trial (METEOR). Two dose reductions were required in 19.3% of patients. The median time to first dose reduction was 55 days, and to first dose interruption was 38 days.

In treatment-naïve renal cell carcinoma, dose reductions and dose interruptions occurred in 46% and 73%, respectively, of cabozantinib-treated patients in the clinical trial (CABOSUN).

When cabozantinib is given in combination with nivolumab in first-line advanced renal cell carcinoma, dose reduction and dose interruption of cabozantinib due to an AE occurred in 54.1% and 73.4% of patients in the clinical trial (CA2099ER). Two dose reductions were required in 9.4% of patients. The median time to first dose reduction was 106 days, and to first dose interruption was 68 days.

In hepatocellular carcinoma following prior systemic therapy, dose reductions and dose interruptions occurred in 62% and 84%, respectively, of cabozantinib-treated patients in the clinical trial (CELESTIAL). Two dose reductions were required in 33% of patients. The median time to first dose reduction was 38 days, and to first dose interruption was 28 days. Closer monitoring is advised in patients with mild or moderate hepatic impairment.

In differentiated thyroid carcinoma, dose reductions and dose interruptions occurred in 67% and 71% respectively of cabozantinib treated patients in the clinical trial (COSMIC-311). Two dose reductions were required in 33% of patients. The median time to first dose reduction was 57 days and to first dose interruption was 38.5 days.

<u>Hepatotoxicity</u>
Abnormalities of liver function tests (increases in alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with cabozantinib. It is recommended to perform liver function tests (ALT, AST and bilirubin) before initiation of cabozantinib treatment and to monitor closely during treatment. For patients with worsening of liver function tests considered related to cabozantinib treatment (i.e. where no alternative cause is evident), the dose modification advice in Table 1 should be followed (see section 4.2).
When cabozantinib is given in combination with nivolumab, higher frequencies of Grades 3 and 4 ALT and AST elevations have been reported relative to cabozantinib monotherapy in patients with advanced RCC (see section 4.8). Liver enzymes should be monitored before initiation of and periodically throughout treatment. Medical management guidelines for both medicines should be followed (see section 4.2 and refer to the SmPC for nivolumab).
Cabozantinib is eliminated mainly via the hepatic route. Closer monitoring of the overall safety is recommended in patients with mild or moderate hepatic impairment (see also sections 4.2 and 5.2). A higher relative proportion of patients with moderate hepatic impairment (Child-Pugh B) developed hepatic encephalopathy with cabozantinib treatment. Cabozantinib is not recommended for use in patients with severe hepatic impairment (Child-Pugh C, see section 4.2).

<u>Hepatic encephalopathy</u>
In the HCC study (CELESTIAL), hepatic encephalopathy was reported more frequently in the cabozantinib than the placebo arm. Cabozantinib has been associated with diarrhoea, vomiting, decreased appetite and electrolyte abnormalities. In HCC patients with compromised livers, these non-hepatic effects may be precipitating factors for the development of hepatic encephalopathy. Patients should be monitored for signs and symptoms of hepatic encephalopathy.

<u>Perforations and fistulas</u>
Serious GI perforations and fistulas, sometimes fatal, have been observed with cabozantinib. Patients who have inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis, peritonitis, diverticulitis, or appendicitis), have tumour infiltration in the GI tract, or have complications from prior GI surgery (particularly when associated with delayed or incomplete healing) should be carefully evaluated before initiating cabozantinib therapy and subsequently they should be monitored closely for symptoms of perforations and fistulas including abscesses and sepsis. Persistent or recurring diarrhoea while on treatment may be a risk factor for the development of anal fistula. Cabozantinib should be discontinued in patients who experience a GI perforation or a fistula that cannot be adequately managed.

<u>Gastrointestinal (GI) disorders</u>
Diarrhoea, nausea/vomiting, decreased appetite, and stomatitis/oral pain were some of the most commonly reported GI events (see section 4.8). Prompt medical management, including supportive care with antiemetics, antidiarrhoeals, or antacids, should be instituted to prevent dehydration, electrolyte imbalances and weight loss. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant GI adverse reactions (see Table 1).

<u>Thromboembolic events</u>
Events of venous thromboembolism, including pulmonary embolism, and arterial thromboembolism, sometimes fatal, 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.

In the HCC study (CELESTIAL), portal vein thrombosis was observed with cabozantinib, including one fatal event. Patients with a history of portal vein invasion appeared to be at higher risk of developing portal vein thrombosis. Cabozantinib should be discontinued in patients who develop an acute myocardial infarction or any other clinically significant thromboembolic complication.

Haemorrhage

Severe haemorrhage, sometimes fatal, has been observed with cabozantinib. Patients who have a history of severe bleeding prior to treatment initiation should be carefully evaluated before initiating cabozantinib therapy. Cabozantinib should not be administered to patients that have or are at risk for severe haemorrhage. In the HCC study (CELESTIAL), fatal haemorrhagic events were reported at a higher incidence with cabozantinib than placebo. Predisposing risk factors for severe haemorrhage in the advanced HCC population may include tumour invasion of major blood vessels and the presence of underlying liver cirrhosis resulting in oesophageal varices, portal hypertension, and thrombocytopenia. The CELESTIAL study excluded patients with concomitant anticoagulation treatment or antiplatelet agents. Subjects with untreated, or incompletely treated, varices with bleeding or high risk for bleeding were also excluded from this study.

The study of cabozantinib in combination with nivolumab in first-line advanced RCC (CA2099ER) excluded patients with anticoagulants at therapeutic doses.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating cabozantinib, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Thrombocytopenia

In the HCC study (CELESTIAL) and in the DTC study (COSMIC-311), thrombocytopenia and decreased platelets were reported. Platelet levels should be monitored during cabozantinib treatment and the dose modified according to the severity of the thrombocytopenia (see Table 1).

Wound complications

Wound complications have been observed with cabozantinib. Cabozantinib treatment should be stopped at least 28 days prior to scheduled surgery, including dental surgery or invasive dental procedures, 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.

Hypertension

Hypertension, including hypertensive crisis has been observed with cabozantinib. Blood pressure should be well-controlled prior to initiating cabozantinib. After cabozantinib initiation, blood pressure should be monitored early and regularly and treated as needed with appropriate antihypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensives, the cabozantinib treatment should be interrupted until blood pressure is controlled, after which cabozantinib can be resumed at a reduced dose. 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.

Osteonecrosis

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. Cabozantinib treatment should be held at least 28 days prior to scheduled dental surgery or invasive dental procedures, 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.

Palmar-plantar erythrodysaesthesia syndrome

Palmar-plantar erythrodysaesthesia syndrome (PPES) has been observed with cabozantinib. When PPES is severe, interruption of treatment with cabozantinib should be considered. Cabozantinib should be restarted with a lower dose when PPES has been resolved to grade 1.

Proteinuria
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.

Posterior reversible encephalopathy syndrome
Posterior reversible encephalopathy syndrome (PRES) has been observed with cabozantinib. This syndrome should be considered in any patient presenting with multiple symptoms, including seizures, headache, visual disturbances, confusion or altered mental function. Cabozantinib treatment should be discontinued in patients with PRES.

Prolongation of QT interval
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.

Thyroid dysfunction
Baseline laboratory measurement of thyroid function is recommended in all patients. Patients with pre-existing hypothyroidism or hyperthyroidism should be treated as per standard medical practice prior to the start of cabozantinib treatment. All patients should be observed closely for signs and symptoms of thyroid dysfunction during cabozantinib treatment. Thyroid function should be monitored periodically throughout treatment with cabozantinib. Patients who develop thyroid dysfunction should be treated as per standard medical practice.

Biochemical laboratory test abnormalities
Cabozantinib has been associated with an increased incidence of electrolyte abnormalities (including hypo- and hyperkalaemia, hypomagnesaemia, hypocalcaemia, hyponatremia). Hypocalcaemia has been observed with cabozantinib at a higher frequency and/or increased severity (including Grade 3 and 4) in patients with thyroid cancer compared to patients with other cancers. It is recommended to monitor biochemical parameters during cabozantinib treatment and to institute appropriate replacement therapy according to standard clinical practice if required. Cases of hepatic encephalopathy in HCC patients can be attributed to the development of electrolyte disturbances. Dose interruption or reduction, or permanent discontinuation of cabozantinib should be considered in case of persistent or recurrent significant abnormalities (see Table 1).

CYP3A4 inducers and inhibitors
Cabozantinib is a CYP3A4 substrate. Concurrent administration of cabozantinib with the strong CYP3A4 inhibitor ketoconazole resulted in an increase in cabozantinib plasma exposure. Caution is required when administering cabozantinib with agents that are strong CYP3A4 inhibitors. Concurrent administration of cabozantinib with the strong CYP3A4 inducer rifampicin resulted in a decrease in cabozantinib plasma exposure. Therefore, chronic administration of agents that are strong CYP3A4 inducers with cabozantinib should be avoided (see sections 4.2 and 4.5).

P-glycoprotein substrates
Cabozantinib was an inhibitor (IC_{50} = 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 section 4.5).

MRP2 inhibitors
Administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations. Therefore, concomitant use of MRP2 inhibitors (e.g. cyclosporine, efavirenz, emtricitabine) should be approached with caution (see section 4.5).

Excipient

Lactose

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on cabozantinib

CYP3A4 inhibitors and inducers

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%. Therefore, co-administration of strong CYP3A4 inhibitors (e.g., ritonavir, itraconazole, erythromycin, clarithromycin, grapefruit juice) with cabozantinib should be approached with caution.

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%. Chronic co-administration of strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, phenobarbital or herbal preparations containing St. John’s Wort *[Hypericum perforatum]*) with cabozantinib should therefore be avoided.

Gastric pH modifying agents

Co-administration of proton pump inhibitor (PPI) esomeprazole (40 mg daily for 6 days) with a single dose of 100 mg cabozantinib to healthy volunteers resulted in no clinically-significant effect on plasma cabozantinib exposure (AUC). No dose adjustment is indicated when gastric pH modifying agents (i.e., PPIs, H2 receptor antagonists, and antacids) are co-administered with cabozantinib.

MRP2 inhibitors

In vitro data demonstrate that cabozantinib is a substrate of MRP2. Therefore, administration of MRP2 inhibitors may result in increases in cabozantinib plasma concentrations.

