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EMA/CHMP/616303/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report

Zemfirza

International non-proprietary name: Cediranib maleate

Procedure No. EMEA/H/C/004003

Note

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

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List of abbreviations

ADR	Adverse drug reaction
AE	Adverse event
AUC	Area under the plasma concentration-time curve
AUCss	Area under plasma concentration-time curve during a dosing interval atsteady state
BCRP	Breast cancer resistance protein
BICR	Blinded independent central review
BRCA	Breast cancer susceptibility protein
BRCAm	BRCA mutation
BRCAwt	BRCA wild type
CA125	Cancer antigen 125
CI	Confidence interval
c-kit	Stem cell factor receptor
Cmax	Maximum plasma concentration
CR	Complete response
CRC	Colorectal cancer
CRF	Case report form
CSR	Clinical study report
Css,max	Maximum (peak) steady state drug concentration in plasma during dosing interval
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
CYP3A4	Cytochrome P450-3A4
DC	Direct compression
DCE-MRI	Dynamic contrast-enhanced magnetic resonance imaging
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FaSSIF	Fasted state small intestinal fluid
GCIG	Gynaecological Cancer InterGroup
HR	Hazard ratio
HRQoL	Health-related quality of life

iAUC60	Area under the tumour contrast enhancement curve over first 60 seconds
ICON6	International Collaboration for Ovarian Neoplasia 6
KM	Kaplan-Meier
LS	Least square
LVD	Left ventricular dysfunction
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
MDR1	Multi-drug resistance 1 protein
MRC	Medical Research Council
MRC-CTU	Medical Research Council – Clinical Trials Unit
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute (at the National Institutes of Health), the US Federal Government's principal agency for cancer research and training
NCIC	National Cancer Institute of Canada
NSCLC	Non-small cell lung cancer
od	Once daily
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptor
Pgp	P-glycoprotein
PFS	Progression-free survival
PK	Pharmacokinetics
PLD	Pegylated liposomal doxorubicin
PR	Partial response
PRES	Posterior reversible encephalopathy syndrome
PSR	Platinum-sensitive relapsed
PT	Preferred Term
QC	Quality control
QLQ-C30 (EORTC)	quality of life questionnaire-core 30
QLQ-OV28 (EORTC)	quality of life questionnaire - ovarian cancer module

QTc	Corrected QT interval
RECIST	Response Evaluation Criteria in Solid Tumours
rGBM	Recurrent glioblastoma
RMP	Risk Management Plan
RMST	Restricted mean survival time
SAE	Serious adverse events
SAP	Statistical Analysis Plan
SDV	Source data verification
SmPC	Summary of Product Characteristics
t1/2	Half-life
t1/2λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
TKI	Tyrosine kinase inhibitor
TSH	Thyroid stimulating hormone
UGT	Glucuronidation
UK	United Kingdom
US	United States of America
VEGFR	Vascular endothelial growth factor receptor

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Cediranib, an orphan medicinal product in the following indication:

in combination with platinum-based chemotherapy followed by maintenance monotherapy is indicated for the treatment of adult patients with platinum sensitive relapsed (PSR) ovarian cancer (including fallopian tube or primary peritoneal).

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time.

Proposal for questions to be posed to additional experts

No

Proposal for inspection

GMP inspection(s)

No routine or triggered GMP inspections are requested.

GCP inspection(s)

A GCP inspection in a number of sites has raised significant issues, which require further discussion.

New active substance status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that cediranib maleate is qualified as a new active substance.

2. Executive summary

2.1. Problem statement

Ovarian cancer is a serious and life-threatening disease that ranks as the seventh most common type of cancer and the seventh most common cause of cancer death in women worldwide (Ferlay et al 2012). In the European Union (EU) in 2012, ovarian cancer was estimated to be the sixth most common type of female cancer (13.1 new cases per 100,000) and the fifth leading cause of cancer mortality in women (7.6 deaths per 100,000) (Ferlay et al 2013).

Ovarian cancer is predominantly a disease of older, postmenopausal women with the majority (>80%) of cases being diagnosed in women over 50 years. It is one of the most difficult cancers to diagnose early, due to the absence of disease-specific symptoms, and the low predictive value of screening strategies. Consequently, >70% of women with ovarian cancer present with advanced disease at diagnosis. Advanced disease is characterised by metastatic deposits over the peritoneum that cause ascites and can form fibrous adhesions binding adjacent loops of the intestine, causing bowel obstruction. Extension of the disease beyond the abdominal cavity can be presented by pleural effusions causing dyspnoea and other respiratory symptoms. Bowel obstruction is a distinctive dismal characteristic of ovarian cancer, leading to deterioration in performance status, weight loss, nausea, vomiting and malnutrition. In general, the outcome for women with advanced disease with distant

metastases is relatively poor; 5-year survival rates for woman with local, regional and distant disease are 92%, 72% and 27%, respectively (American Cancer Society 2014).

Front-line chemotherapy for epithelial ovarian cancer (FIGO stage II–IV)

The risks of recurrence for disease spread beyond the ovary are significant, and chemotherapy is recommended for all patients with FIGO stage II–IV disease post-surgery. Standard chemotherapy consists of a combination of paclitaxel 175 mg/m^2 and carboplatin AUC 6-5, both administered intravenously every 3 weeks. This has been the standard treatment of more than 15 years, and clinical trials in the last decade adding a third drug, such as the large Gynaecologic Cancer Inter Group (GCIG) ICON-5/GOG 182 trial, have not been shown to improve PFS or OS in these patients. The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. Usually six cycles of treatment are given; no evidence exists to suggest that more than six cycles results in a better outcome. While survival benefits are seen in trials with platinum-based therapy, many women undergo several lines of treatment, making dissection of the contribution of individual therapies, particularly first-line therapy, more complex (Ledermann, 2013).

Targeted therapy

Angiogenesis is an important component driving the growth of ovarian cancer. Two large randomised clinical trials (GOG-218 and ICON-7) have assessed the addition of bevacizumab to the combination of paclitaxel and carboplatin in front-line therapy. Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor. In both trials patients in the experimental arm received bevacizumab intravenously every 3 weeks during the chemotherapy phase, followed by a limited period of maintenance with the same schedule of bevacizumab. GOG-218 included a second experimental arm of bevacizumab with chemotherapy, followed by maintenance with a placebo. There were significant differences in both trials in terms of dose (7.5 mg/kg in the ICON-7 versus 15 mg/kg in the GOG-218), duration (12 months in the ICON-7 versus 15 months in the GOG-218) and patient characteristics (GOG-218 included only patients with stage III–IV and macroscopic residual disease after surgery, but ICON-7 included patients also with high-risk early stage, and patients in a more advanced stage but without macroscopic residual disease after surgery). Both trials met their primary end point, which was PFS for the two bevacizumab maintenance arms. The test for interaction in the ICON-7 trial showed that a greater benefit was observed in the 'high-risk' population, defined as those patients with stage III–IV and residual disease >1 cm. In an interim analysis, OS was prolonged in this group. No survival difference was observed in GOG-218 and mature survival results from ICON-7 are awaited. Bevacizumab has been authorised by the European Commission at 15 mg/kg, with carboplatin and paclitaxel and for ≤15 months or until progression. Bevacizumab is not licensed for ovarian cancer in the USA.

Chemotherapy in recurrent ovarian cancer

Despite optimal upfront surgery and the administration of front-line paclitaxel–carboplatin chemotherapy, approximately 70% of patients will relapse in the first 3 years. The prognosis and probability of response to second-line therapy and subsequent lines depends in great part on the progression-free interval after the last dose of the preceding line of chemotherapy. These categories are based on the response to a rechallenge with platinum-based drugs but probably apply to non-platinum therapies as well. A categorisation, recently updated and confirmed by the GCIG 4th Ovarian Cancer Consensus Meeting, defines 'platinum-refractory' as patients progressing during therapy or within 4 weeks after the last dose; 'platinum-resistant' patients progressing within 6 months of platinum-based therapy; 'partially platinum-sensitive, patients progressing between 6 and 12 months;

and ‘platinum-sensitive’ patients progressing with an interval of more than 12 months (GCIG Consensus).

Treatment of patients with ‘platinum-resistant or refractory’ disease should be focused on quality of life and control of symptoms. Traditionally, this is a poor prognosis population with a short expected OS, usually <12 months. Four different agents, weekly or 3-weekly paclitaxel, topotecan, PLD and gemcitabine, have been shown to have some activity in phase III trials, with overall response rates no >15% and a median PFS of 3–4 months.

Several choices of treatment exist for patients with ‘platinum sensitive’ relapse. As this can occur on more than one occasion, it allows for different combinations to be selected. Most of these combinations involve platinum, but in the ‘partially platinum sensitive’ group, a survival benefit was seen in a subgroup analysis of the OVA-301 trial when trabectedin was combined with PLD, when compared with PLD alone. It has been hypothesised that this benefit is due to the restoration of ‘platinum-sensitivity’ by artificially prolonging the platinum free interval. This is now being explored in two prospective randomised trials.

Targeted therapy in recurrent ovarian cancer

Bevacizumab has shown to improve the PFS of recurrent ovarian cancer in two randomised phase III trials. The first (OCEANS trial) included patients with measurable recurrent ovarian cancer after first-line and a platinum-free interval longer than 6 months. All patients received a combination of carboplatin and gemcitabine at standard doses and were randomised to receive bevacizumab (15 mg/kg) or placebo administered every 3 weeks until progression. The addition of bevacizumab to chemotherapy increased significantly the PFS (HR 0.48, 95% CI 0.38–0.60) and produced an increment in the response rate of 21% (ORR 78.5% versus 57.4%, P < 0.0001)]. A more mature survival analysis has not proven any additional benefit in OS, probably due to the high rate of crossover (41% of patients in the control arm received bevacizumab at some point during progression). Bevacizumab in combination with this chemotherapy is currently authorised for the treatment of patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents (Ledermann, 2013; EPAR Avastin).

2.2. About the product

Cediranib is a VEGF signalling inhibitor that targets all 3 VEGF receptors, which act as receptors for VEGF-A, B, C, D, placental growth factor (PIGF)) and has additional activity against stem cell factor receptor (c-kit)- dependent tumour growth. Cediranib treatment gives dose-dependent inhibition of the growth of tumours.

The applied indication is: Cediranib in combination with platinum-based chemotherapy followed by maintenance monotherapy is indicated for the treatment of adult patients with platinum sensitive relapsed (PSR) ovarian cancer (including fallopian tube or primary peritoneal).

The recommended dose of cediranib (free base) is 20 mg daily. This corresponds with 25.2 mg cedinarib maleate.

An orphan designation has been granted for this medicinal product on 2014-07-29 based on the criterion of ‘significant benefit’. Number in the Community Register of Orphan Medicinal Products: EU/3/14/1303.

2.3. The development programme/compliance with CHMP guidance/scientific advice

A number of scientific advice meetings were scheduled by AstraZeneca. Scientific advice was provided in 2005 by the CHMP to the company on the clinical development of the indication of AZD2171 (cediranib) for the treatment of colorectal cancer. As cediranib with mFOLFOX6 versus bevacizumab with mFOLFOX6 as 1st treatment for patients with advanced colorectal cancer did not result in substantial benefit for the cediranib approach, this indication was not further pursued (refer also to HJ Schmoll et al. J Clin Oncol 30:3588-3595). In September 2007, scientific advice was sought from the EMA on the use of cediranib in comination with platinum-based chemotherapy for the treatment of non small cell lung cancer (NSCLC). Among other issues, the CHMP raised a concern regarding the risk of unblinding: "The study is designed as a double blind study. There are concerns, however, that adverse reactions, e.g. hypertension might unblind the use AZD2171 in a too high proportion of patients to exclude the possibility that investigator bias might influence the study results. If the sponsor decides not to use an independent review committee in the assessment of tumour progression a justification based on study data is expected in relation to the unblinding concern."