Bile salt-sequestering agents

Bile salt-sequestering agents such as cholestyramine and cholestagel may interact with cabozantinib and may impact absorption (or reabsorption) resulting in potentially decreased exposure (see section 5.2). The clinical significance of these potential interactions is unknown.

Effect of cabozantinib on other medicinal products

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.

The effect of cabozantinib on the pharmacokinetics of warfarin has not been investigated. An interaction with warfarin may be possible. In case of such combination, INR values should be monitored.

P-glycoprotein substrates

Cabozantinib was an inhibitor (IC_{50} = 7.0 μM), but not a substrate, of 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

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 section 4.5).

Pregnancy

There are no studies in pregnant women using cabozantinib. Studies in animals have shown embryo-foetal and teratogenic effects (see section 5.3). 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.

Breast-feeding

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.

Fertility

There are no data on human fertility. Based on non-clinical safety findings, male and female fertility may be compromised by treatment with cabozantinib (see section 5.3). Both men and women should be advised to seek advice and consider fertility preservation before treatment.

4.7 Effects on ability to drive and use machines

Cabozantinib has 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.

4.8 Undesirable effects

Cabozantinib as monotherapy

Summary of safety profile

The most common serious adverse drug reactions in the RCC population (≥1% incidence) are abdominal pain, diarrhoea, nausea, hypertension, embolism, hyponatraemia, pulmonary embolism, vomiting, dehydration, fatigue, asthenia, decreased appetite, deep vein thrombosis, dizziness, hypomagnesaemia and palmar-plantar erythrodysaesthesia syndrome (PPES).

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the RCC population included diarrhoea, fatigue, nausea, decreased appetite, PPES, hypertension, weight decreased, vomiting, dysgeusia, constipation, and AST increased. Hypertension was observed more frequently in the treatment naïve RCC population (67%) compared to RCC patients following prior VEGF-targeted therapy (37%).

The most common serious adverse drug reactions in the HCC population (≥1% incidence) are hepatic encephalopathy, asthenia, fatigue, PPES, diarrhoea, hyponatraemia, vomiting, abdominal pain and thrombocytopenia.
The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the HCC population included diarrhoea, decreased appetite, PPES, fatigue, nausea, hypertension and vomiting.

The most common serious adverse drug reactions in the DTC population (≥1% incidence) are diarrhoea, pleural effusion, pneumonia, pulmonary embolism, hypertension, anaemia, deep vein thrombosis, hypocalcemia, osteonecrosis of jaw, pain, palmar-plantar erythrodysaesthesia syndrome, vomiting and renal impairment.

The most frequent adverse reactions of any grade (experienced by at least 25% of patients) in the DTC population included diarrhoea, PPES, hypertension, fatigue, decreased appetite, nausea, alanine aminotransferase increased, aspartate aminotransferase increased and hypocalcaemia.

Tabulated list of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with cabozantinib monotherapy in RCC, HCC and DTC (n=1128) or reported after post-marketing use of cabozantinib are listed in Table 2. The adverse reactions are listed by 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse drug reactions (ADRs) reported in clinical trials or after post-marketing use in patients treated with cabozantinib in monotherapy

Infections and infestations	
Common	abscess
Blood and lymphatic disorders	
Very common	anaemia, thrombocytopenia
Common	neutropenia, lymphopenia
Endocrine disorders	
Very common	hypothyroidism[*]
Metabolism and nutrition disorders	
Very common	decreased appetite, hypomagnesaemia, hypokalaemia, hypoalbuminaemia
Common	dehydration, hypophosphataemia, hyponatraemia, hypocalcaemia, hyperkalaemia, hyperbilirubinemia, hyperglycaemia, hypoglycaemia
Nervous system disorders	
Very common	dysgeusia, headache, dizziness
Common	peripheral neuropathy [a]
Uncommon	convulsion, cerebrovascular accident, posterior reversible encephalopathy syndrome
Ear and labyrinth disorders	
Common	tinnitus
Cardiac disorders	
Uncommon	acute myocardial infarction
Vascular disorders	
Very common	hypertension, haemorrhage[b*]
Common	venous thrombosis[c],
Uncommon	hypertensive crisis, arterial thrombosis
Not known	aneurysms and artery dissections
Respiratory, thoracic, and mediastinal disorders	
Very common	dysphonia, dyspnoea, cough
Common	pulmonary embolism
Uncommon	pneumothorax
Gastrointestinal disorders	
Very common	diarrhoea[*], nausea, vomiting, stomatitis, constipation, abdominal pain, dyspepsia
Common	gastrointestinal perforation[*], pancreatitis, fistula[*], gastroesophageal reflux disease, haemorrhoids, oral pain, dry mouth, dysphagia,
Hepatobiliary disorders	
Common	hepatic encephalopathy[*]
Uncommon	hepatitis cholestatic
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash

Common	pruritus, alopecia, dry skin, dermatitis acneiform, hair colour change, hyperkeratosis, erythema
Not known	cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very common	pain in extremity
Common	muscle spasms, arthralgia
Uncommon	osteonecrosis of the jaw
Renal and urinary disorders	
Common	proteinuria
General disorders and administration site conditions	
Very common	fatigue, mucosal inflammation, asthenia, peripheral oedema
Investigations[d]	
Very common	weight decreased, serum ALT increased, AST increased
Common	blood ALP increased, GGT increased, blood creatinine increased, amylase increased, lipase increased, blood cholesterol increased, blood triglycerides increased
Injury, poisoning and procedural complications	
Uncommon	wound complications[e]

[*]See section 4.8 Description of selected adverse reactions for further characterisation.
[a] including polyneuropathy; peripheral neuropathy is mainly sensory
[b] Including epistaxis as the most commonly reported adverse reaction
[c]All venous thrombosis including deep vein thrombosis
[d] Based on reported adverse reactions
[e] Impaired healing, incision site complication and wound dehiscence

Cabozantinib in combination with nivolumab in first-line advanced RCC
<u>Summary of safety profile</u>
When cabozantinib is administered in combination with nivolumab, refer to the SmPC for nivolumab prior to initiation of treatment. For additional information on the safety profile of nivolumab monotherapy, please refer to the nivolumab SmPC.

In a dataset of cabozantinib 40 mg once daily in combination with nivolumab 240 mg every two weeks in RCC (n =320), with a minimum follow-up of 16 months, the most common serious adverse drug reactions (≥1% incidence) are diarrhoea, pneumonitis, pulmonary embolism, pneumonia, hyponatremia, pyrexia, adrenal insufficiency, vomiting, dehydration.

The most frequent adverse reactions (≥25%) were diarrhoea, fatigue, palmar-plantar erythrodysaesthesia syndrome, stomatitis, musculoskeletal pain, hypertension, rash, hypothyroidism, decrease appetite, nausea, abdominal pain. The majority of adverse reactions were mild to moderate (Grade 1 or 2).

<u>Tabulated list of adverse reactions</u>
Adverse reactions identified in the clinical study of cabozantinib in combination with nivolumab are listed in Table 3, 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); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3: Adverse reactions with cabozantinib in combination with nivolumab

Infections and infestations	
Very Common	upper respiratory tract infection
Common	pneumonia
Blood and lymphatic system disorders	
Common	eosinophilia
Immune system disorders	

Common	hypersensitivity (including anaphylactic reaction)
Uncommon	infusion related hypersensitivity reaction
Endocrine disorders	
Very common	hypothyroidism, hyperthyroidism
Common	adrenal insufficiency
Uncommon	hypophysitis, thyroiditis
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration
Nervous system disorders	
Very common	dysgeusia, dizziness, headache
Common	peripheral neuropathy
Uncommon	encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome
Ear and labyrinth disorders	
Common	tinnitus
Eye disorders	
Common	dry eye, blurred vision
Uncommon	uveitis
Cardiac disorders	
Common	atrial fibrillation, tachycardia
Uncommon	myocarditis
Vascular disorders	
Very common	hypertension
Common	thrombosis[a]
Respiratory, thoracic and mediastinal disorders	
Very common	dysphonia, dyspnoea, cough
Common	pneumonitis, pulmonary embolism, epistaxis, pleural effusion
Uncommon	pneumothorax
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia
Common	colitis, gastritis, oral pain, dry mouth, haemorrhoids
Uncommon	pancreatitis, small intestine perforation[b], glossodynia
Hepatobiliary disorders	
Common	hepatitis
Skin and subcutaneous tissue disorders	
Very common	palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus
Common	alopecia, dry skin, erythema, hair colour change
Uncommon	psoriasis, urticaria
Not known	cutaneous vasculitis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain[d], arthralgia, muscle spasm,
Common	arthritis
Uncommon	myopathy, osteonecrosis of the jaw, fistula
Renal and urinary disorders	
Very common	proteinuria
Common	renal failure, acute kidney injury
Uncommon	nephritis
General disorders and administration site conditions	
Very common	fatigue, pyrexia, oedema
Common	pain, chest pain

Investigations[e]	
Very common	increased ALT, increased AST, hypophosphataemia, hypocalcaemia, hypomagnesaemia, hyponatraemia, hyperglycaemia, lymphopenia, increased alkaline phosphatase, increased lipase, increased amylase, thrombocytopaenia, increased creatinine, anaemia, leucopenia, hyperkalaemia, neutropenia, hypercalcaemia, hypoglycaemia, hypokalaemia, increased total bilirubin, hypermagnesaemia, hypernatraemia, weight decreased
Common	blood cholesterol increased, hypertriglyceridaemia

Adverse reaction frequencies presented in Table 3 may not be fully attributable to cabozantinib alone but may contain contributions from the underlying disease or from nivolumab used in a combination.

[a] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, venous thrombosis limb

[b] Fatal cases have been reported

[c] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic and drug eruption

[d] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain

[e] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements with the exception of weight decreased, blood cholesterol increased and hypertriglyceridaemia

Description of selected adverse reactions

Data for the following reactions are based on patients who received CABOMETYX 60 mg orally once daily as monotherapy in the pivotal studies in RCC following prior VEGF-targeted therapy and in treatment-naïve RCC, in HCC following prior systemic therapy and in DTC in patient refractory or not eligible to radioactive iodine (RAI) who have progressed during or after prior systemic therapy or in patients who received CABOMETYX 40 mg orally once daily in combination with nivolumab in first-line advanced RCC (section 5.1).