Neither this indication was sought, probably because of disappointing results: the addition of cediranib 20 mg daily to carboplatin/paclitaxel chemotherapy increased RR and toxicity, but not survival (refer to SA Laurie et al. Eur J Cancer 50: 706-712).

Scientific advice on the use of cediranib in combination with platinum-based chemotherapy in EOC was obtained from the MHRA (November 2013) and the DKMA (December 2013).

According to the MHRA, the main issue was the credibility of the trial results from a single trial in ovarian cancer in light of the multiple trial failures observed with cediranib in combination with chemotherapy in other indications, for example colorectal cancer and glioblastoma. It is known that if a particular trial result is pursued simply because it is the most impressive observed across a series of trials conducted then, on average when selecting results in this manner, effects will be over-estimated.

Furthermore, the MHRA agreed that the results of the ICON6 study conducted primarily in the UK and Canada could be generalised to the whole EU population, provided that the Company presents adequate discussion that the comparator arm which was primarily carboplatin/paclitaxel doublet chemotherapy (in approximately 75% of patients) is a widely used combination across the EU for the treatment of PSR ovarian cancer. This is particularly important given that bevacizumab in combination with carboplatin and gemcitabine is a recently licensed EU for the indication sought.

In their SA as provided by DHMA on December 5th 2013 it was pointed out –in excerpt- that, regarding the development of cediranib for PSR serous EOC, ICON6 results seem convincing and thus in support for filing an MAA with ICON6 as a single pivotal study. Blinded independent central review on all data from ICON6 will strengthen the presentation of the study results. It is appropriate to present the monotherapy data by dose (supporting the maintenance aspect of ICON6) separately to the combination data (relevant chemotherapy at the 20mg dose). All significant AEs from HORIZON and other AZ- and ISS-sponsored trials should be summarised in the submission documents. Furthermore, in the SA as provided by DHMA on October 29th 2014 it was pointed out, among other issues, that the PFS is clinically meaningful, updated survival data as part of the submission was considered needed, and that 65% maturity would be acceptable. (At that time AZ committed to including the updated survival data in the original submission) It was agreed that the overall clinical evidence base was sufficient to allow a benefit: risk assessment. Study NCI 8348 was also considered supportive in this assessment.

At a pre-submission meeting with the MEB on 27 October, 2014, AstraZeneca (AZ) confirmed that this study did not allow cross over to cediranib but patients could go onto other therapies after progression, though very few received bevacizumab after study entry.

2.4. General comments on compliance with GMP, GLP, GCP

A request for GCP inspection has been adopted for the following clinical study D8480C0037. This was a routine GCP inspection. No specific concerns were known to have been identified by the assessment at the time of adoption of the inspection request. However, in this particular case, the fact that a national inspection conducted at one site in UK revealed critical findings in relation to safety and data integrity has been considered.

A total of four study sites were inspected (of 62 participating study centers). The inspections revealed several GCP findings. The main issues were related to:

- Oversight by the study sponsor which resulted in non-uniform conduct and reporting of data.
- The impact of post-unblinding activities on the reported data
- Lack of available documentation of the appearance of test and control product meant the blinding process is not verifiable.
- The safety profile was considered incomplete.

Please refer to section 5 for a discussion of the impact of the inspection findings on the benefit/risk.

Toxicology studies and safety pharmacology studies were performed in compliance with GLP regulations.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

Article 8(3) of Directive 2001/83/EC as amended. The application is a complete and independent application, for a new active substance.

- Accelerated procedure

  N/A

- Conditional approval

  N/A

- *Exceptional circumstances*

  N/A

- *Significance of paediatric studies*

  Treatment of ovarian carcinoma is listed in the consolidated EMA decision on class waivers, adopted on 19 December 2011 (CW/1/2011).

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Active Substance

General Information

The active substance cediranib maleate is designated as a new active substance. Cediranib maleate has been manufactured consistently as polymorphic form A throughout development and for marketing. Cediranib maleate has no stereocentres and is not hygroscopic. Cediranib maleate is soluble in water with higher solubility at low pH.

Manufacture, characterisation and process controls

The active substance is manufactured by manufacturer 1 and the particle size is reduced by manufacturer 2. An API intermediate is manufactured by manufacturer 3. All three sites have been confirmed to be GMP compliant.

The synthesis is adequately described from the defined starting materials. The definition of the starting materials has been adequately justified based on a scientific understanding of impurity formation and purging.

The development of the synthesis is described where the changes introduced are clearly stated for the 12 early development batches, 10 late development batches and 7 commercial production batches. The impurity level is presented for the specified impurities for all batches showing an acceptable impurity level already in the second half of early development.

An extensive impurity discussion is presented including impurities in the proposed starting materials. Related substances, residual solvents and genotoxic impurities have been adequately discussed and the control has been justified scientifically and with spiking studies. The control of metal catalysts is acceptable. In the impurity discussion, both the new guideline on genotoxic impurities (M7) and on elemental impurities have been considered.

Specification

The active substance specification includes all the relevant tests to control the active substance. All specified impurities are limited above the qualification threshold and the limits have been justified with non-clinical data. Assay of cediranib is limited to 97.5-102.0%, although the active substance is very stable, based on the variability in the batch results on assay. The particle size is limited to ensure processability, it is not critical for dissolution. The analytical methods proposed are in accordance with current standards and have been adequately validated.

Stability

Three batches have been put on stability: 48 months at 25°C/60% RH and 6 months at 40°C/75% RH. In the stability studies, no significant changes in one of the test parameters have been observed. The proposed re-test period of 60 months is accepted when the active substance is stored in the proposed LDPE bag in the rigid container. The storage condition “Do not store above 30°C” is not necessary, but accepted. The active substance is not sensitive to moisture, heat or light.

3.1.2. Finished Medicinal Product

Description of the product

The finished product is a film-coated tablet containing 15 mg or 20 mg of cediranib equivalent to 18.9 mg and 25.2 mg of cediranib maleate. The drug product will be marketed in PVC/PVDC/Al blisters. The two tablet strengths are dose proportional and each film-coated tablet contains 12.6% of cediranib maleate. The two tablet strengths can be differentiated by their appearance/debossing. The excipients used are common for tablets and are described in the European Pharmacopoeia.

Pharmaceutical Development

The development of the drug product is extensively described and justifies the choice of excipients and in-process controls. The film-coated tablet is an immediate release tablet, which is quickly dissolved in media with a pH within the physiological range. BCS class 3 is proposed (high solubility, low permeability).

For patients who have difficulty swallowing tablets, the drug product may be dispersed in half a glass of non-carbonated drinking water. This is adequately described in the SPC section 6.6.

Manufacture of the product and process controls

The drug product manufacturer proposed is AstraZeneca AB, Södertälje, Sweden. Other manufacturers were used during development and the main stability data are on batches manufactured by another manufacturer reporting 48 months of stability data (see below). The manufacturing process is a standard process where the 15 mg and 20 mg film-coated tablets are manufactured from a quantitatively identical common granule using conventional mixing, dry granulation by roller compaction, compression and film coating. Critical manufacturing process parameters have been identified and adequate in-process controls have been set. No validation data is presented on the manufacturing process, which is acceptable. An acceptable validation protocol is presented. The proposed batch size range is 35-80 kg and batch analysis data have been provided supporting this range.

Product specification

The drug product specification is justified and includes the common tests for film-coated tablets. No degradation product is specified in the specification as none is found above the identification threshold in the stability study. The analytical methods are of current standards and are adequately validated.

The absence of specifications for microbial quality and water content has been sufficiently justified.

Stability of the product

For each strength 3 batches from IPR, Canovanas, Puerto Rico (2008 batches, 15 mg: 470.000-490.000 tablets, 20 mg: 340.000-367.000 tablets) and AstraZeneca Södertälje (Mar 2014 batches, 15 mg: 215.000-220.000 tablets, 20 mg: 158.000-161.000 tablets) have been put on stability. The IPR batches have been stored for 48 months at 25°C/60% RH and 30°C/75% RH, and 6 months at 40°C/75% RH. The Södertälje batches have been stored for 12 months at 30°C/75% RH and 3 or 6 months at 40°C/75% RH. All stability data presented show little or no change in the physical and chemical characteristics studied at both long-term conditions. None of the known degradation products are detected above 0.15% w/w. In general all dissolution results remain high during stability, i.e., > 90%. In conclusion, the proposed shelf-life of 36 months if stored in PVC/PVDC-Alu blisters without a specific storage temperature condition can be accepted. No specific product labelling is required. The

applicant is asked to provide additional stability data when these have become available, as support for the satisfactory quality of batches from the intended commercial manufacturing site.

Adventitious agents

None of the excipients used for this pharmaceutical product are of animal or human origin. Magnesium stearate is from vegetable origin.

3.1.3. Discussion on chemical, pharmaceutical and biological aspects

The quality documentation provided complies with current guidelines and the European Pharmacopoeia. The control strategy is extensively justified based on the development data. The drug product is stable and easily dissolved.

3.1.4. Conclusions on the chemical, pharmaceutical and biological aspects

There are no remaining quality issues in relation to the questions assessed by CHMP.

3.2. Non clinical aspects

3.2.1. Pharmacology

Cediranib is a potent small molecule vascular endothelial growth factor (VEGF) receptor tyrosine kinase inhibitor of all three VEGF receptors (VEGFR-1, -2 and -3) at nanomolar concentrations. Inhibition of VEGF signalling leads to the inhibition of angiogenesis, lymphangiogenesis, neovascular survival and vascular permeability. Cediranib is developed as an anti-tumour agent for potential monotherapy of ovarian cancer. Based on steady-state free plasma concentrations achieved with 20 mg once daily in patients, cediranib has additional activity against c-kit tyrosine kinase-dependent tumour growth and limited or no impact on platelet-derived growth factor receptor (PDGFR) tyrosine kinases. Cediranib is inactive against other kinases tested. Pharmacodynamics of cediranib was assessed *in vitro* and *in vivo.*

In vitro

Cediranib inhibited receptor phosphorylation of VEGFR-1, -2, and 3, as well as c-kit at low nanomolar concentrations in a number of cell types (IC50 = 0.0005 to 0.001 µM), in line with data obtained in kinase assays. Dependent on the cell type tested, 10 to 46-fold higher concentrations of cediranib were required to inhibit PDGFR-α phosphorylation than for comparable inhibition of VEGFR-2 phosphorylation. For PDGFR-β, 16 to 64-fold higher concentrations achieved similar inhibition of phosphorylation compared to VEGFR-2. Cediranib also demonstrated a high degree of selectivity (420 fold to >20,000 fold) for inhibition of VEGFR-2 phosphorylation versus the remaining PDGFR-family members, CSF-1R and Flt-3, and versus FGFR-1, EGFR and erbB2.

Cediranib can selectively inhibit VEGFR-dependent proliferation in endothelial cells, compared with proliferation mediated by FGFR1 or EGFR. These data are in line with those of the enzyme assays and phosphorylation assays in cells and show that cediranib is a potent inhibitor of VEGFRs but not of FGFR and EGFR. Inhibition of c-kit by cediranib is seen in enzyme assays, as well as cellular phosphorylation assays with IC50 values of 0.001 to 0.006 µM. Stem cell factor (SCF)-driven proliferation, a functional measure of inhibition of c-kit, was inhibited at 0.013 µM. Dependent on the cell type tested, 80 to 160-fold higher concentrations of cediranib were required to inhibit PDGFR-AA- or PDGF-BB-stimulated proliferation to a similar level as VEGF-driven cell proliferation and inhibition of VEGFR-2 phosphorylation.

Consistent with the activity versus VEGFR-1, -2, -3 cediranib inhibited VEGF-stimulated human umbilical vein endothelial cell (HUVEC) proliferation (IC50 0.0004 μM), but not basal, bFGF or EGF-stimulated proliferation. It also inhibited VEGFR-2 and VEGFR-3 driven proliferation, as well as survival and migration of blood endothelial cells (BECs) and lymphatic endothelial cells (LECs). Cediranib reduces endothelial tube formation in a fibroblast-endothelial co-culture assay.

In vitro kinase assays and cellular functional assays reveal that cediranib most potently inhibits kinase activity of VEGFR 1, 2 and 3 and c-kit. Thereby Cediranib influences VEGF and SCF driven cell proliferation and endothelial tube formation.

In vivo

Influence of cediranib on phosphorylation of VEGFR, c-kit and PEDGFR was assessed *in vivo* in nude mice or tumour (xenograft) bearing mice. In mice, acute 0.75 mg/kg cediranib reduced pVEGFR-2 levels in lung by 52% and at 6 mg/kg by 89%. Cediranib inhibits c-Kit phosphorylation in SCLC lung tumour xenografts in mice greater than 80% at 0.75 mg/kg/day for 2 weeks. When dosed at 6 mg/kg/day cediranib inhibits PDGFR-α, and -β signalling in addition to VEGFR signalling. However, cediranib is clearly less effective at inhibiting PDGFR signalling than VEGFR signalling. When dosed at 3 mg/kg and below in rat glial tumour xenografts in mice, VEGFR-2 phosphorylation is inhibited, but PDGFR-α and -β are not fully inhibited. It is presently unclear whether this level of activity could contribute to efficacy of cediranib, when PDGFRs are present on certain tumours.

The mechanistic effects of cediranib treatment on angiogenesis and lymphangiogenesis in mice and on luteal vascular growth in rat were explored in vivo. Daily oral administration of 1.5 or 6 mg/kg cediranib for 7 days completely abolished VEGF-induced vessel formation in mice. Cediranib inhibits VEGFR-2 and VEGFR-3 signalling, angiogenesis and lymphangiogenesis in mice treated with 6 mg/kg cediranib for 7 days. To activate the VEGFRs, recombinant retroviruses expressing VEGF-C, VEGFC156S, VEGF-A, and VEGF-E were intradermally injected into ears of mice. Also, tumours from animals treated with cediranib showed a decreased number of blood and lymphatic vessels. Chronic administration of cediranib (5 mg/kg/day orally for 28 days) showed a marked reduction of luteal formation (67% inhibition) compared to control, consistent with an inhibition of physiological angiogenesis. Therefore, cediranib is a potent inhibitor of VEGF-induced angiogenesis.

The antitumour effect of cediranib was assessed in human xenograft bearing mice and rat. In human colon, ovarian and breast tumour xenografts in mice doses from 0.75 mg/kg on, and in prostate and lung tumour xenographs from 1.5 mg/kg/day on, cediranib generated statistically significant inhibition of tumour growth in all the xenografts examined. In the human SKOV-3 ovary tumour xenograft cediranib caused 52% inhibition of tumour volume at 0.75 mg/kg and more than 100% at 3 mg/kg, after 4 weeks of treatment. In a Calu-6 human lung xenograft model in female athymic rats, cediranib inhibited tumour growth already significant at 0.1 mg/kg after 4 weeks of treatment, up to 94% at 3 mg/kg.

Cediranib inhibited VEGF-C mediated tumour progression in the IGROV1 human ovarian tumour cells transplanted into the mouse ovary at 6 mg/kg/day for 3 weeks. In a panel of epithelial ovarian cancer patient derived xenograft (EOC-PDX) models in nude mice treated with cediranib at 3 mg/kg/day for 3 weeks, cediranib increased the life span by 5 to 90%. Longer treatment until 7 weeks improved survival. Also the combination with cisplatin improved survival.

The effect of continuous dosing versus intermittent dosing was tested in female nude mice bearing CALU-6 human lung tumour xenografts. An intermittent dosing schedule with 3 mg/kg/day cediranib of 5 days on and 2 days off for 3 weeks showed similar efficacy to the once a day continuous dosing schedule in female nude mice bearing CALU-6 human lung tumour xenografts. However, the

continuous dosing of 6 mg/kg/day cediranib for 3 weeks showed a significantly higher (30%, $p<0.05$) degree of tumour growth inhibition compared to a 7 days on 7 days off schedule.

The broad anti-tumour activity of cediranib has also been confirmed in other tumour xenograft models implanted subcutaneously (colon, gastric, NSCLC, SCLC, renal, head and neck, anaplastic thyroid, fibrosarcoma and a range of pediatric tumours including rhabdoid, Wilms, Ewings, medulloblastoma, rhabdomyosarcoma, glioblastoma, neuroblastoma and osteosarcoma). This was consistent with inhibition of VEGF signalling and predominantly indirect (anti-angiogenic) anti-tumour effects. No activity was observed against 7 acute lymphoblastic leukaemia models. With the exception of c-kit expressing cell lines, direct effects on proliferation of tumour cell lines were only observed at 3 µM or higher concentrations of cediranib.

Antitumour effect of cediranib monotherapy versus combination therapy other chemotherapeutic agents or in combination with radiation therapy was tested in vivo and in vitro. In the LS174T human colorectal xenograft model in mice, treatment with cediranib combined with the antitumour agents 5-fluorouracil, oxiplatin or irinotecan, and in the MX-1 human breast xenograft model cediranib treatment combined with docetaxel or pemetrexed, showed significantly more inhibition of tumour growth than treatment with either agent alone. Also in the Calu-6 human lung xenograft, cediranib in combination with antitumour agents cisplatin or gemcitabine inhibited tumour growth significantly more than treatment with either agent alone. In different radiation in in vitro and in vivo models, combination with cediranib improved inhibition of tumour growth. Thus cediranib treatment seems more effective in combination with another anti-tumour therapy compared to monotherapy in xenograft bearing mice.

The mechanism of tumour inhibition by Cediranib was also investigated. Cediranib (6 mg/kg/day) affected the survival and morphology of tumour vasculature in mice bearing established Calu-6 human lung tumours. Tumour growth was inhibited by 68% and vessel number (by 47%) and area (by 70%), as detected by CD31 (platelet endothelial cell adhesion molecule 1) fluorescent immunostaining were reduced by 47% and 70% respectively. Cediranib (6 mg/kg/day) inhibits VEGFR-2 phosphorylation and decreases vascular density in Calu-6 human lung xenografts in mice within 28 hours (2 doses) and maintained at 52 hours (3 doses) of treatment. In a murine fibrosarcoma model, using murine fibrosarcoma tumour cells implanted in the ears of nude mice, overexpressing VEGF-C, cediranib (3 mg/kg/day 5 days on, 2 days off for 3 weeks) inhibits lymphatic metastasis and hyperplasia in the tumour margin and prevents arrival of tumour cells in the draining lymph node. Thus, it seems that Cediranib, by inhibition of VEGFR kinase activity, influences VEGF mediated proliferation of endothelial cells, thereby affecting survival and morphology of (lymph) vasculature in tumours, which inhibits growth of tumour and also reduces lymphatic metastasis and hyperplasia.

Secondary pharmacodynamics

Cediranib was tested in a panel of 338 *in vitro* radioligand binding and enzyme assays covering a diverse range of enzymes, receptors, ion channels and transporters. Because of the relatively high IC50 values, none of these targets are expected to be activated at the human maximum mean free steady state plasma concentration for the 20 mg dose (6.8 nM).

Safety Pharmacology

Cediranib showed no effects on CNS and respiratory functions in rats up to 25 mg/kg. Cediranib decreased hERG channel current and increased Purkinje fiber action potential with IC50 values of 5 to 9 times the human Cmax at the intended dose of 20 mg/day.

Cediranib increased blood pressure in animals at 0.03 (rat), 0.2 (dog) and 0.12 (cynomolgus monkey) times the human AUC at 20 mg/day, which is considered pharmacologically-related. No evidence of QTc prolongation was observed during studies involving cediranib administration for 7 days in dog (0.5 mg/kg/day) and cynomolgus monkey (doses up to 2.5 mg/kg/day).

3.2.2. Pharmacokinetics

Nonclinical absorption, distribution, metabolism and excretion (ADME) studies have been performed to support the development of cediranib using the same species and, where possible, the same strains of laboratory animal (rat and cynomolgus monkey) and dose formulations that were used in the general toxicology and reproductive toxicology studies. In addition, absorption, metabolism and excretion were also assessed in dog. Tissue distribution was investigated in albino and pigmented rats.

The pharmacokinetics of cediranib have been investigated in the rat, dog, monkey and humans using [^{14}C]-cediranib. The oral pharmacokinetics was examined in all three preclinical species and human; intravenous (iv) pharmacokinetics was examined in the rat and dog.

Oral absorption of cediranib was not formally assessed in nonclinical species. However, estimates of oral bioavailability were derived following single oral and iv doses of [^{14}C]-cediranib to male (71%) and female (75%) rats and female dogs (24 & 74%). No iv dosing was performed in monkey, therefore, the bioavailability was not determined in monkey but exposure per unit dose was comparable with that in rat and higher than in dog. Absorption was relatively slow with peak concentrations occurring 3 - 4 hours after dosing in rats, monkeys and dogs upon single dosing and 4 – 8 hours upon multiple dosing. Cediranib pharmacokinetics indicated high clearance and high volumes of distribution. The volume of distribution was high in rats (19 L/kg) and dogs (20 L/kg), larger than body water, indicating extensive tissue penetration. Elimination was relatively slow in all three species leading to average terminal elimination half-lives of 12h, 20h and 15h, in rat, dog and monkey respectively. There was no consistent evidence of a pharmacokinetic sex difference in rats or monkey. In humans similar pharmacokinetics was found, oral absorption was moderately slow with a median T_{max} of cediranib in plasma of 3 hours (range 2 to 6 hours) and terminal elimination half-life was 23 h.

Upon multiple dosing (data obtained from toxicokinetic studies), over the dose range examined in rat, cediranib plasma concentrations and exposure generally increased in proportion to dose and there was evidence of limited accumulation (1.5 - 2-fold) of exposure and no sex difference. Similar trends were observed in monkeys although accumulation was greater (up to 3-fold) at the higher doses (≥0.5 mg/kg). Exposure in female rats at 26 weeks of dosing was about slightly (30%) lower than in male rats. At the MTD used in pivotal 6 months toxicity studies cediranib plasma exposure upon multiple dosing was 8-fold and 5-fold lower in rat and monkey, respectively, than exposure in humans at the clinical dose of 20 mg/day. Furthermore, taken into account the species difference in plasma protein binding, free cediranib levels will be 4-fold and 3-fold lower in rat and monkey, respectively, than in humans.

Plasma protein binding of cediranib (90% to 93%) was relatively high across all species examined and was independent of concentration (range: 0.03 to 10.0 µg/mL). Cediranib was approximately 95% bound to human plasma proteins, binds to human serum albumin and α1-acid glycoprotein and does not preferentially bind to blood cells.

In tissue distribution studies using radiolabelled [^{14}C]-cediranib, radioactive material was rapidly and extensively distributed to most tissues in the rat. A large number of tissues were exposed to markedly higher concentrations of radioactivity than the blood, although lower levels relative to blood appeared in brain and spinal cord. Highest tissue concentrations (>25 times blood) were detected in the adrenal cortex, choroid layer of the eye, kidney cortex, pancreas, pituitary gland, preputial gland, spleen and gastrointestinal (GI) tract. And moderate concentrations (>10 times blood) in bone marrow, Harderian gland, lachrymal gland, kidney medulla, liver, lung, parotid gland, pineal body, lymph node, salivary

gland, thyroid gland and GI tract structures. As only male rats were used for the tissue distribution studies, no information is available on female (fertility-related) organs including the therapeutic efficacy target organ ovary. In general, for most tissues, the highest tissue concentration of radioactivity was found 4 h post-dose, declining thereafter. While radioactivity was eliminated from most tissues after 72h post-dose, protracted binding of radioactivity to the melanin-containing choroid layer of the eye was observed for more than 504h post-dose. This contrasted with the findings in the eye of albino rats and skin of both pigmented and albino rats. Uptake into the pigmented skin was about 2 – 3 fold higher than non-pigmented skin and found to be reversible but for the choroid layer of the eye, and the eye, radioactivity exposure remained more or less the same over the whole study period (21d) indicating a half-life of more than 400h. In toxicology studies, no toxicological findings were reported for the (pigmented) eye in dog and monkey, suggesting that melanin binding apparently has no toxicological consequences.