Gastrointestinal (GI) perforation (see section 4.4)

In the study in RCC following prior VEGF-targeted therapy (METEOR), GI perforations were reported in 0.9% (3/331) of cabozantinib-treated RCC patients. Events were Grade 2 or 3. Median time to onset was 10.0 weeks.
In the treatment-naïve RCC study (CABOSUN), GI perforations were reported in 2.6% (2/78) of cabozantinib-treated patients. Events were Grade 4 and 5.
In the HCC study (CELESTIAL), GI perforations were reported in 0.9% of cabozantinib-treated patients (4/467). All events were Grade 3 or 4. Median time to onset was 5.9 weeks.
In the DTC study (COSMIC-311), GI perforation grade 4 was reported in one patient (0.6%) of cabozantinib-treated patients and occurred after 14 weeks of treatment.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of GI perforations was 1.3% (4/320) treated patients. One event was grade 3, two events were grade 4 and one event was grade 5 (fatal).
Fatal perforations have occurred in the cabozantinib clinical program.

Hepatic encephalopathy (see section 4.4)

In the HCC study (CELESTIAL), hepatic encephalopathy (hepatic encephalopathy, encephalopathy, hyperammonaemic encephalopathy) was reported in 5.6% of cabozantinib-treated patients (26/467); Grade 3-4 events in 2.8%, and one (0.2%) Grade 5 event. Median time to onset was 5.9 weeks.
No cases of hepatic encephalopathy were reported in the RCC studies (METEOR, CABOSUN and CA2099ER) and in the DTC study (COSMIC-311).

Diarrhoea (see section 4.4)

In the study in RCC following prior VEGF-targeted therapy (METEOR), diarrhoea was reported in

74% of cabozantinib-treated RCC patients (245/331); Grade 3-4 events in 11%. Median time to onset was 4.9 weeks.
In the treatment-naïve RCC study (CABOSUN), diarrhoea was reported in 73% of cabozantinib-treated patients (57/78); Grade 3-4 events in 10%.
In the HCC study (CELESTIAL), diarrhoea was reported in 54% of cabozantinib-treated patients (251/467); Grade 3- 4 events in 9.9%. Median time to onset of all events was 4.1 weeks. Diarrhoea led to dose modifications, interruptions and discontinuations in 84/467 (18%), 69/467 (15%) and 5/467 (1%) of subjects, respectively.
In the DTC study (COSMIC-311), diarrhoea was reported in 62% of cabozantinib treated patients (105/170); Grade 3-4 events in 7.6%. Diarrhoea led to dose reduction and interruption in 24/170 (14%) and 36/170 (21%) of subjects respectively.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER), the incidence of diarrhoea was reported in 64.7% (207/320) of treated patients; Grade 3-4 events in 8.4% (27/320). Median time to onset of all events was 12.9 weeks. Dose delay or reduction occurred in 26.3% (84/320) and discontinuation in 2.2% (7/320) of patients with diarrhoea, respectively.

Fistulas (see section 4.4)
In the study in RCC following prior VEGF-targeted therapy (METEOR), fistulas were reported in 1.2% (4/331) of cabozantinib-treated patients and included anal fistulas in 0.6% (2/331) cabozantinib-treated patients. One event was Grade 3; the remainder were Grade 2. Median time to onset was 30.3 weeks.
In the treatment-naïve RCC study (CABOSUN), no cases of fistulas were reported.
In the HCC study (CELESTIAL), fistulas were reported in 1.5% (7/467) of the HCC patients. Median time to onset was 14 weeks.
In the DTC study (COSMIC-311), fistulas (two anal and one pharyngeal fistula) were reported in 1.8 % (3/170) of the cabozantinib treated patients.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of fistula was reported in 0.9% (3/320) of treated patients and the severity was Grade 1.
Fatal fistulas have occurred in the cabozantinib clinical program

Haemorrhage (see section 4.4)
In the study in RCC following prior VEGF-targeted therapy (METEOR), the incidence of severe haemorrhagic events (Grade ≥ 3) was 2.1% (7/331) in cabozantinib-treated RCC patients. Median time to onset was 20.9 weeks.
In the treatment-naïve RCC study (CABOSUN), the incidence of severe haemorrhagic events (Grade ≥ 3) was 5.1% (4/78) in cabozantinib-treated RCC patients.
In the HCC study (CELESTIAL), the incidence of severe haemorrhagic events (Grade ≥ 3) was 7.3% in cabozantinib-treated patients (34/467). Median time to onset was 9.1 weeks.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of ≥ Grade 3 haemorrhage was in 1.9% (6/320) of treated patients.
In the DTC study (COSMIC-311), the incidence of severe haemorrhagic events (grade ≥ 3) was 2.4% in cabozantinib-treated patients (4/170). Median time to onset was 80.5 days.
Fatal haemorrhages have occurred in the cabozantinib clinical program.

Posterior reversible encephalopathy syndrome (PRES) (see section 4.4)
No case of PRES was reported in the METEOR,CABOSUN, CA2099ER or CELESTIAL studies, but PRES has been reported in one patient in the DTC study (COSMIC-311) and rarely in other clinical trials (in 2/4872 subjects; 0.04%).

Elevated liver enzymes when cabozantinib is combined with nivolumab in RCC
In a clinical study of previously untreated patients with RCC receiving cabozantinib in combination with nivolumab, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to cabozantinib monotherapy in patients with advanced RCC (ALT increased of 3.6% and AST increased of 3.3% in METEOR study). The median time to onset of grade ≥ 2 increased ALT or AST was 10.1 weeks (range: 2 to 106.6 weeks; n=85). In patients with grade ≥ 2 increased ALT or AST, the elevations resolved to Grades 0-1in 91% with median time to resolution of 2.29 weeks (range: 0.4 to 108.1 weeks).

Among the 45 patients with Grade ≥2 increased ALT or AST who were rechallenged with either cabozantinib (n=10) or nivolumab (n=10) administered as a single agent or with both (n=25), recurrence of Grade ≥2 increased ALT or AST was observed in 4 patients receiving cabozantinib, in 3 patients receiving nivolumab and 8 patients receiving both cabozantinib and nivolumab.

Hypothyroidism
In the study in RCC following prior VEGF-targeted therapy (METEOR), the incidence of hypothyroidism was 21% (68/331).
In the treatment-naïve RCC study (CABOSUN), the incidence of hypothyroidism was 23% (18/78) in cabozantinib-treated RCC patients.
In the HCC study (CELESTIAL), the incidence of hypothyroidism was 8.1% (38/467) in cabozantinib-treated patients and Grade 3 events in 0.4% (2/467).
In the DTC study (COSMIC-311), the incidence of hypothyroidism was 2.4% (4/170), all grade 1-2, none requiring modification of treatment.
In combination with nivolumab in advanced RCC in first-line treatment (CA2099ER) the incidence of hypothyroidism was 35.6% (114/320) of treated patients.

Reporting of suspected adverse reactions
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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

4.9 Overdose

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agent, protein kinase inhibitor, ATC code: L01EX07.

Mechanism of action
Cabozantinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, 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 the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.

Pharmacodynamic effects
Cabozantinib exhibited dose-related tumour growth inhibition, tumour regression, and/or inhibited metastasis in a broad range of preclinical tumour models.

Cardiac electrophysiology
An increase from baseline in corrected QT interval by Fridericia (QTcF) of 10 – 15 ms on Day 29 (but not on day 1) following initiation of cabozantinib treatment (at a dose of 140 mg once daily) was observed in a controlled clinical trial in medullary thyroid cancer patients. This effect was not associated with a change in

cardiac wave form morphology or new rhythms. No cabozantinib-treated subjects in this study had a confirmed QTcF >500 ms, nor did any cabozantinib-treated subjects in the RCC or HCC studies (at a dose of 60 mg).

Clinical efficacy and safety

Renal cell carcinoma

Randomized study in RCC patients who have received prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)

The safety and efficacy of CABOMETYX for the treatment of renal cell carcinoma following prior vascular endothelial growth factor (VEGF)-targeted therapy were evaluated in a randomized, open-label, multicenter phase 3 study (METEOR). Patients (N=658) with advanced RCC with a clear cell component who had previously received at least 1 prior VEGF receptor tyrosine kinase inhibitor (VEGFR TKI) were randomized (1:1) to receive cabozantinib (N=330) or everolimus (N=328). Patients could have received other prior therapies, including cytokines, and antibodies targeting VEGF, the programmed death 1 (PD-1) receptor, or its ligands. Patients with treated brain metastases were allowed. Progression-free survival (PFS) was assessed by a blinded independent radiology review committee, and the primary analysis was conducted among the first 375 subjects randomized. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumour assessments were conducted every 8 weeks for the first 12 months, then every 12 weeks thereafter.

The baseline demographic and disease characteristics were similar between the cabozantinib and everolimus arms. The majority of the patients were male (75%), with a median age of 62 years. Seventy-one percent (71%) received only one prior VEGFR TKI; 41% of patients received sunitinib as their only prior VEGFR TKI. According to the Memorial Sloan Kettering Cancer Center criteria for prognostic risk category, 46% were favourable (0 risk factors), 42% were intermediate (1 risk factor), and 13% were poor (2 or 3 risk factors). Fifty-four percent (54%) of patients had 3 or more organs with metastatic disease, including lung (63%), lymph nodes (62%), liver (29%), and bone (22%). The median duration of treatment was 7.6 months (range 0.3 – 20.5) for patients receiving cabozantinib and 4.4 months (range 0.21 – 18.9) for patients receiving everolimus.

A statistically significant improvement in PFS was demonstrated for cabozantinib compared to everolimus (Figure 1 and Table 4). A planned interim analysis of OS was conducted at the time of the PFS analysis and did not reach the interim boundary for statistical significance (202 events, HR=0.68 [0.51, 0.90], p=0.006). In a subsequent unplanned interim analysis of OS, a statistically significant improvement was demonstrated for patients randomized to cabozantinib as compared with everolimus (320 events, median of 21.4 months vs. 16.5 months; HR=0.66 [0.53, 0.83], p=0.0003; Figure 2). Comparable results for OS were observed with a follow-up analysis (descriptive) at 430 events.