Placental transfer studies and transfer to the milk were not studied. Based on the demonstrated adverse findings on embryofetal development and post-partum survival in the rat, which is expected from its pharmacological action critical role of VEGF in fetal development, this suggests that in rats cediranib does reach the embryo/fetus and/or adverse effects on placenta occur.

In rat, monkey and man, the metabolic fate of cediranib was complex and analysis was further complicated by the relatively low doses used and the high volume of distribution. In each species, plasma contained a wide range of drug related components but cediranib was generally the most abundant accounting for up to 47-84% (rat) and 14-20% (monkey) of drug related material following oral dosing and up to 16-45% of drug related material in man. Although most of the plasma metabolites were not definitively identified, plasma from rat and human contained one or more products of oxidation (single or multiple oxidations at various positions); these included a propyl-pyrrolidine monooxygenated metabolite in human plasma (P7, 7% - 63%). Another component in human plasma, which was tentatively identified by comparison with in vitro data, was a pyrrolidine *N*-glucuronic acid conjugate (P5, << 1% - 18%) and formation was in vitro mediated by the human uridine diphosphate glucuronosyl-transferase (UDPGT) 1A4 isozyme. There was, however, no evidence that this metabolite was present in either rat, dog or monkey indicating toxicology species may not have been exposed to this metabolite. The remaining metabolites (eg P2, 4% - 16%) were not fully characterised in any species but tentative identification indicated that a mixture of mono and dioxygenated components were present and that in rat, oxidation occurred on both the indole and *N*-pyrrolidine moieties. However, precise comparison between species was not undertaken, which made it difficult to be certain whether the toxicology species were exposed to the same range of metabolites as human.

Investigations in human in vitro systems indicated that cytochrome P450 (CYP) enzymes either do not metabolize, or only minimally metabolize, cediranib. However, Phase I metabolism of cediranib to form the cediranib pyrrolidine *N*-oxide (P7, a major human plasma metabolite that frequently co-eluted with parent) was shown to be at least mediated by both flavin monooxygenase 1 (FMO1) and FMO3 isozymes. The Applicant states that this is the preferred oxidative pathway in vivo but it is, however, not clear whether this is how the oxidized metabolites are formed in humans and the preclinical species.

Both after oral and after intravenous administration, excretion of [^{14}C]-cediranib and associated radioactivity via faeces was the major route of elimination in rat (77%), monkey (76%), dog (66%) and human (59%). Analysis of samples from each species following oral dosing demonstrated that the largest component was cediranib and that this accounted for 53%, 32% and 29% of the dose in rat, monkey and human faeces, respectively. Excretion in urine was a minor route (rat 9%, monkey 8%, dog 19% and human 21%). Biliary elimination in the rat was 9 – 19% indicating a role in the clearance of this compound. There was no evidence of excretion of [$^{14}CO_2$] in expired air of rats after oral dosing

of [^{14}C]-cediranib confirming that the radiolabel was in a metabolically stable position. Elimination was rapid and essentially complete by 7 days with <1% still present in the carcass of rats and no significant sex related differences were found.

3.2.3. Toxicology

Single dose toxicity

Due to moribund conditions, male and female rats were sacrificed at single oral doses of 250 mg/kg cediranib and higher. Effects observed up to 100 mg/kg in male and 50 mg/kg in female rat included decreased body weight, food consumption and water consumption, behavioural effects, decreased organ weights and histopathological changes in multiple organs.

Repeat-dose toxicity

Repeat dose toxicity of orally dosed cediranib was assessed in GLP studies in rat and monkey during up to 6 months. Additionally, non-pivotal dose-range finding studies have been performed in the dog, but further studies in the dog were rejected due to low plasma levels of cediranib. Cediranib induced a wide range of mostly pharmacologically mediated effects on various organs in both rat and monkey.

Epiphyseal growth plate:

Dysplasia and hypertrophy of the epiphyseal growth plate was observed in both rat (≥1.25 mg/kg/day) and monkey (≥0.05 mg/kg/day) after exposure of one month or longer. This is a recognized effect of inhibitors of angiogenesis and an indicator of pharmacological action of cediranib. Effects on growth plate are more distinct in rat and young primate, due to marked growth and remodelling in these animals, in which VEGF plays a role and not of known relevance for the adult clinical population.

Ovary and reproductive tract:

Anoestrous and reduced ovarian corpora lutea were observed in rat after one month 5 mg/kg/day cediranib treatment, with exposure levels comparable to the human exposure (1.3 rat/human AUC ratio). These effects have been observed with other anti-angiogenic inhibitors. Conversion of the Graafian follicle to corpus luteum requires increased angiogenesis and inhibition of this process leads to effects as observed in the rat after cediranib exposure.

Adrenal glands:

Haemocysts in the adrenals (in the zona glomerulosa and fasiculata, characterised by widened inter-epithelial cords or lake-like blood filled spaces secondary to adrenal cortical cell loss) were observed only in rat at doses of 5 mg/kg/day (1 month study) and 0.5 mg/kg/day (6 month study). This effect is probably due to the anti-angiogenic effect of cediranib, because endocrine endothelium is dependent upon VEGF signalling and inhibition of VEGF causes capillary regression in the adrenal cortex, which is likely to result in haemorrhage and hypoxia.

Incisor teeth:

Effects on the incisors were only observed in the rat at doses of 0.5 mg/kg/day and higher. Incisor tooth dysplasia was observed, often resulting in discoloured, broken or lost incisors. Rodent incisors grow more rapidly than monkey or human tooth, making them more susceptible to disturbances in growth/development compared to monkey and human. Continuous growth of the incisors requires a constantly renewing vascular supply to allow dentine and enamel growth towards the distal occlusal surface. Angiogenic inhibition interrupts this process, resulting in abnormalities in tooth formation. This effect is rodent specific and has no relevance to the adult human population of cediranib.

Kidneys:

Adverse effects on the kidney have been observed in both rat and Cynomolgus monkey. Tubular degeneration (1 month, 5 mg/kg/day) and nephropathy/chronic progressive glomerulononephropathy (6 months, 2 mg/kg/day) were observed in rat. In monkey, glomerulosclerosis and tubular degeneration were observed (1 month, 0.5 mg/kg/day), which correlated with an increase in creatinine and urea noted in the 6 month study. VEGF signalling is important for maintenance of endothelial cell fenestration and podocyte and mesangial cell maintenance. Loss of VEGF *in vivo* has been described to lead to glomerulosclerosis, tubulointerstitial fibrosis and proteinuria. Effects may have been exacerbated by increases in blood pressure, which clinically results in complex kidney changes. Effects on the kidney have been reported with similar agents in patients treated with bevacizumab, VEGF-Trap and sunitinib, and may be secondary to VEGF signalling inhibition.

Thyroid:

Atrophy of thyroid follicular epithelium and increases in TSH levels were observed in rat (5 mg/kg/day 1 month, 2 mg/kg/day 6 month), and increased colloid accumulation was observed in the 3 month monkey study. The relation between thyroid follicular atrophy and increased levels of TSH is unfamiliar. A possible explanation can be a block in response of the thyroid epithelium to TSH. TSH is normally released in response to reduced levels of TH. Hypothyroidism has been observed as an adverse effect in human after cediranib exposure and sunitinib (which also inhibits VEGF).

Brain:

Effects in the choroid plexus were observed in both rat and monkey. Choroid plexus pigmentation and vasculitis was found in a 1 month rat study at 5 mg/kg/day and choroid plexus vasculitis, pigmentation, intimal proliferation and sclerosis were observed in monkey studies at doses of ≥0.2 mg/kg/day. Endothelium in the choroid plexus is dependent upon VEGF signalling. Similar findings were observed in a 9 month study with sunitinib. Furthermore, cediranib has a hypertensive pharmacology, and anti-hypertensive agents such as diltiazem have shown to minimally decrease these hypertensive effects. An MRI study investigating the effects of cediranib on choroid plexus function suggested a decrease of normal viable choroid plexus volume or a decrease of blood volume. However, no correlation between the severity of effects observed by MRI and histopathology findings in individual animals was observed.

Eye:

Adverse effects on the eye were observed in rat only in the 1 and 6 month studies at 5 and 2 mg/kg/day, respectively. Effects included prominent hyaloid artery remnants, vitreous haemorrhage, lens opacities and retinal detachment (n=1, 1 month). This finding is probably of limited relevance to the adult clinical population of cediranib.

Heart:

Cardiac changes were observed in the rat 1 month study (5 mg/kg/day) and in the 3 week dog studies (2 and 0.2 mg/kg/day). In both species ventricular myocarditis with haemosiderosis/pigment macrophages and arteritis were observed. Additionally in dog papillary muscle fibrosis and haemorrhage were observed and in rat creatine kinase (marker for muscle damage) and ALT (marker for liver damage) were increased, which were in line with the histopathological findings on the heart. These changes are consistent with observation of cardiac events in the clinic with other VEGF targeting agents (bevacizumab and sunitinib). The cardiac effects could be secondary to hypertension as result of peripheral or coronary artery vasoconstriction or cardiomyocyte VEGF/VEGFR signalling inhibition. In mouse myocardial infarction models the VEGF/VEGFR signalling axis protects the heart from loss of

cardiac mass and maintains cardiac contractility. Co-administration of cediranib with the anti-hypertensive agent nifedipine showed a minimal reduction of adverse effects (less reduced body weight, food consumption and a reduced arteritis in the heart) induced by cediranib. Myocardial ischaemia is due to either vasoconstriction and/or systemic hypertension as a consequence of VEGF receptor inhibition by cediranib. Also myocarditis may be a direct effect of cediranib, exacerbated by hypertension. The papillary muscle of the dog is particularly at risk from ischaemic damage. Preclinical studies may be a sign for possible heart effects in human.

Bone marrow and haematology:

Bone marrow changes were observed in the rat 1 and 6 month studies at ≥2 mg/kg/day. Hypocellularity (with bone marrow necrosis, fatty change and myelofibrosis) was observed, but not associated with concurrent reduction in blood cell count. In a single dose rat study this effect was accompanied by red pulp single cell necrosis and increased extramedullary haematopoiesis in the spleen. Bone marrow hypocellularity has been observed earlier in rats and monkeys treated with sunitinib. Myelosuppression has been seen in patients treated with sunitinib and sorafenib (but not bevacizumab). These effects may be mediated by VEGF and c-kit inhibition or through a VEGFR2 autocrine loop which modulates haemopoietic stem cell survival.

Bone:

Effects on bone were observed in rat, including bone necrosis in the 1 month study (5 mg/kg/day) and periosteal mineralisation in the 6 month study (2 mg/kg/day). In growing rats, the metaphyseal region of bones undergo endochondral ossification. Necrosis of metaphyseal bone was observed with marrow necrosis and myelofibrosis indicating perturbation of endochondral ossification. These types of effects have not been reported earlier with anti-angiogenic compounds, although vascular necrosis of the femur head was rarely induced by anti-VEGF agents.

Gastro-intestinal tract:

Cediranib induced effects on the gastro-intestinal system were observed in both rat and monkey. Ulceration, necrosis and mineralisation was observed in the 1 month rat studies only. This is a common finding and reflects route specific tissue irritation. Additionally in the 1 month rat study Brunner's gland inflammation was observed. This seems a result of VEGF inhibition, which may be rodent specific. Apoptosis in jejunum and ilium with pigment macrophages was observed in monkey (≥2.5 mg/kg/day). This has been reported for other anti-angiogenic compounds, including sunitinib, in both preclinical and clinical settings. Therefore these changes are probably secondary to VEGF inhibition.

In the rat, gingivitis of the oral cavity was observed in the 6 month study (≥0.5 mg/kg/day) and muco-cutaneous erosion, ulcers and micro-abscesses were observed in the oral cavity and parakeratosis and hyperplasia were observed in the oesophagus and tongue in monkey ((≥0.3 mg/kg/day). Similar findings described for sunitinib suggest effects are secondary to VEGF inhibition.

Pancreas:

Necrosis and zymogen degranulation and atrophy in the pancreas were observed in the rat at ≥2 mg/kg/day. Zymogen degranulation was also seen in monkey at ≥0.2 mg/kg/day and acinar degeneration and necrosis was observed in dog (0.5 mg/kg/day). The mechanism behind these effects is unclear, but may be related to VEGF signalling. Similar effects were observed in rat and monkey treated with sunitinib.

Liver and bile-duct:

In rat, cholangitis, bile duct thickening, enlargement and adhesions were observed ≥ 2 mg/kg/day. Ulceration of the bile duct and peritonitis probably caused the death of two animals in the 6-month study. In monkey bile duct hypertrophy (1 and 3 month studies) and hyperplasia (1 month) were observed at ≥0.5 mg/kg/day.

In rat, hepatocyte necrosis (1 month) and hepatocyte pigmentation and multinucleate hepatocytes (6 month) were observed, which was accompanied by elevated levels of ALT. The cause of these findings is unknown but could be due to VEGF inhibition, since hepatocytes express VEGF.

Mesenteric lymph node:

In rat, mast cell infiltration in the lymph node and haemorrhage were observed at ≥0.5 mg/kg/day. Haemorrhage is a known consequence of VEGF signalling inhibition in the clinic. The mechanism behind mast cell infiltration is unknown, but may be due to VEGF/VEGFR signalling or c-kit inhibition.

Salivary glands:

In rat, acinar vacuolation and increased basophilic acinar cells were observed after 6 months (2 mg/kg/day). Basophilic acinar cells are common background change in the salivary gland of rodents and are considered hypertrophic in nature. Changes are therefore thought to be exacerbation of spontaneous background pathology induced by chronic cediranib treatment. No effects were observed in dog or monkey.

Lungs:

Increased alveolar macrophages in minimal to mild severity were only noted in the 6-month rat study at 2 mg/kg/day. This effect was not observed in other rat, dog or monkey studies. The cause of this effect is uncertain , but may present phospholipidosis, as cediranib is a cationic drug and this effect is associated with cationic lipophilic structures.

Stress related changes:

Lymphoid atrophy of thymus was observed in rat (2 mg/kg/day) and monkey (≥0.2 mg/kg/day) together with atrophy of the germinal centres in the spleen/mesenteric lymph nodes of monkey in the 1 month study. These changes are commonly encountered in toxicology studies and are likely to be related to stress.

Reversibility:

A number of adverse effects of cediranib were reversible or showed reduced incidence or severity at the end of recovery. Most significant findings still present after recovery in rat were hepatic cholangitis and bile duct proliferation, choroid plexus vasculitis, myocarditis, arteritis and pancreatitis in the 1 month study and bile duct luminal dilatation and fibrosis and renal tubular basophilia with nephrocalcinosis in the 6 month study. Other findings present at end of the recovery period, such as effects on growth plates and teeth, were often related to cediranib pharmacology. In the monkey 1 month study after recovery choroid plexus and glomerulosclerosis was still present. In the 6 month monkey study, no non-reversible changes were observed.

Genotoxicity and carcinogenicity

Cediranib has no genotoxic potential, as tested in a battery of in vitro and an vivo tests. An assessment of carcinogenicity potential has not been conducted for the proposed indication in accordance with ICH S9.

Reproductive and developmental toxicity

Fertility

Female fertility was adversely affected by cediranib, inducing changes in the ovaries (decrease in number of corpora lutea) at 2.5 mg/kg/day, and anoestrus and atrophy in the reproductive tract at 5 mg/kg/day. This is likely due to the pharmacological effect of cediranib, as VEGF is important in angiogenesis during corpora lutea formation. Additionally, increase in oestrus cycle irregularity, decrease in mean number of implantations and live embryos with increased intrauterine death was observed at 2.5 mg/kg/day cediranib.

Fertility in male Wistar rat was not affected up to a dose of 2 mg/kg/day cediranib.

The NOAEL for male fertility is 2 mg/kg/day and for female fertility is 1.25 mg/kg/day. At the NOAELs for fertility, the rat/human AUC ratio is between 0.3 and 0.6.

Embryo-foetal development

Cediranib induced major cardiovascular teratogenicity at 1 mg/kg/day and embryo foetal mortality and impaired embryo-foetal growth at 0.1 mg/kg/day. Teratogenicity of the cardiovascular system is expected due to the mechanism of action of cediranib, as VEGF is an important growth factor during cardiovascular development. Developmental toxicity was observed at an exposure much lower than the expected therapeutic exposure in human.

Embryo-foetal development has only been assessed in rat, because, according to the ICH S9 guideline "Nonclinical Evaluation for Anticancer Pharmaceuticals (EMEA/CHMP/ICH/646107/2008)", it is not warranted to perform a confirmatory study in a second species when the first study shows embryo-foetal lethality or teratogenicity.

Prenatal and postnatal development

Although according to ICH S9 peri- and postnatal studies are generally not required for anticancer products, these studies were performed in accordance with ICH M3(R2). Cediranib exposure from GD16 through day 20 post weaning decreased foetal survival during gestation and pup bodyweight during lactation. Furthermore, balanopreputial separation for the F1 males was delayed, but did not have an effect on F1 male mating ability. No further adverse effects were observed post weaning. Exposure at 1 mg/kg/day resulted in an AUC of 160 ng.h/mL, which is 0.2 times the human exposure.

Metabolites

The Applicant has spent a considerable effort to investigate a major human specific N-glucuronide metabolite, but was unable to find a non-clinical species which formed the metabolite and was unable to synthesize the metabolite. ICH S9 states that "*for human specific metabolites, a separate general toxicology evaluation might not be warranted for patients with late stage or advanced cancer, as the human safety of the metabolite would have been assessed in phase I clinical trials. If the parent compound is considered positive in an evaluation for embryo-foetal toxicity or genotoxicity then separate studies for the disproportionate metabolite might not be warranted. Unless there is a specific cause for concern, nonclinical testing of the metabolite is not warranted.*" Although thus an evaluation of the N-glucuronide metabolite is not strictly warranted, the applicant has submitted a discussion regarding N-glucuronidation as a detoxification step for a wide range of nucleophilic endogenous and exogenous agents in mammals. N-Glucuronides can be formed from many molecules including pharmaceuticals. Based on submitted literature glucuronidation is regarded as an essential clearance and detoxification mechanism that increases polarity and water solubility.

According to the applicant based on available data and literature on other N-glucoronic metabolites there is no evidence suggesting that N-glucuronic conjugates of drugs are considered pharmacological active or toxic to humans or non-clinical species, which is agreed.

Studies on impurities

Fourteen impurities of the product were tested in a bacterial reverse mutagenicity assay. Based on the delivered studies, thirteen impurities of the product were found negative, and one impurity was weakly positive. Further investigation of this impurity in the *in vivo* mouse micronucleus assay was negative.

Also three impurities in the manufacturing process were tested in a bacterial reverse mutagenicity assay, and found positive. Besides, a forth one was concluded genotoxic on a theoretical base. However, these four genotoxic compounds are not expected to be present in cediranib maleate at levels greater than the TTC, as these are fully in control in the production process.

Phototoxicity

The phototoxicity of cediranib was assessed in Balb/c 3T3 fibroblast cells using neutral red uptake. No phototoxicity was observed.

3.2.4. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): cediranib maleate			
CAS-number (if available): 857036-77-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} 2.57 (pH 5) log D_{ow} 2.20 (pH 7) log D_{ow} >3.99 (pH 11)	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	log D_{ow} 2.57 (pH 5) log D_{ow} 2.20 (pH 7) log D_{ow} >3.99 (pH 11)	not B
Persistence	ready biodegradability	not readily biodegradable	
	DT50	$DT_{50,\ sediment}$ = 195 and 121 d	DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	64 µg/L 0.38 µg/L TBD	T
	C M R	not investigated not mutagenic Repr. 2 STOT RE 1.	T Data: notified CLP classification, plus reproduction toxicity data from dossier
PBT-statement:	Cediranib is not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, refined GLOBOCAN prevalence data	0.0010	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)	Cediranib affects reproduction (female fertility) and embryofetal development in vertebrates (rats)		Y
Phase II Physical-chemical properties and fate			

Study type	Test protocol	Results			Remarks
Adsorption-Desorption	OPPTS 835.1110	$K_{oc\ sludge}$ = 17100			1 sludge tested
	OECD 106	$K_{oc\ soil}$ TBD			study not submitted
Ready Biodegradability Test	OECD 301F	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ sediment}$ = 92 d, 57 d 88 and 91% shifting to sediment at day 14			DT_{50} values at 20°C; significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	64	µg/L	growth rate
Daphnia magna Reproduction Test	OECD 211	NOEC	0.38	µg/L	growth
Fish, Early Life Stage Toxicity Test / PM	OECD 210	NOEC	PM	µg/L	endpoint
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	32	mg/L	respiration
Phase IIb Studies					
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	0.3 %effect 5.1% effect	0.3 1.5	µg/kg µg/kg	nitrification rate
Terrestrial Plants, Growth Test/*T. aestivum*	OECD 208	NOEC	100	mg/kg	appearance, weight
Terrestial plants *B. oleracea*	OECD 208	NOEC	100	mg/kg	appearance, weight
Terrestial plants. *G. max*	OECD 208	NOEC	1000	mg/kg	appearance
Earthworm, Acute Toxicity Tests/ *E. fetida*	OECD 207	LC50, EC50	>1000	mg/kg	mortality, weight
Collembola, Reproduction Test/*F. candida*	ISO 11267	NOEC	≥1000	mg/kg	mortality, reproduction
Sediment dwelling organism/*C. riparius*	OECD 218	NOEC	≥218	mg/kg	development, emergence, normalised to 10% o.c.

TBD: To be determined

$PEC_{surfacewater}$ for cediranib is 1.00 ng/L, which is below the action limit of 0.01 µg/L. However, the applicant has proceeded with the ERA, which is agreed based on the reprotoxic properties of cediranib.

Cediranib is not PBT, nor vPvB.

Considering the above data, cediranib is not expected to pose a risk to the sewage treatment plant (STP), the sediment and the groundwater compartment.

A risk to the terrestrial compartment cannot be excluded.

However, the dossier is still incomplete (see below), and the available data do not allow to conclude definitively on the potential risk of cediranib to the environment.

3.2.5. Discussion on non-clinical aspects

Pharmacology

The *in vitro* pharmacological data support potent inhibition of VEGFR-2, and -3 in functional assays in cells. In addition c-kit dependent proliferation was also inhibited. The data reveal ≥80 fold selectivity for inhibition of VEGF-stimulated cell proliferation compared with PDGF stimulated proliferation.

No kinetic studies were performed on the xenograft mice models, but based on the pharmacokinetic measurements in the rat toxicity studies, Cmax and AUC levels at 0.1 mg/kg would be ca. 1/73 resp. 1/39 times the human exposures, and at 3 mg/kg ca. 1 and ½ times resp. This may be indicative that the exposure to humans at the therapeutic dose could be sufficient.

Cediranib decreased hERG channel current at a concentration of 5 times the human Cmax at MRHD. Purkinje fiber action potential was affected at 8.5 times the human Cmax. However, no effects on QTc were observed in vivo.

In vivo, cediranib decreased blood pressure in rat, dog and cynomolgus monkey at AUCs 0.03, 0.2 and 0.12 times the human AUC at MRHD, respectively. This is probably pharmacologically related and hypertension has been commonly observed in clinical studies with cediranib and other VEGF inhibitors and is listed as an identified risk in the Patient Risk Management Plan.

In conclusion, cediranib was shown to have an acceptable in vitro and in vivo secondary pharmacodynamic/safety pharmacology profile for the proposed indication.