Exploratory analyses of PFS and OS in the ITT population have also shown consistent results in favour of cabozantinib compared to everolimus across different subgroups according to age (<65 vs. ≥65, sex, MSKCC risk group (favourable, intermediate, poor), ECOG status (0 vs. 1), time from diagnosis to randomisation (<1 year vs. ≥1 year), tumour MET status (high vs. low vs. unknown), bone metastases (absence vs. presence), visceral metastases (absence vs. presence), visceral and bone metastases (absence vs. presence), number of prior VEGFR-TKIs (1 vs. ≥2), duration of first VEGFR-TKI (≤6 months vs. >6 months).

Objective response rate findings are summarized in Table 5.

Figure 1: Kaplan Meier curve for progression-free survival by independent radiology review committee, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (first 375 subjects randomized) (METEOR)

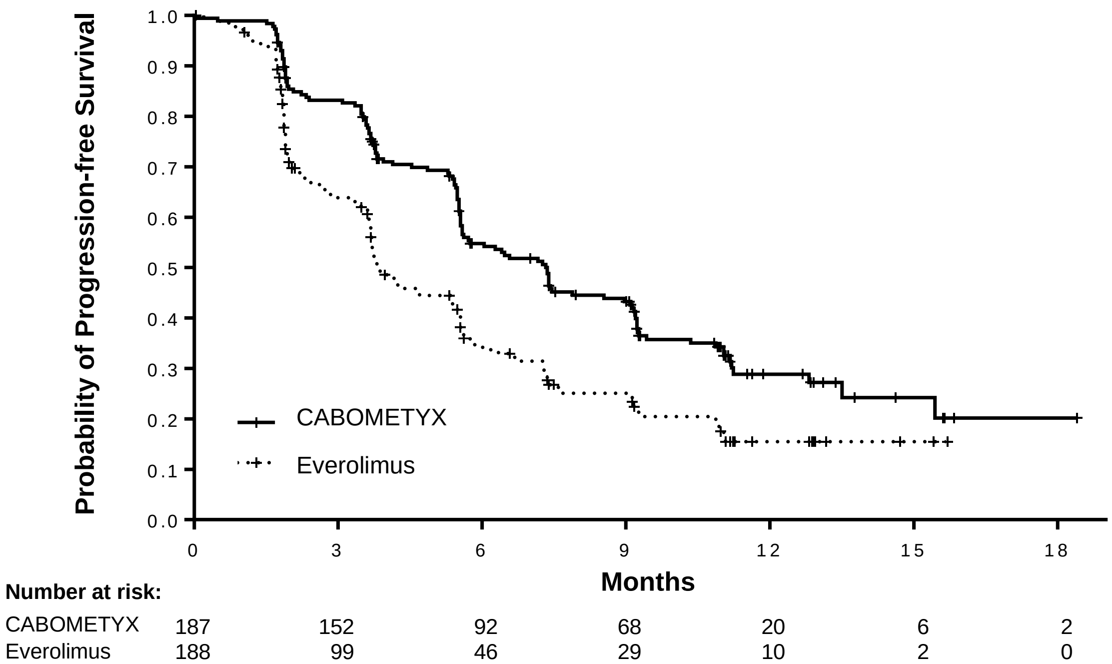
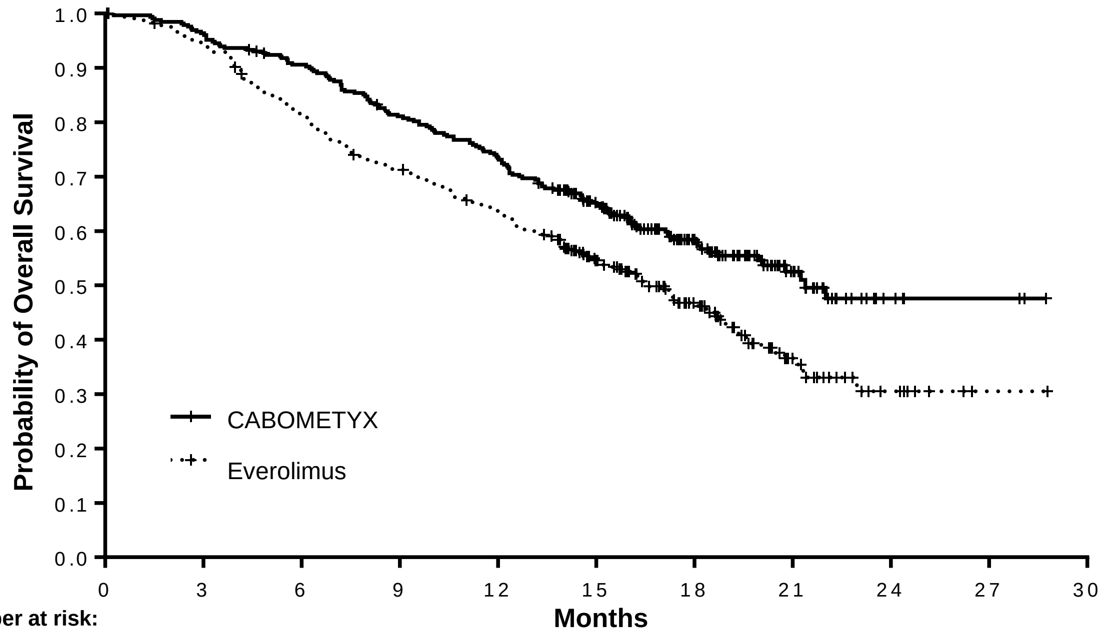


Table 4: Summary of PFS findings by independent radiology review committee in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy **(METEOR)**

	Primary PFS analysis population		**Intent-to-treat population**	
Endpoint	**CABOMETYX**	**Everolimus**	**CABOMETYX**	**Everolimus**
	N = 187	N = 188	N = 330	N = 328
Median PFS (95% CI), months	7.4 (5.6, 9.1)	3.8 (3.7, 5.4)	7.4 (6.6, 9.1)	3.9 (3.7, 5.1)
HR (95% CI), p-value[1]	0.58 (0.45, 0.74), p<0.0001		0.51 (0.41, 0.62), p<0.0001	

[1] stratified log-rank test

Figure 2: Kaplan-Meier curve of overall survival in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy (METEOR)



Number at risk:

CABOMETYX	330	318	296	264	239	178	105	41	6	3	0
Everolimus	328	307	262	229	202	141	82	32	8	1	0

Table 5: Summary of ORR findings per independent radiology committee review (IRC) and investigator review, in RCC subjects following prior vascular endothelial growth factor (VEGF)-targeted therapy

	Primary analysis ORR intent-to-treat population (IRC)		ORR per investigator review intent-to-treat population	
Endpoint	**CABOMETYX**	**Everolimus**	**CABOMETYX**	**Everolimus**
	N = 330	N = 328	N = 330	N = 328
ORR (partial responses only) (95% CI)	17% (13%, 22%)	3% (2%, 6%)	24% (19%, 29%)	4% (2%, 7%)
p-value[1]	p<0.0001		p< 0.0001	
Partial response	17%	3%	24%	4%
Median time to first response, months (95% CI)	1.91 (1.6, 11.0)	2.14 (1.9, 9.2)	1.91 (1.3, 9.8)	3.50 (1.8, 5.6)
Stable disease as best response	65%	62%	63%	63%
Progressive disease as best response	12%	27%	9%	27%

[1] chi-squared test

Randomized study in treatment-naïve renal cell carcinoma patients (CABOSUN)

The safety and efficacy of CABOMETYX for the treatment of treatment-naïve renal cell carcinoma were evaluated in a randomized, open-label, multicenter study (CABOSUN). Patients (N=157) with previously untreated, locally advanced or metastatic RCC with a clear cell component were randomized (1:1) to receive cabozantinib (N=79) or sunitinib (N=78). Patients had to have intermediate or poor risk disease as defined by the International Metastatic RCC Database Consortium (IMDC) risk group categories. Patients were stratified by IMDC risk group and presence of bone metastases (yes/no). Approximately 75% of patients had a nephrectomy prior to onset of treatment.

For intermediate risk disease, one or two of the following risk factors were met, while for poor risk, three or more factors were met: time from diagnosis of RCC to systemic treatment < 1 year, Hgb < LLN, corrected calcium > ULN, KPS < 80%, neutrophil count > ULN and platelet count > ULN.

The primary endpoint was PFS. Secondary efficacy endpoints were objective response rate (ORR) and overall survival (OS). Tumour assessments were conducted every 12 weeks.

The baseline demographic and disease characteristics were similar between the cabozantinib and sunitinib arms. The majority of the patients were male (78%) with a median age of 62 years. Patient distribution by IMDC risk groups was 81% intermediate (1-2 risk factors) and 19% poor (≥3 risk factors). Most patients (87%) had ECOG performance status of 0 or 1; 13% had an ECOG performance status of 2. Thirty-six percent (36%) of patients had bone metastases.

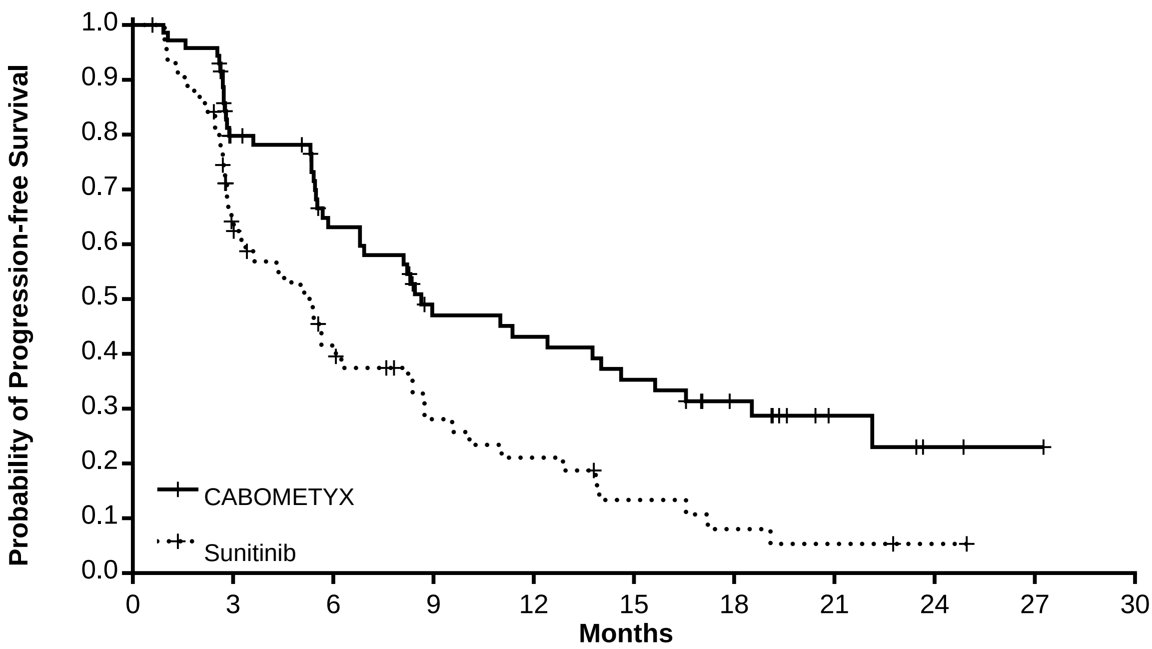
A statistically significant improvement in PFS as retrospectively assessed by a blinded Independent Radiology Committee (IRC) was demonstrated for cabozantinib compared to sunitinib (Figure 3 and Table 6). The results from the investigator determined analysis and IRC-determined analysis of PFS were consistent.