Pharmacokinetics

The Applicant provided an overview of the metabolites formed in vivo in human, rat and monkey but failed to show a definitive identification of the oxidised metabolites present in the different species, leaving it unclear whether the oxidised metabolites, which are substantially present in human (e.g. regions P7 & P2), are also covered in the animal species used in pivotal toxicity studies. Therefore, the Applicant statement that “though it appears likely most of the circulating human metabolites were also formed by at least one of the major toxicology species” cannot be followed.

It can be concluded that the metabolite identification is poorly resolved and incomplete. Given the inherent toxicity of cediranib itself, the low dose used in humans (20 mg), the indication relapsed ovarian cancer and the intended use in combination with platinum therapy, one may conclude that any potential toxicity of these metabolites is expected to marginally contribute to the overall safety profile. Therefore, additional information on the metabolite identification is not expected to enhance the safety evaluation. Yet, from a clinical pharmacokinetic point of view, it is essential that the contribution of major metabolites to the pharmacological activity is clarified. This issue will be included in the clinical LoQ and may call for further non-clinical data to resolve this issue.

Toxicology

Target organs for toxicity in animals are epiphyseal growth plate, ovary, adrenal glands, incisor teeth, kidneys, brain, eye, heart, bone marrow and haematology, bone, gastro-intestinal tract, pancreas, liver and bile-duct and mesenteric lymph node. Furthermore, cediranib was shown to increase blood pressure in rat, dog and monkey. Adverse effects were observed at exposure well below human exposure levels, and effects are for a large part related to the pharmacological action of cediranib mainly the VEGF and c-kit inhibition. The NOAEL of 0.1 mg/kg in rats can be accepted for the 6 month rat study if further literature information regarding the pharmacology of VEGF inhibitors can be provided in relation to the observed miniralisation observed in the femur at the low dose level.

The adverse effects on the eye in rat in the 1 and 6 month studies included prominent hyaloid artery remnants, vitreous haemorrhage, lens opacities and retinal detachment. The Applicant discusses that the hyaloid artery is the terminal branch of the primitive ophthalmic artery, which nourishes the

developing lens. In human, regression of this artery starts during the third trimester of pregnancy, in rats regression takes place several weeks post-partum. Hyaloid remnants are therefore common in the age of rats used for the cediranib studies. The Applicant argues that the process of regression is triggered by loss of growth factors and reduced blood flow concurrent with increasing blood flow to developing retinal vasculature. Inhibition of VEGF may interfere with this process. The Applicant states that observed retinal haemorrhage and lens opacities are due to the vitreous haemorrhage from the hyaloid artery instead of a direct effect from cediranib. Furthermore, in pigmented rats, high accumulation of cediranib (≥25 times blood level) with a long retention time (T1/2 > 21 days) was observed in the choroid layer of the eye, whereas this was not observed in albino rats. No effects on the eye are observed in dog or monkey studies, which are conducted with older animals, when regression of the hyaloid artery is completed. In addition earlier systemic use of anti-angiogenic agents was only associated with minimal risk of direct ocular toxicity in human. The Applicant states that therefore this finding is of limited relevance to the adult clinical population of cediranib. This is agreed.

Also the effects on incisor teeth, epiphyseal growth plate are probably not relevant for the intended adult human population. The other targets may be affected at the intended human exposure and should therefore be part of the benefit-risk assessment. Especially pre-clinical findings on the heart may be a sign for possible heart effects in human. Overall, the findings in the toxicity studies collectively give rise to a concern regarding clinical safety of cediranib, in particular for maintenance therapy. Total and free plasma levels of cediranib archived at tolerated doses in long term non-clinical studies were below those observed at the human dose of 20 mg. Although this may be considered acceptable for anti-cancer products, the Applicant justified the clinical safety profile considering cediranib to be a selective inhibitor, primarily for VEGRF 1, 2 and as well as c-kit which is demonstrated by using in in vitro biochemical assays. High binding was also observed for receptors. However, cediranib was most potent against VEGRF-1, 2 and 3. Collectively, at clinical relevant concentrations, cediranib is considered selective for VEGFR 1, 2 and 3.

The Applicant acknowledges that cediranib is extensively distributed in the body and in nonclinical toxicology species was associated with findings in a wide range of tissues. However, the Applicant considers Cediranib to be a selective inhibitor, primarily for VEGRF 1, 2 and as well as c-kit which is demonstrated by using in in vitro biochemical assays. High binding was also observed for receptors. However, cediranib was the most potent against VEGRF-1, 2 and 3.

VEGF receptors are expressed in nearly all organs and tissues and are considered essential for normal endothelia cell biology. Hence, the observed findings are attributed to the blockade of the VEGF/VEGFR signalling axis. According to the Applicant, the non-clinical safety profile is considered consistent with the class effect known for VEGF inhibitors. Furthermore, the majority of findings in the nonclinical studies were shown to be reversible on cessation of treatment. In addition, the Applicant considers the clinical safety and tolerability profile of Cediranib to be consistent with the class effects known for VEGF inhibitors. Collectively, the justification provided by the Applicant is considered acceptable.Cediranib is not genotoxic or phototoxic, but is reproductive toxic regarding female fertility and developmental toxicity, which is stated in the SmPC. In total, 18 impurities were tested for their genotoxic potential. None of the impurities in the final product were found to be genotoxic. Four impurities in the production process were found to be genotoxic, but they are not expected to be present in cediranib maleate at levels greater than the TTC. The 2.5 mg/kg/day dose level was a tolerated dose in the rat study and the observed histopathological findings were considered related to the pharmacological activity of cediranib and inhibition of the VEGF/VEGFR signalling axis, and therefore not considered related to the impurity levels. The majority of the observed treatment related findings are considered related to the pharmacology of cediranib, which is considered acceptable. Furthermore, the applied

product is intended for treatment of cancer and the non-clinical development is therefore based on ICH S9 which state that higher impurity levels could be exceeded.

VEGF inhibitors are known to decrease vascular density of VEGF dependent capillaries in a variety of normal tissues with high levels of VEGFR-2 and VEGFR-3 expression and endothelial fenestrations including the chroid plexus in mice. Due to the observed choroid plexus findings in rats, the Applicant conducted a MRI study with Cediranib 5 mg/kg to investigate possible relationship between functional changes and choroid plexus histopathology findings. MRI showed a decrease of normal viable choroid plexus volume or a decrease of blood volume in the choroid plexus tissue along with evidence of changes to the blood-cerebrospinal fluid barrier. There was no correlation between severity of the histopathological findings and the effects observed by MRI.

In monkeys inflammatory changes were noted in choroid plexus after repeated administration with another VEGF inhibitor (sunitinib). The findings are therefore considered consistent with VEGFR signalling axis inhibition.

The clinical relevance of the observed findings are considered unknown. However, according to the Applicant choroid plexus disorders are rare and the risk is therefore considered small in relation to the overall benefit risk balance for cancer patients, which is agreed.

ERA

The Applicant has submitted the underlying reference regarding the prevalence of PSR ovarian cancer in the UK. Furthermore, the Applicant has presented for PSR ovarian cancer in another EU member state where prevalence of ovarian cancer is highest (Latvia). Based on these data a modified Fpen is estimated and the applicant proposes to calculate the refined PECsurface water based on these data. From GLOBOCAN 2012, it follows that Latvia has the highest prevalence of the EU 28. The 1 year prevalence is 20.3 per 100,000. The CHMP agrees to use 1 y prevalence data. These data are for females only, which can be seen when the data table is retrieved from http://globocan.iarc.fr/Pages/summary_table_site_prev_sel.aspx: it is not possible to retrieve ovary cancer data for both sexes. This means that the prevalence for the population is half as high: 10 per 100,000 or 1.0 per 10,000. Since at present, the ratio of PSR OC prevalence over OC prevalence is unknown, 1 per 10,000 will be used for the Fpen refinement. Since the product is administered on a daily basis, Fpen equals prevalence. Since this value is equal to the value used by the applicant, and is a worst-case assumption (highest prevalence in the EU, for OC instead of PSR OC), the CHMP agrees to use this value.

The applicant has submitted an extended analysis of the OECD 308 data. TLC data for the water samples at day 0 were presented. The applicant states that cediranib rapidly degraded at day 0 and therefore specific analysis of water phase data after day 0 was not performed. This is agreed upon. It can be concluded that the DT50 for dissipation from the water phase is <14 d for both sediments. Issue solved for this question. Water phase data for day 0: The TLC data showed that for the high o.m. sediment, only 45% (mean, n=2) of RA in the water phase was parent. The total sum of recovered RA in the day 0 water phase samples (high o.m. system) was 80% AR. Total mass balance at this time point was 90.2%, hence 10% of AR was not in the water phase and had likely partitioned to sediment. If it is assumed that this 10% of AR is parent, the starting concentration at day 0 is maximally 55%, but likely a bit lower. The same calculation for the low o.m. sediment gives a maximal starting concentration (day 0) of 47% of parent. The starting concentrations of 97.4% used in the kinetic analysis of the applicant (Table 7) are therefore incorrect. Setting these values at 55 and 47% of AR for the parent is a better approximation also not entirely correct since the fraction of parent that is present in the sediment is unknown.

The applicant performed 'total system' kinetic fits on the % parent (% of AR) that was extractable from sediment, plus the total radioactivity (parent+metabolites as % of AR) in the water phase. As pointed out above, the initial concentrations (t=0) used for these fits were incorrect (too high). In addition, the CHMP does not agree that the total radioactivity in the water phase should be added to %parent extractable from sediment. The water phase %AR is unlikely to represent the %parent as indicated by the applicant, since appreciable degradation appears to have occurred already at day 0. Hence, 'total system' values for parent (parent in sediment + parent in water) cannot be derived from this study.

Moreover, the t=0 percentages for parent in sediment are unavailable, only t=0 water phase values for parent are available. For the remainder of sampling points, the water phase parent concentrations are missing. We conclude that a meaningful degradation half-life value for parent can only be derived for sediment, based on the data that were already presented in original study report. The CHMP has therefore re-assessed the data for parent (extractable) in sediment and investigated whether the kinetic fits could be improved by other than the SFO models employed by the authors of the study report. However, for both FOMC as well as the DFOP model, acceptable fitting was not possible with these models. The SFO based DT50 values presented in the report can be reproduced and are 92 d for the high o.m. system and 57 d for the low o.m. system, respectively, equal to what was reported in the Day 80 ERA evaluation. In summary, DissT50water for both systems are < 14 d at 20°C; DegT50sediment is 92 d for high o.m. and 57 d for low o.m. system at 20°C, meaningful DT50sytem values cannot be derived based on the data presented.

It is agreed with the applicant's proposal that the planned fish reproduction toxicity study will supersede the outcome of a separate OECD 210 study. The CHMP will await submission of the chronic fish study and updated ERA.

It is a borderline case that the log Dow is apparently around 2.2 to 2.6 in the pH range 5 to 7, where the charge of the molecule does not change considerably. However, between pH 7 and 11, at increasing amounts of neutral molecule, the rate of increase of Dow is unknown, since log Dow could not be adequately determined at pH 11. It is certainly > 3.99, but Kow estimates range from 3.85, 4.71 to 5.0. EMA's Q&A document on ERA (Q6iii) states that if the pH lipophilicity profile shows that log Dow at pH 7 is close to a trigger value (4.5 for B criterion or 3 for performing a bioaccumulation study) a case by case assessment is necessary. Since log Dow at pH 7 is not considered to be close to 3 (viz. 2.2), the CHMP agrees that a bioconcentration study is not triggered. The request for performance of a bioconcentration study is withdrawn.

The dossier is incomplete and the applicant is requested to submit an adsorptiondesorption study using a batch equilibrium method (OECD 106) using at least 3 soil types. The applicant has made a commitment to submit a new OECD 106 study and update the ERA accordingly post-approval.