Patients with both positive and negative MET status showed a favourable effect with cabozantinib compared to sunitinib, with greater activity in patients with a positive MET status compared to patients with a negative MET status (HR=0.32 (0.16, 0.63) vs 0.67 (0.37, 1.23)) respectively.

Cabozantinib treatment was associated with a trend for longer survival compared to sunitinib (Table 6). The study was not powered for the OS analysis and the data are immature.

Objective response rate (ORR) findings are summarized in Table 6.

Figure 3: Kaplan Meier curve for progression-free survival by IRC in treatment-naïve RCC subjects



Number at risk:

CABOMETYX	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

Table 6: Efficacy results in treatment-naïve RCC subjects (ITT population, CABOSUN)

	CABOMETYX (N=79)	**Sunitinib (N=78)**

Progression-free survival (PFS) by IRC [a]		
Median PFS in months (95% CI)	**8.6 (6.2, 14.0)**	**5.3 (3.0, 8.2)**
HR (95% CI); stratified [b,c]	0.48 (0.32, 0.73)	
Two-sided log-rank p-value: stratified [b]	p=0.0005	
Progression-free survival (PFS) by investigator		
Median PFS in months (95% CI)	8.3 (6.5, 12.4)	5.4 (3.4, 8.2)
HR (95% CI); stratified [b,c]	0.56 (0.37, 0.83)	
Two-sided log-rank p-value: stratified [b]	p=0.0042	
Overall survival		
Median OS in months (95% CI)	30.3 (14.6, NE)	21.0 (16.3, 27.0)
HR (95% CI); stratified [b,c]	0.74 (0.47, 1.14)	
Objective response rate n (%) by IRC		
Complete responses	0	0
Partial responses	16 (20)	7 (9)
ORR (partial responses only)	16 (20)	7 (9)
Stable disease	43 (54)	30 (38)
Progressive disease	14 (18)	23 (29)
Objective response rate n (%) by investigator		
Complete responses	1 (1)	0
Partial responses	25 (32)	9 (12)
ORR (partial responses only)	26 (33)	9 (12)
Stable disease	34 (43)	29 (37)
Progressive disease	14 (18)	19 (24)

[a] in accord with EU censoring
[b] Stratification factors per IxRS comprise IMDC risk categories (intermediate risk, poor risk and bone metastasis (yes, no)
[c] Estimated using the Cox proportional hazard model adjusted for stratification factors per IxRS. Hazard ratio < 1 indicates progression-free survival in favour of cabozantinib

Randomised phase 3 study of cabozantinib in combination with nivolumab vs. sunitinib (CA2099ER)
The safety and efficacy of cabozantinib 40 mg orally daily in combination with nivolumab 240 mg intravenously every 2 weeks for the first-line treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open label study (CA2099ER). The study included patients (18 years or older) with advanced or metastatic RCC with a clear cell component, Karnofsky Performance Status (KPS) ≥ 70%, and measurable disease as per RECIST v1.1 were included regardless of their PD-L1 status or IMDC risk group. The study excluded patients with autoimmune disease or other medical conditions requiring systemic immunosuppression, patients who had prior treatment with an anti-PD-1, anti PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, poorly controlled hypertension despite antihypertensive therapy, active brain metastases and uncontrolled adrenal insufficiency. Patients were stratified by IMDC prognostic score, PD-L1 tumour expression, and region.

A total of 651 patients were randomised to receive either cabozantinib 40 mg once daily orally in combination with nivolumab 240 mg (n=323) administered intravenously every 2 weeks or sunitinib (n = 328) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off. Treatment continued until disease progression or unacceptable toxicity with nivolumab administration up to 24 months. Treatment beyond initial Investigator-assessed RECIST version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug, as determined by investigator. First tumour assessment post-baseline was performed at 12 weeks (± 7 days) following randomisation. Subsequent tumour assessments occurred at every 6 weeks (± 7 days) until Week 60, then every 12 weeks (± 14 days) until radiographic progression, confirmed by the Blinded Independent Central review (BICR). The primary efficacy outcome measure was PFS as determined by a BICR. Additional efficacy measures included OS and ORR as key secondary endpoints.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 28-90) with 38.4% ≥ 65 years of age and 9.5% ≥ 75 years of age. The majority of patients were male (73.9%) and white (81.9%). Eight percent of patients were Asian, 23.2% and 76.5% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. Patient distribution by IMDC risk categories was 22.6% favourable, 57.6% intermediate, and 19.7% poor. For tumour PD-L1 expression, 72.5% of patients had PD-L1 expression < 1% or indeterminate and 24.9% of patients had PD-L1 expression ≥ 1%. 11.5% of patients had tumours with sarcomatoid features. The median duration of treatment was 14.26 months (range: 0.2-27.3 months) in cabozantinib with nivolumab-treated patients and was 9.23 months (range: 0.8-27.6 months) in sunitinib-treated patients.

The study demonstrated a statistically significant benefit in PFS, OS, and ORR for patients randomised to cabozantinib in combination with nivolumab as compared to sunitinib. Efficacy results from the primary analysis (minimum follow-up 10.6 months; median follow-up 18.1 months) are shown in Table 7.

Table 7: Efficacy results (CA2099ER)

	nivolumab + cabozantinib (n = 323)	**sunitinib (n = 328)**
PFS per BICR		
Events	144 (44.6%)	191 (58.2%)
Hazard ratio[a]	0.51	
95% CI	(0.41, 0.64)	
p-value[b, c]	< 0.0001	
Median (95% CI)[d]	16.59 (12.45, 24.94)	8.31 (6.97, 9.69)
OS		
Events	67 (20.7%)	99 (30.2%)
Hazard ratio[a]	0.60	
98.89% CI	(0.40, 0.89)	
p-value[b,c,e]	0.0010	
Median (95% CI)	N.E.	N.E. (22.6, N.E.)
Rate (95% CI)		
At 6 months	93.1 (89.7, 95.4)	86.2 (81.9,89.5)
ORR per BICR (CR + PR)	180 (55.7%)	89 (27.1%)
(95% CI)[f]	(50.1, 61.2)	(22.4, 32.3)
Difference in ORR (95% CI)[g]	28.6 (21.7, 35.6)	
p-value[h]	< 0.0001	
Complete response (CR)	26 (8.0%)	15 (4.6%)
Partial response (PR)	154 (47.7%)	74 (22.6%)
Stable disease (SD)	104 (32.2%)	138 (42.1%)
Median duration of response[d]		
Months (range)	20.17 (17.31, N.E.)	11.47 (8.31, 18.43)
Median time to response		
Months (range)	2.83 (1.0-19.4)	4.17 (1.7-12.3)

[a] Stratified Cox proportional hazards model. Hazard ratio is nivolumab and cabozantinib over sunitinib.
[b] 2-sided p-values from stratified regular log-rank test.
[c] Log-rank test stratified by IMDC prognostic risk score (0, 1-2, 3-6), PD-L1 tumour expression (≥1% versus <1% or indeterminate) and region (US/Canada/W Europe/N Europe, ROW) as entered in the IRT.
[d] Based on Kaplan-Meier estimates.
[e] Boundary for statistical significance p-value <0.0111.
[f] CI based on the Clopper and Pearson method.
[g] Strata adjusted difference in objective response rate (nivolumab+cabozantinib - Sunitinib) based on DerSimonian and Laird
[h] 2-sided p-value from CMH test.
NE = non-estimable

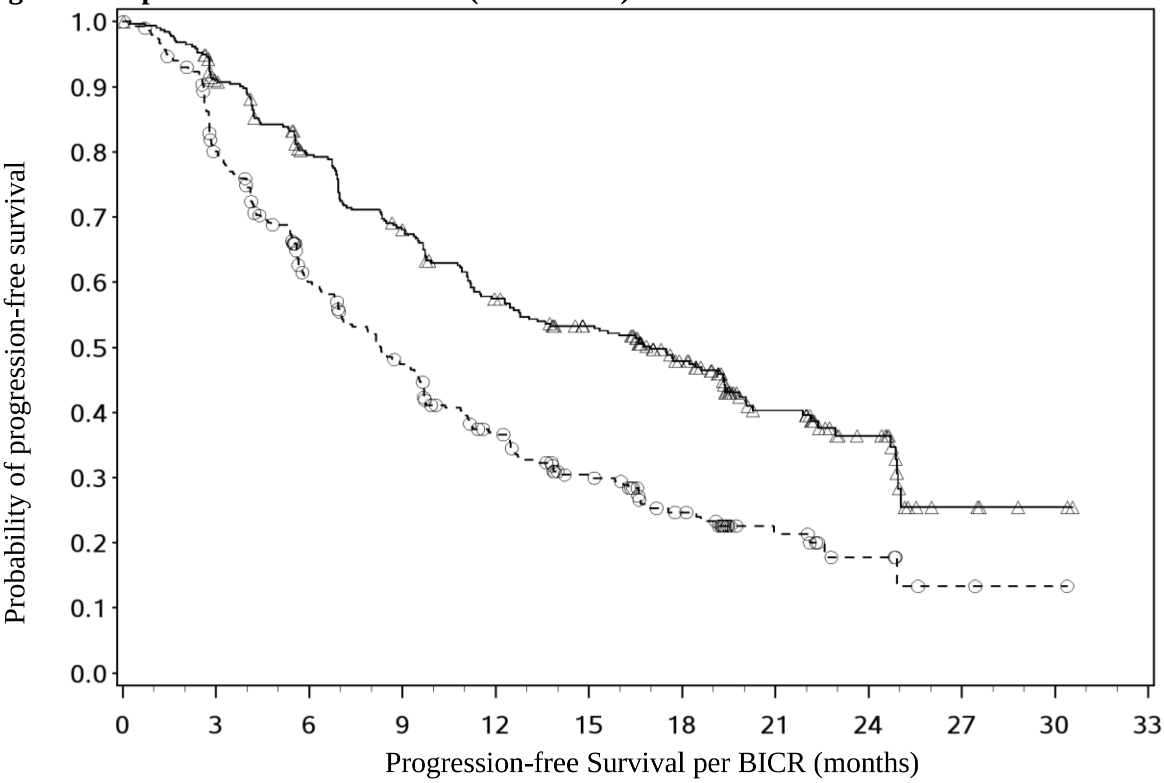
The primary analysis of PFS included censoring for new anti-cancer treatment (Table 7). Results for PFS with and without censoring for new anti-cancer treatment were consistent.