The applicant has submitted a draft protocol that has been commented on by the CHMP before day 120 as agreed during the clarification meeting. The CHMP appreciates the commitment and will await the updated protocol, subsequent performance of the study and update of the ERA.

It is agreed that the submitted OECD 307 cannot be used for the terrestrial risk assessment, as the respective study has too many short-comings, e.g. too few soils tested, strong decrease in microbial biomass, CO2 assessment failed, no parent and metabolite analysis. The reported DT50 represents a half-life for the dissipation of total radioactivity, predominantly caused by a shift from the extractable fraction to non-extractable fraction. No information on the rate of degradation can be derived from the study. Therefore, this study is considered unreliable.

The applicant should repeat the study per OECD TG 307, and report for cediranib a reliable DT50 in soil.

That said, it is agreed with the applicant that the extraction of cediranib is difficult, as illustrated by the soxhlet extraction of sediment in the water-sediment simulation study, and that repetition of the study might not result in useful or reliable DT50 values for degradation in soil.

The Applicants proposal to assume no degradation or removal, i.e. a DT50 soil of 10^6 days, for the PECsoil calculations is indeed a worst-case scenario that could be agreed upon in this specific case.

But contrary to what the applicant argues, a potential risk for the soil compartment has been identified. For soil microorganisms, the applicant followed the 'agrochemicals approach' from OECD 106 and tested only two test concentrations (1x and 5x PEC), and the NOEC could therefore only be reported as being ≥3 µg/kgdw. Applying an AF of 10, a PEC/PNEC of ≥1.6 is obtained. Thus, a risk to the soil compartment cannot be excluded.

The PEC_{soil} calculated using all ECHA methodology (REACH R.16 as implemented in EUSES v. 2.1.2) is: 0.249 $\mu g/kg_{dw}$ soil. With respect to the calculation of the risk quotient (RQ) for the terrestrial risk assessment, the following applies. First, the OECD 216 guideline is clear in that for non-agrochemicals a series of concentrations (≥ 5) should be tested to enable derivation ECx values. This was not the test set up chosen by the applicant. The outcome of the submitted test is the agrochemical set up, which does not allow for ECx, nor NOEC determination and feeds into a different type of risk assessment (PPPs), than referenced to by the EMA guideline (EMEA/CHMP/SWP/4447/00 corr 2). EMA guidance clearly refers to the TGD for the terrestrial risk assessment and not the CVMP guidance for veterinary pharmaceuticals. The TGD (replaced by ECHA REACH guidance) is based on application of an assessment factor (AF) to the lowest test result of a series of standardised ecotoxicity tests with representative species from three trophic levels in the terrestrial ecosystem (REACH guidance R.10.6.2). Following this TGD/ECHA guidance, an AF of 10 applies to the lowest reliable test result when the test suite provided by EMA guidance (chronic studies at three trophic levels) is complete. The latter is the case in the ERA dossier of Zemfirza. Hence, an AF of 10 applies to the lowest test result. Since the lowest test result here is not an EC10 or NOEC (due to the incorrect test set up of the OECD 216), but a 'no effect at the higher test concentration', the AF of 10 has to be applied to this higher test concentration. It is noted that this highest of two test concentrations is relatively low as compared to the test concentrations used in the OECD 216 test. The PNEC is thus derived as being ≥1.5 /10 = ≥0.15 $\mu g/kg_{dw}$. With a PEC_{soil} of 0.25 $\mu g/kg_{dw}$, the RQ for the terrestrial compartment is ≤1.7. Based on the data submitted, a risk to the terrestrial compartment cannot be excluded. This conclusion will be communicated in results of the ERA.

It is agreed that this RQ may represent a worst-case situation, however, the options where the risk assessment could be refined (F_{pen} and an OECD 216 with accurate determination of NOEC or EC10) have not been performed by the Applicant.

The above conclusion remains in the risk assessment.

3.3. Clinical aspects

Dose-response studies and main clinical studies

Table 1. Tabular listing of clinical efficacy studies

Study ID Phase	Number of Centres Location(s)	Enrolment status (dates of first and last patients enrolled) Total/planned enrolment	Design Control type	Treatment arms[a]	Patients by treatment: randomised/ discontinued treatment at data cut-off	Median age (range) years	Patient population	Duration	Primary endpoint
Pivotal efficacy study									
ICON6 D8480C00037 Phase III	62 Australia and New Zealand Canada Spain UK	Enrolment completed (first patient enrolled 04 December 2007; last patient enrolled 07 December 2011) Data cut-off (19 April 2013) **Stage I:** 60/33 **Stage II**[b]**:** 456/470	Multi-centre, 2-stage, randomised, 3-arm, double-blind, placebo-controlled, study	**Chemotherapy + placebo arm:** placebo od during chemotherapy then as maintenance therapy **Cediranib concurrent arm:** cediranib 20 mg od during chemotherapy then placebo od as maintenance therapy **Cediranib concurrent/ maintenance arm:** cediranib 20 mg od during chemotherapy then as maintenance therapy	118/113 174/163 164/156	62.0 (30-86)	Platinum sensitive, relapsed ovarian epithelial cancer, fallopian tube cancer, or primary peritoneal cancer	Chemotherapy: 6 cycles (18 weeks) Maintenance therapy: Up to 18 months from randomisation (or until disease progression)	**Stage I:** Safety **Stage II:** PFS
Key supportive study									
NCI 8348 Phase I/II	11 United States	Enrolment completed (Study activation date: 25 March 2010 Date of last patient enrolled not stated in CSR) Data cut-off (31 March 2014) **Phase I:** 28/no planned number due to 3+3 dose escalation scheme **Phase II:** 90/90	Multi-centre, 2-stage, open-label, randomised study	**Phase I** Cediranib (20 mg or 30 mg) od plus olaparib (100-400 mg) bd **Phase II** **Olaparib alone:** olaparib capsules 400 mg bd **Cediranib/olaparib:** cediranib 30 mg od plus olaparib capsules 200 mg bd	28/26 46/38 44/28	57.5 (32–85)	Histologically or cytologically confirmed epithelial ovarian cancer, primary peritoneal serous cancer, fallopian tube cancer (Grade 2 or 3 for Phase II), or triple-negative breast cancer (Phase I only)	Duration of therapy was dependent upon individual response, evidence of disease progression and tolerance.	**Phase I:** Safety **Phase II:** PFS

[a] The recommended chemotherapy regimen for ICON6 was carboplatin AUC6 over 30-60 minutes in combination with paclitaxel 175 mg/m^2 over 3 hours, once every 3 weeks for 6 cycles. Alternative platinum-based chemotherapy regimens were allowed including: carboplatin alone; cisplatin alone or in combination with paclitaxel; carboplatin (or cisplatin) in combination with gemcitabine. These chemotherapy agents were administered at the following starting doses: carboplatin AUC4 (with gemcitabine only), AUC5 or AUC6; cisplatin 75 mg/m^2; paclitaxel 175 mg/m^2; gemcitabine 1000 mg/m^2 on Days 1 and 8 of each 3-week cycle.

[b] The total number of patients enrolled in ICON6 Stage II included those patients enrolled during Stage I.

bd twice daily; od once daily; PFS progression-free survival; UK United Kingdom.

Tabular overview of clinical studies with pharmacology data

Study identifier	Study description	**Cediranib doses**	**Patients (randomized/treated)**
Monotherapy PK and initial tolerability studies			
D8480C00001 (Study 01)	single dose followed by multiple ascending doses to determine MTD	0.5, 1, 2.5, 5, 10, 20, 30, 45, 60 mg	83/83 patients with advanced solid tumours
D8480C00002 (Study 02)	multiple ascending doses to determine MTD	10, 20, 30 mg	49/35 patients with AML
D8480C00003 (Study 03)	Multiple ascending doses to determine MTD	1, 2.5, 5, 10, 20, 30 mg	26/26 patients with advanced prostate adenocarcinoma
D8480C00015 (Study 15)	Exploratory study to assess the effects of cediranib on tumours and biomarkers	30 mg	26/19 patients with NSCLC or head and neck cancer
D8480C00019 (Study 19)	PK and mass balance study	45 mg	6 /6 patients with advanced solid tumours
Combination PK and initial tolerability studies			
D8480C00004 (Study 04)	Part A1 and B1: multiple ascending doses to determine MTD in combination with gefitinib	20, 25, 30, 37.5, 45 mg	92/90 patients with advanced solid tumours
D8480C00008 (Study 08)	Cediranib in combination with 5 standard chemotherapy regimens (mFOLFOX6, pemetrexed, irinotecan (+/- cetuximab), docetaxel).	20, 30, 45 mg	109/106 patients with advanced solid tumours
D8480C00009 (Study 09) (NCIC-IND171)	Dose seeking study in combination with standard chemotherapy agents (paclitaxel, carboplatin, capecitabine)	30, 45 mg	20/20 patients with NSCLC
D8480C00022 (Study 22) (NCIC-IND175)	Dose seeking study in combination with standard chemotherapy agents (gemcitabine/cisplatin)	30, 45 mg	15 patients with NSCLC

Intrinsic factor PK studies			
D8480C00023 (Study 23)	Phase 1 PK study (bridge to Study 1) in the Japanese population Single dose followed by multiple ascending doses	10, 20, 30, 45 mg	40/40 Japanese patients with advanced solid tumours
D8480C00032 (Study 32)	PK and safety in patients with hepatic impairment.	30, 45 mg	30/30 patients with advanced solid tumours and various degrees of hepatic impairment
D8480C00039 (Study 39)	Phase I/II study in combination with mFOLFOX6 in Japanese subjects with untreated metastatic colorectal cancer	20, 30 mg	185/185 Japanese patients
D8480C00060 (Study 60)	Phase I single-dose/multiple-dose safety and PK study in Chinese patients with advanced solid malignancies	20, 30 mg	20/20 Chinese patients with advanced solid malignancies
D8480C00066 (Study 66)	Phase I safety, PK and efficacy study in combination with capecitabine/cisplatin or S-1/cisplatin in Japanese patients with gastric cancer	20 mg	14/14 Japanese patients with previously untreated locally advanced or metastatic unrectable gastric cancer
Extrinsic factor PK studies			
D8480C00020 (Study 20)	Drug-drug interaction study with ketoconazole (a CYP inhibitor)	20, 30, 45 mg	46/46 patients with advanced solid tumours
D8480C00021 (Study 21)	effect of food on single dose PK effect of a single dose on QTc	45 mg, 30 to 90 mg	60/54 patients with advanced solid tumours
D8480C00029 (Study 29)	Drug-drug interaction study with rifampicin (a CYP inducer)	45 mg	64/64 patients with advanced solid tumours
Pharmacology studies			
D8480C00038 (Study 38)	Randomised study to investigate hypertension management strategies	30, 45 mg	126/119 patients with advanced solid tumours (except prostate cancer)
Phase II efficacy and safety studies			
D8480C00030 (Study 30)	Randomised study to compare the efficacy and safety of cediranib compared with placebo in RCC	45 mg	71/71 patients with metastatic or recurrent RCC
D8480C00046 (Study 46)	Signal searching study in GIST and STS.	45 mg	35/34 patients with metastatic GIST or STS

3.3.1. Pharmacokinetics

Pharmacokinetics of cediranib have been characterized in 19 clinical studies in patients with solid tumours following single and multiple doses both as monotherapy, and in combination with chemotherapy including platinum agents. All clinical studies with cediranib have been performed in cancer patients because of pre-clinical studies observed toxicities at clinically relevant doses. In addition, evaluation of intrinsic and extrinsic factor on the pharmacokinetics of cediranib was conducted by popPK analysis, PKPD relationships and in vitro studies were submitted that were pertinent to PK processes.

Methods: Analytical methods for cediranib were adequately validated. Cross-validation between the different methods had been demonstrated. Incurred sample reanalysis was conducted in a few (newer) clinical studies, the outcome of which and was within acceptance limits.