PFS benefit was observed in the cabozantinib in combination with nivolumab arm vs. sunitinib regardless of tumour PD L1 expression. Median PFS for tumour PD L1 expression ≥ 1% was 13.08 for cabozantinib in combination with nivolumab, and was 4.67 months in the sunitinib arm (HR = 0.45; 95% CI: 0.29, 0.68). For tumour PD L1 expression < 1%, the median PFS was 19.84 months for the cabozantinib in combination with nivolumab, and 9.26 months in the sunitinib arm (HR = 0.50; 95% CI: 0.38, 0.65).

PFS benefit was observed in the cabozantinib in combination with nivolumab arm vs. sunitinib regardless of the (IMDC) risk category. Median PFS for the favourable risk group was not reached for cabozantinib in combination with nivolumab, and was 12.81 months in the sunitinib arm (HR = 0.60; 95% CI: 0.37, 0.98). Median PFS for the intermediate risk group was 17.71 months for cabozantinib in combination with nivolumab and was 8.38 months in the sunitinib arm (HR = 0.54; 95% CI: 0.41, 0.73). Median PFS for the poor risk group was 12.29 months for cabozantinib in combination with nivolumab and was 4.21 months in the sunitinib arm (HR = 0.36; 95% CI: 0.23, 0.58).

An updated PFS and OS analysis were performed when all patients had a minimum follow-up of 16 months and a median follow-up of 23.5 months (see figures 4 and 5). The PFS hazard ratio was 0.52 (95% CI: 0.43; 0.64). The OS hazard ratio was 0.66 (95% CI: 0.50; 0.87). Updated efficacy data (PFS and OS) in subgroups for the IMDC risk categories and PD-L1 expression levels confirmed the original results. With the updated analysis, median PFS is reached for the favourable risk group.

Figure 4: Kaplan-Meier curves of PFS (CA2099ER)



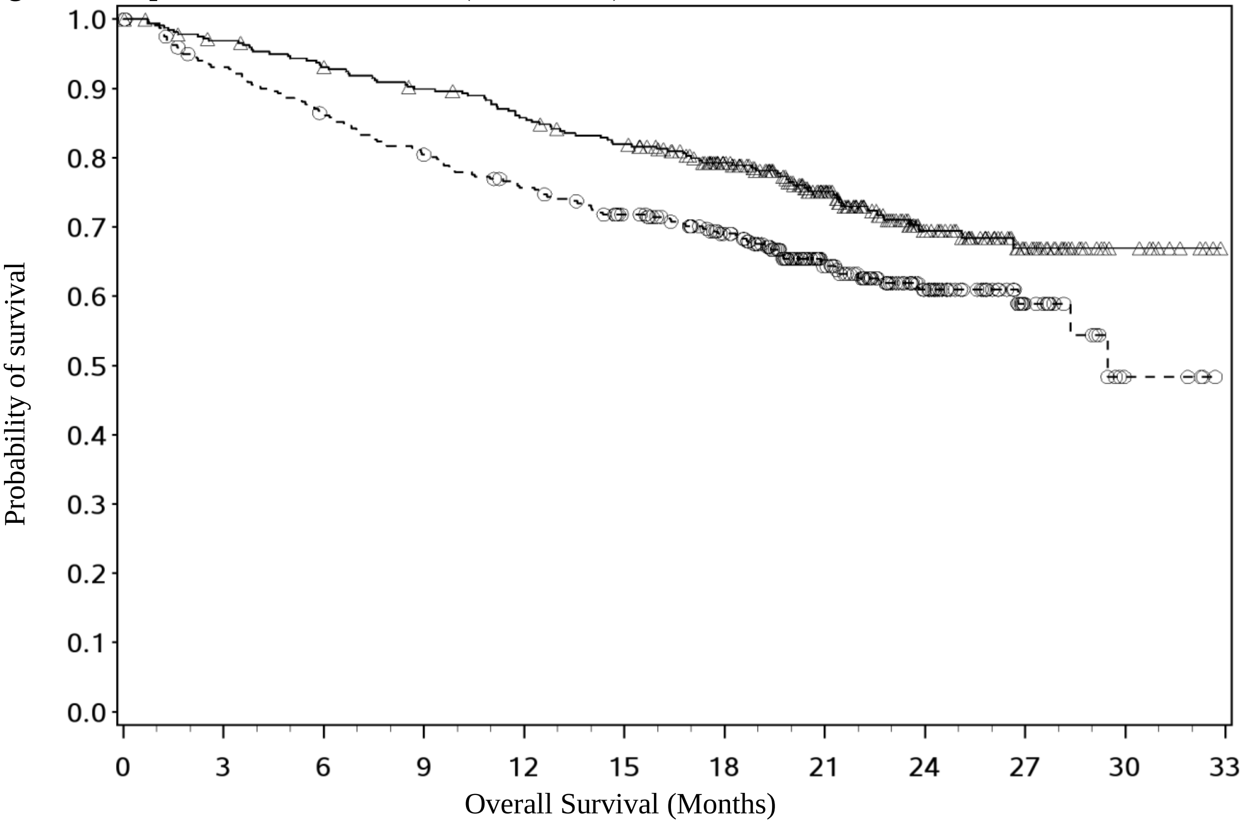
Number of subjects at risk

Nivolumab + cabozantinib											
323	280	236	201	166	145	102	56	26	5	2	0
Sunitinib											
328	230	160	122	87	61	37	17	7	2	1	0

—△— Nivolumab + cabozantinib (events: 175/323), median and 95.0% CI: 16.95 (12.58, 19.38)

- -⊖- - Sunitinib (events: 206/328), median and 95.0% CI:8.31 (6.93, 9.69)

Figure 5 : Kaplan Meier curves of OS (CA2099ER)



Number of subjects at risk

Nivolumab + cabozantinib											
323	308	295	283	269	255	220	147	84	40	10	0
Sunitinib											
328	295	272	254	236	217	189	118	62	22	4	0

Nivolumab + cabozantinib (events: 86/323), median and 95% CI: NE

Sunitinib (events: 116/328), median and 95% CI:29.47 (28.35, NE)

Hepatocellular carcinoma

Controlled study in patients who have received sorafenib (CELESTIAL)

The safety and efficacy of CABOMETYX were evaluated in a randomized, double-blind, placebo-controlled phase 3 study (CELESTIAL). Patients (N=707) with HCC not amenable to curative treatment and who had previously received sorafenib for advanced disease were randomized (2:1) to receive cabozantinib (N=470) or placebo (N=237). Patients could have received one other prior systemic therapy for advanced disease in addition to sorafenib. Randomization was stratified by aetiology of disease (HBV [with or without HCV], HCV [without HBV], or other), geographic region (Asia, other regions) and by presence of extrahepatic spread of disease and/or macrovascular invasions (Yes, No).

The primary efficacy endpoint was overall survival (OS). Secondary efficacy endpoints were progression-free survival (PFS) and objective response rate (ORR), as assessed by the investigator using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1. Tumour assessments were conducted every 8 weeks. Subjects continued blinded study treatment after radiological disease progression whilst they experienced clinical benefit or until the need for subsequent systemic or liver-directed local anticancer therapy. Crossover from placebo to cabozantinib was not allowed during the blinded treatment phase.

The baseline demographic and disease characteristics were similar between the cabozantinib and placebo arms and are shown below for all 707 randomised patients.

The majority of patients (82%) were male: the median age was 64 years. The majority of patients (56%) were Caucasian and 34% of patients were Asian. Fifty three percent (53%) of patients had ECOG performance status (PS) 0 and 47% had ECOG PS 1. Almost all patients (99%) were Child Pugh A and 1%

were Child Pugh B. Aetiology for HCC included 38% hepatitis B virus (HBV), 21% hepatitis C virus (HCV), 40% other (neither HBV nor HCV). Seventy-eight percent (78%) had macroscopic vascular invasion and/ or extra-hepatic tumour spread, 41% had alfa-fetoprotein (AFP) levels ≥400µg/L, 44% had been treated by loco-regional transarterial embolisation or chemoinfusion procedures, 37% had radiotherapy prior to cabozantinib treatment. Median duration of sorafenib treatment was 5.32 months. Seventy-two percent (72%) of patients had received 1 and 28% had received 2 prior systemic therapy regimens for advanced disease.
A statistically significant improvement in OS was demonstrated for cabozantinib compared to placebo (Table 8 and Figure 6).

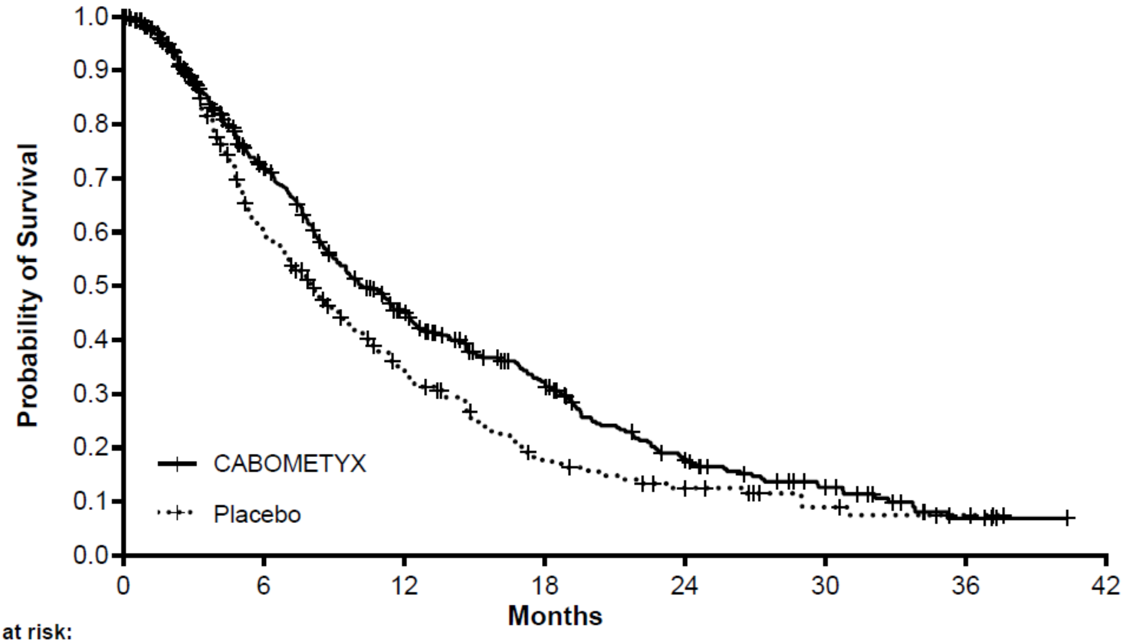
PFS and ORR findings are summarized in Table 8.

Table 8: Efficacy results in HCC (ITT population, CELESTIAL)

	CABOMETYX (N=470)	**Placebo (N=237)**
Overall survival		
Median OS (95% CI), months	10.2 (9.1, 12.0)	8.0 (6.8, 9.4)
HR (95% CI)[1,2]	0.76 (0.63, 0.92)	
p-value[1]	p=0.0049	
Progression-free survival (PFS)[3]		
Median PFS in months (95% CI)	5.2 (4.0, 5.5)	1.9 (1.9, 1.9)
HR (95% CI)[1]	0.44 (0.36, 0.52)	
p-value[1]	p<0.0001	
Kaplan-Meier landmark estimates of percent of subjects event-free at 3 months		
% (95% CI)	67.0% (62.2%, 71.3%)	33.3% (27.1%, 39.7%)
Objective response rate n (%)[3]		
Complete responses (CR)	0	0
Partial responses (PR)	18 (4)	1 (0.4)
ORR (CR+PR)	18 (4)	1 (0.4)
p-value[1,4]	p=0.0086	
Stable disease	282 (60)	78 (33)
Progressive disease	98 (21)	131 (55)

[1] 2-sided stratified log-rank test with aetiology of disease (HBV [with or without HCV], HCV [without HBV], or other), geographic region (Asia, other regions), and presence of extrahepatic spread of disease and/or macrovascular invasion (Yes, No) as stratification factors (per IVRS data)
[2] estimated using the Cox proportional-hazard model
[3] as assessed by investigator per RECIST 1.1
[4] stratified Cochran-Mantel-Haenszel (CMH) test

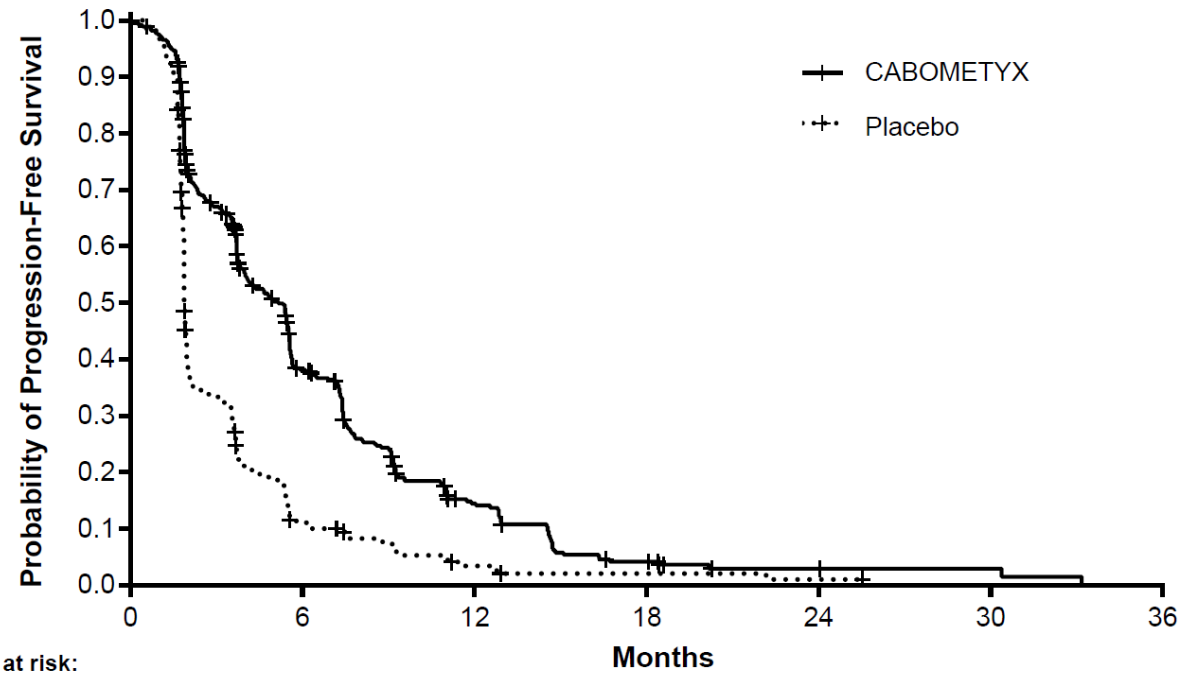
Figure 6: Kaplan-Meier curve of overall survival (CELESTIAL)



Number at risk:

	0	6	12	18	24	30	36	42
CABOMETYX	470	281	159	93	44	22	4	0
Placebo	237	117	57	25	15	7	3	0

Figure 7: Kaplan Meier curve for progression-free survival (CELESTIAL)



Number at risk:

	0	6	12	18	24	30	36
CABOMETYX	470	131	39	10	3	2	0
Placebo	237	21	5	2	1	0	0

The incidence of systemic non-radiation and local liver-directed systemic non-protocol anticancer therapy (NPACT) was 26% in the cabozantinib arm and 33% in the placebo arm. Subjects receiving these therapies had to discontinue study treatment. An exploratory OS analysis censoring for the use of NPACT supported the primary analysis: the HR, adjusted for stratification factors (per IxRS), was 0.66 (95% CI: 0.52, 0.84; stratified logrank p-value = 0.0005). The Kaplan- Meier estimates for median duration of OS were 11.1

months in the cabozantinib arm versus 6.9 months in the placebo arm, an estimated 4.2-month difference in the medians.

Non-disease specific quality of life (QoL) was assessed using the EuroQoL EQ-5D-5L. A negative effect of cabozantinib versus placebo on the EQ-5D utility index score was observed during the first weeks of treatment. Only limited QoL data are available after this period.

Differentiated thyroid carcinoma (DTC)
Placebo -Controlled study in adult patients who have received prior systemic therapy and are refractory or not eligible to radioactive iodine (COSMIC-311)
The safety and efficacy of CABOMETYX was evaluated in COSMIC-311, a randomised (2:1), double-blind, placebo-controlled, multicenter trial in adult patients with locally advanced or metastatic disease with differentiated thyroid cancer that had progressed following up to two prior VEGFR-targeting therapy (including, but not limited to, lenvatinib or sorafenib) and were radioactive iodine-refractory or not eligible. Patients with measurable disease and documented radiographic progression per RECIST 1.1 per the Investigator, during or following treatment with VEGFR- targeting TKI, were randomised (N=258) to receive cabozantinib 60 mg orally once daily (N=170) or placebo (N=88).

Randomisation was stratified by prior receipt of lenvatinib (yes vs. no) and age (≤ 65 years vs. > 65 years). Eligible patients randomised to placebo were allowed to cross-over to cabozantinib upon confirmation of progressive disease by blinded independent radiology review committee (BIRC).
Subjects continued blinded study treatment as long as they experienced clinical benefit or until there was unacceptable toxicity. The primary efficacy outcome measures were progression-free survival (PFS) in the ITT population, and objective response rate (ORR) in the first 100 randomised patients, as assessed by BIRC per RECIST 1.1. Tumour assessments were conducted every 8 weeks after randomisation during the first 12 months on study, then every 12 weeks thereafter. Overall survival (OS) was an additional endpoint.

The primary analysis of PFS included 187 randomised patients, 125 to cabozantinib and 62 to placebo. Baseline demographics and disease characteristics were generally balanced for both treatment groups. The median age was 66 years (range 32 to 85 years), 51% being ≥ 65 years of age, 13% being ≥ 75 years of age. The majority of patients were white (70%), 18% of patients were Asian and 55% were female. Histologically, 55% had a confirmed diagnosis of papillary thyroid carcinoma, 48% had follicular thyroid carcinoma including 17% patients with Hürthle cell thyroid cancer.
Metastases were present in 95% of the patients: lungs in 68%, lymph nodes in 67%, bone in 29%, pleura in 18% and liver in 15%. Five patients had not received prior RAI due to ineligibility, 63% had received prior lenvatinib, 60% had received prior sorafenib and 23% had received both sorafenib and lenvatinib. Baseline ECOG performance status was 0 (48%) or 1 (52%).
The median duration of treatment was 4.4 months in the cabozantinib arm and 2.3 months in the placebo arm.

The results of the primary analysis (with a cut-off date of 19 August 2020 and median follow up 6.2 months for the PFS), and the updated analysis (with a cut-off date of 08 February 2021 and median follow-up 10.1 months for the PFS) are presented in Table 9. The trial did not demonstrate a statistically significant improvement in ORR for patients randomised to cabozantinib (n=67) compared with placebo (n=33): 15% vs. 0%. The trial demonstrated a statistically significant improvement in PFS (median follow up 6.2 months) for patients randomised to cabozantinib (n=125) compared with placebo (n=62).
An updated analysis of PFS and OS (median follow up 10.1 months) was performed including 258 randomised patients, 170 to cabozantinib and 88 to placebo.
The overall survival analysis was confounded as placebo-treated subjects with confirmed disease progression had the option to cross over to cabozantinib.

Table 9: Efficacy Results from COSMIC-311

	Primary Analysis[1] (ITT)		**Updated Analysis[2] (Full ITT)**	
	CABOMETYX (n=125)	**Placebo (n=62)**	**CABOMETYX (n=170)**	**Placebo (n=88)**
Progression-Free Survival*				
Number of Events, (%)	31 (25)	43 (69)	62 (36)	69 (78)
Progressive Disease	25 (20)	41 (66)	50 (29)	65 (74)
Death	6 (4.8)	2 (3.2)	12 (7.1)	4 (4.5)
Median PFS in Months (96% CI)	NE (5.7, NE)	1.9 (1.8, 3.6)	11.0 (7.4, 13.8)	1.9 (1.9, 3.7)
Hazard Ratio (96% CI)[3]	0.22 (0.13, 0.36)		0.22 (0.15, 0.32)	
p-value[4]	< 0.0001			
Overall Survival				
Events, n (%)	17 (14)	14 (23)	37 (22)	21 (24)
Hazard Ratio[3] (95% CI)	0.54 (0.27, 1.11)		0.76 (0.45, 1.31)	
	Primary Analysis[1]			
Objective response rate (ORR)[5]				
	CABOMETYX (n=67)		**Placebo (n=33)**	
Overall response, (%)	10 (15)		0 (0)	
Complete response	0		0	
Partial response	10 (15)		0	
Stable disease	46 (69)		14 (42)	
Progressive disease	4 (6)		18 (55)	

* The primary analysis of PFS included censoring for new anti-cancer treatment. Results for PFS with and without censoring for new anti-cancer treatment were consistent.

CI, confidence interval; NE, not evaluable

[1] The cut-off date of the primary analysis is 19 August 2020.

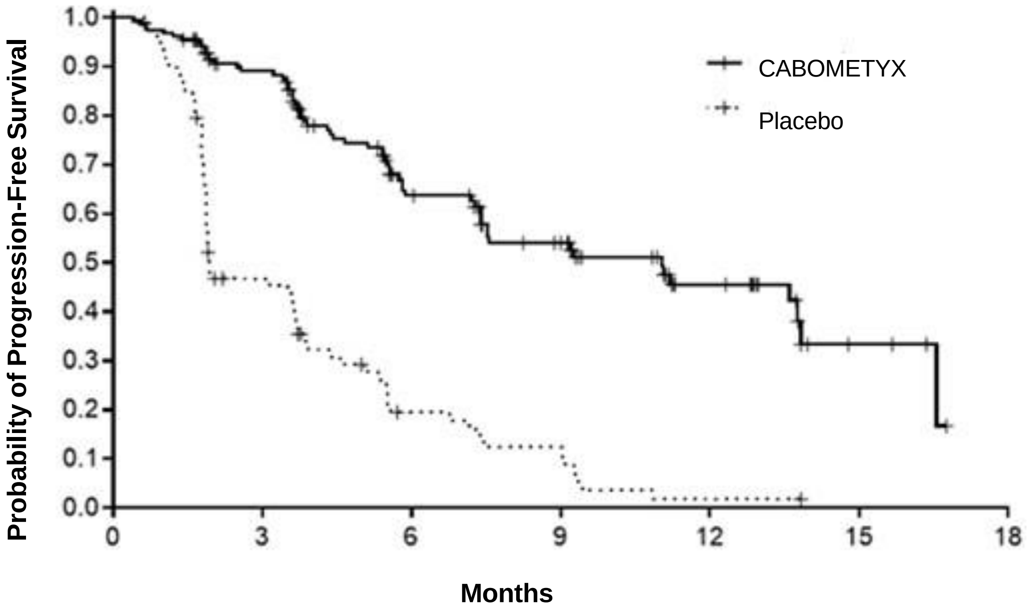
[2] The cut-off date of the secondary analysis is 08 February 2021.

[3] Estimated using the Cox proportional-hazard model.

[4] Log-rank test stratified by receipt of prior lenvatinib (yes vs. no) and age (≤ 65 years vs. > 65 years) as stratification factors (per IXRS data).

[5] Based on the first 100 patients included in the study with a median follow-up of 8.9 months, n=67 in CABOMETYX group and n=33 in placebo group. The improvement in ORR was not statistically significant.

Figure 8: Kaplan-Meier Curve of Progression-Free Survival in COSMIC-311 (updated analysis [cut-off date: 08 February 2021], N=258)



Number at risk:							
CABOMETYX	170	117	59	41	20	4	0
Placebo	88	33	11	7	1	0	0

5.2 Pharmacokinetic properties

Absorption

Following oral administration of cabozantinib, peak cabozantinib plasma concentrations are reached at 3 to 4 hours post-dose. Plasma-concentration time profiles show a second absorption peak approximately 24 hours after administration, which suggests that cabozantinib may undergo enterohepatic recirculation.

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 C_{max} 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.

Bioequivalence could not be demonstrated between the cabozantinib capsule and tablet formulations following a single 140 mg dose in healthy subjects. A 19% increase in the C_{max} of the tablet formulation compared to the capsule formulation was observed. A less than 10% difference in the AUC was observed between cabozantinib tablet and capsule formulations.

Distribution

Cabozantinib is highly protein bound *in vitro* in human plasma (≥ 99.7%). Based on the population-pharmacokinetic (PK) model, the volume of distribution of the central compartment (Vc/F) was estimated to be 212 L.

Biotransformation

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-catalysed 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 (ie, a <20% reduction).

Elimination

In a population PK analysis of cabozantinib using data collected from 1883 patients and 140 healthy volunteers following oral administration of a range of doses from 20 to 140 mg, the plasma terminal half-life of cabozantinib is approximately 110 hours. Mean clearance (CL/F) at steady-state was estimated to be 2.48 L/hr. Within a 48-day collection period after a single dose of ^{14}C-cabozantinib in healthy volunteers, approximately 81% of the total administered radioactivity was recovered with 54% in faeces and 27% in urine.

Pharmacokinetics in special patient populations

Renal impairment

In a renal impairment study conducted with a single 60 mg dose of cabozantinib, the ratios of geometric LS mean for total plasma cabozantinib, C_{max} and $AUC_{0\text{-}inf}$ were 19% and 30% higher, for subjects with mild renal impairment (90% CI for C_{max} 91.60% to 155.51%; $AUC_{0\text{-}inf}$ 98.79% to 171.26%) and 2% and 6-7% higher (90% CI for C_{max} 78.64% to 133.52%; $AUC_{0\text{-}inf}$ 79.61% to 140.11%), for subjects with moderate renal impairment compared to subjects with normal renal function. The geometric LS means for unbound plasma cabozantinib $AUC_{0\text{-}inf}$ was 0.2% higher for subjects with mild renal impairment (90% CI 55.9% to 180%)

and 17% higher (90% CI 65.1% to 209.7%) for subjects with moderate renal impairment compared to subjects with normal renal function. Subjects with severe renal impairment have not been studied.

Hepatic impairment
Based on an integrated population pharmacokinetic analysis of cabozantinib in healthy subjects and cancer patients (including HCC), no clinically significant difference in the mean cabozantinib plasma exposure was observed amongst subjects with normal liver function (n=1425) and mild hepatic impairment (n=558). There is limited data in patients with moderate hepatic impairment (n=15) as per NCI-ODWG (National Cancer Institute – Organ Dysfunction working Group) criteria. The pharmacokinetics of cabozantinib was not evaluated in patients with severe hepatic impairment.

Race
A population PK analysis did not identify clinically relevant differences in PK of cabozantinib based on race.

Paediatrics
Data obtained from simulation performed with the population pharmacokinetic model developed in healthy subjects as well as adult patients with different type of malignancies show that in adolescent patients aged 12 years and older, a dose of 40 mg of cabozantinib once daily for patients < 40 kg, or a dose of 60 mg once daily in patients ≥ 40 kg results in a similar plasma exposure attained in adults treated with 60 mg of cabozantinib once daily (see section 4.2).

5.3 Preclinical safety data

Adverse reactions not observed in clinical trials, 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.

Cabozantinib has shown no mutagenic or clastogenic potential in a standard battery of genotoxicity assays. The carcinogenic potential of cabozantinib has been evaluated in two species: rasH2 transgenic mice and Sprague-Dawley rats. In the 2-year rat carcinogenicity study, cabozantinib-related neoplastic findings consisted of an increased incidence of benign pheochromocytoma, alone or in combination with malignant pheochromocytoma/complex malignant pheochromocytoma of the adrenal medulla in both sexes at exposures well below the intended exposure in humans. The clinical relevance of the observed neoplastic lesions in rats is uncertain, but likely to be low.
Cabozantinib was not carcinogenic in the rasH2 mouse model at a slightly higher exposure than the intended human therapeutic exposure.

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.

Embryo-foetal development studies were performed in rats and rabbits. In rats, cabozantinib caused postimplantation loss, foetal oedema, 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.

Juvenile rats (comparable to a >2 year old paediatric 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 lymph node lymphoid hyperplasia. Findings in uterus/ovaries and decreased haematopoiesis appeared to be transient, while effects on bone parameters and liver pigmentation were sustained. Juvenile rats (correlating to a <2 year paediatric population) showed similar treatment-related findings with additional findings in male reproductive system (degeneration and/or atrophy of seminiferous tubules in testes, reduced luminal sperm in epididymis), and appeared to be more sensitive to cabozantinib-related toxicity at comparable dose levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Tablet content</u>
Microcrystalline cellulose
Lactose anhydrous
Croscarmellose sodium
Hydroxypropyl cellulose
Magnesium stearate
Colloidal silicon dioxide (anhydrous)

<u>Film-coating</u>
Opadry®yellow components:
Hypromellose (HPMC) 2910
Titanium dioxide
Triacetin
Iron oxide yellow

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

HDPE bottle with a polypropylene child-resistant closure and three silica gel desiccant canisters. Each bottle contains 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Ipsen Pharma
65 quai Georges Gorse
92100 Boulogne-Billancourt
France

8. LICENSE HOLDER

Medison Pharma Ltd.

10 Hashiloach St., P.O.B 7090, Petach Tikva

9. REGISTRATION NUMBERS

Cabometyx® 20 mg: 160-99-35263-00
Cabometyx® 40 mg: 161-01-35264-00
Cabometyx® 60 mg: 161-02-35265-00

Revised in January 2023 according to MOH guidelines.