PopPK analysis: PopPK analysis described the time course of cediranib after single and multiple dose administration by a two-compartment disposition model with sequential zero and first order absorption. Plasma concentrations >120 ng/ml for population predictions though is underestimated and seemed to be capped. The parameter estimates for base and final model are shown in Table **2**. The population typical apparent volume of distribution at steady state (Vss; derived from Vc and Vp) was 702 L and typical estimate of CL/F 26.3 L/h.

Table 2. Parameter estimates for the base and final model

		Base model (OFV -4680)			Final model (OFV -4754)		
Parameter	Description	Estimate	RSE (%)	CI 95%	Estimate	RSE (%)	CI 95%
θ_1	Clearance, CL (L/h)	27.1	2.37	25.9 - 28.4	26.3	2.48	25 - 27.6
θ_2	Volume of distribution of central compartment, V_c (L)	491	3.02	462 - 520	489	2.79	462 - 516
θ_6	Distribution rate constant, k_{23} (h^{-1})	0.0239	15.9	0.0164 - 0.0313	0.0242	11.1	0.0189 - 0.0294
θ_7	Distribution rate constant, k_{32} (h^{-1})	0.0554	8.54	0.0461 - 0.0646	0.0555	6.63	0.0483 - 0.0627
Derived	Intercompartmental clearance, Q (L/h)	11.7	14.9	8.3 - 15.1	11.8	11.4	9.18 - 14.4
Derived	Peripheral volume, V_p (L)	212	8.39	177 - 247	213	7.14	183 - 243
θ_3	Absorption rate constant, ka (h^{-1})	2.71	6.51	2.36 - 3.06	2.7	5.65	2.4 - 3
θ_9	Duration of zero order absorption, D1 (h)	1.68	4.14	1.55 - 1.82	1.68	3.88	1.55 - 1.81
θ_8	Relative bioavailability, F1 FIX	1	-	-	1	-	-
θ_{10}	Age effect on Clearance $CL*(AGE/59)^{\theta}$	-	-	-	-0.409	13.2	-0.303 - -0.515
θ_{11}	Body weight effect on Clearance $CL*(WT/73)^{\theta}$	-	-	-	0.517	17.5	0.34 - 0.694
θ_{12}	Body weight effect on Volume $V_c*(WT/73)^{\theta}$	-	-	-	0.65	17.6	0.425 - 0.874
θ_4	Residual variability rich profile	0.266	2.97	0.25 - 0.281	0.265	2.97	0.25 - 0.281
θ_5	Residual variability sparse profile	0.472	3.67	0.438 - 0.506	0.473	3.67	0.439 - 0.507
ω_1	IIV in CL (CV %)	55.7	3.56	51.8 - 59.6	53.7	3.71	49.8 - 57.6
$\omega_{(1,2)}$	Correlation IIV CL and IIV V_c	0.835	2.55	0.793 - 0.877	0.839	2.67	0.795 - 0.883
ω_2	IIV in V_c (CV %)	63.1	4.44	57.6 - 68.6	61.5	4.53	56 - 66.9
ω_3	IIV in Ka (CV %)	152	4.71	138 - 166	151	4.35	138 - 164
π_1	IOV in F1 (CV %)	44.5	8.08	37.5 - 51.6	44.6	7.99	37.6 - 51.6

Shrinkage in ETA1(CL) and ETA2(Vc) were 7.4 and 18% respectively while shrinkage was 32% for ETA3(ka) and Epsilon shrinkage was 12% in the final model.

Covariate analysis was conducted based on all PK data. The included covariate relations explained only little of the intersubject variability: the intersubject variability in CL and Vc was reduced from 55.7 to 53.7 CV% and from 63.1 to 61.5 CV%, respectively. There remains a high unexplained high variability.

Absorption: Following oral administration of cediranib, absorption was moderately slow with maximum plasma concentrations typically attained between 1 and 8 h post-dose (Figure 1). Beyond the peak concentration, plasma concentrations declined rapidly by factor of ~5 till 24 hours, followed by a slow terminal phase.

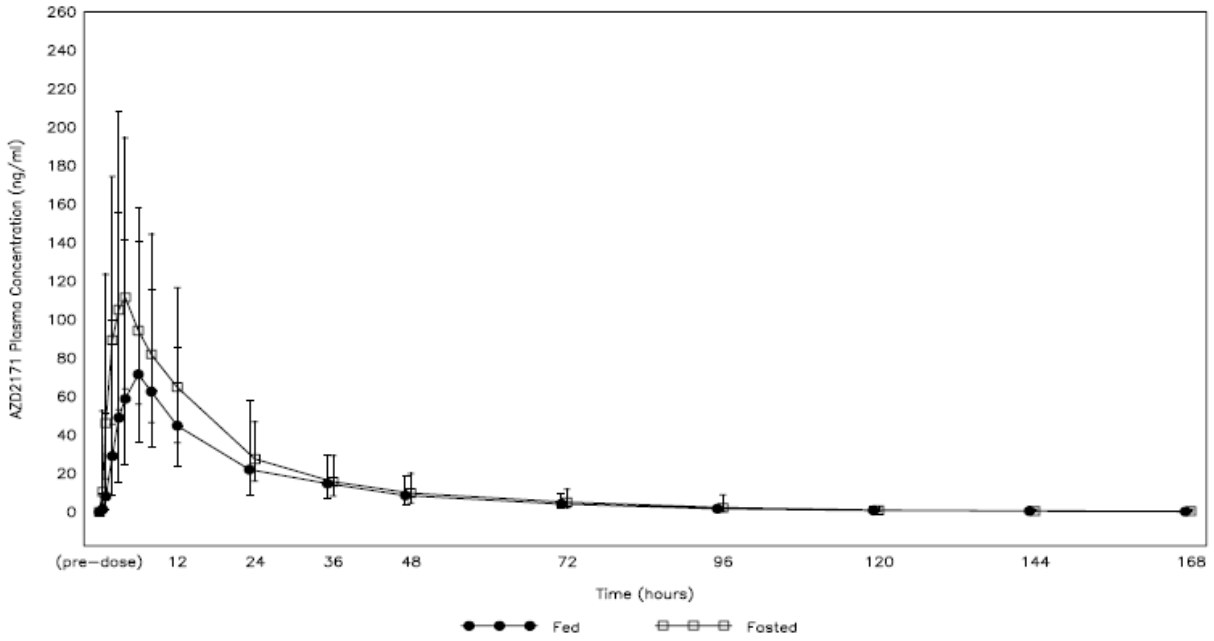

Figure 1. Plasma concentrations of cediranib under fasted and fed conditions (study 21).

The absolute oral bioavailability of cediranib is not known. Absorption of cediranib is minimal at least 20.8% but could be up to ~70%. This is based on excretion of cediranib and cediranib-related radioactivity in urine and faeces following administration of a single oral 45 mg dose of [14C]-cediranib as oral solution (study 19): ~20% of the radioactive dose was excreted in urine, in the faeces ~35% of the administered dose was excreted as metabolites and 33% of the dose as unchanged cediranib. Because the excretion of unchanged cediranib in the urine was <2% of the administered dose, it is established that metabolism is the major elimination pathway of cediranib. Therefore, no absolute bioavailability study is requested.

Cediranib is highly water soluble over the pH range 1.2-7. Studies in cell lines indicated cediranib is a substrate for P-glycoprotein but not for BCRP. Based on high solubility and moderate absorption, cediranib can be classified as a Biopharmaceutics Classification System (BCS) class 3 compound.

Three cediranib tablet formulations have been utilized during clinical development. The two early formulations, direct compression (DC, used in studies 1, 2, 3, 4, 23), early roller compaction (eRC, used in studies 8, 9, 15) tablets were used primarily in the early dose escalation studies. The formulation composition for the commercial film-coated tablet was used in the pivotal Phase 3 study and in most of the clinical studies (studies 2, 5, 8, 9, 13, 15, 21, 22, 29, 30, 32, 37, 38, 39, 40, 46, 51, 55, 57, 60, 66, 98). Across study comparison suggested that the relative bioavailability of various cediranib tablet formulation is comparably high as an oral solution although a large PK variability observed between studies. Therefore, the risk of major differences in pharmacokinetics in the early dose escalation studies compared to the formulation with commercial composition is considered low. Tablets with the commercial composition have been used in most clinical studies. Therefore, no

comparative bioavailability between film-coated tablets and the early DS and eRC formulations is considered necessary.

Food effect: The effect of dosing in the presence of food on the PK of cediranib was assessed in Study 21, a two-period crossover design with cediranib administration with a high-fat meal (FDA-recommended high fat, high calorie meal) compared to administration on a fasted stomach. Forty-four patients received 45 mg cediranib in the first period, 32 patients finished both periods.

Both the AUC and Cmax of cediranib were lower in the presence of food by a mean of 24 and 33%, respectively (94% CI: AUC, 12 to 34% lower and Cmax, 20 to 43% lower). There was also a slight delay in the t_{max} with administration in the fed state (see Table 3).

Table 3. Summary of PK parameters following single oral doses of cediranib 45 mg for fed and fasted states; gMean (CV%) or median (range) (study 21)

PK parameters	N	Cediranib Fed state	N	Cediranib Fasted State	Point estimate (94% CI)
AUC (ng*h/mL)	30	1920 (62.03)	32	2392 (57.23)	
$AUC_{(0-t)}$ (ng*h/mL)	30	1896 (62.59)	32	2348 (57.85)	0.762 (0.663, 0.876)
C_{max} (ng/mL)	31	87.02 (66.01)	33	127.9 (60.48)	0.672 (0.567, 0.796)
t_{max} (h)	31	4.10 (2.0 to 25)	33	3.30 (2.0 to 6.1)	
$t½_{\lambda z}$ (h)	30	25.40 (12.1 to 37.5)	32	24.40 (10.2 to 60.2)	
CL/F (L/h)	30	23.44 (62.06)	32	18.81 (57.24)	

AUC = area under the plasma concentration time curve; $AUC_{(0-t)}$ = area under plasma concentration-time curve from zero to time t; CL/F = clearance associated with formation of a metabolite from a drug; C_{max} = maximum plasma concentration; CV = coefficient of variation; Gmean = geometric mean; $t_{1/2\lambda z}$ = half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve; t_{max} = time to reach maximum concentration

Distribution: Mean apparent volume of distribution of cediranib ranges from 429-1290 L, indicating extensive distribution into tissue. Population parameter estimates were in agreement with the data obtained by non-compartmental analysis.

In vitro plasma protein binding of [14C]cediranib was determined by ultrafiltration (study KPJ007). Binding was determined over the range (0.03 to 10 µM). Plasma protein binding was approximately 95% and independent of the concentration. Cediranib binds to serum albumin and alpha 1-acid glycoprotein. High non-specific binding was observed with equilibrium dialysis (up to 50%) but a lower 12-24% non-specific binding was observed with ultrafiltration technique. Therefore, some of the protein binding may be due to non-specific binding. Ex-vivo protein binding in plasma of treated patients has not been reported.

The mean blood: plasma ratio ranged from 0.543 to 0.652, which indicates that cediranib and metabolites are associated with the plasma compartment.

Elimination: Elimination parameters Cl/F and elimination half-life of cediranib were evaluated in all non-compartmental single dose studies and by popPK analysis. Apparent oral clearance of cediranib was high 17.4-43.1 L/h (non-compartmental analysis) and 26 L/h (54 CV%) (popPK estimate). Mean elimination half-life of cediranib varied between 16.6 -27.9 h following single dose administration. Clearance and elimination half-life were not dose dependent.

Excretion: Excretion of cediranib was evaluated in the mass balance study 19. Six subjects with solid advanced metastatic tumours received a single oral 45 mg dose of [14C]-cediranib as oral solution, and radioactivity was evaluated in plasma, urine and faeces. The overall recovery of radioactive material was in the range 84.7 to 93.1% of dose, with the exception of patient for which the overall recovery was 34.4% of dose. Sampling period for the mass balance is considered acceptable, the low recovery in one patient has been adequately explained.

The majority of radioactive material was excreted in the faeces 68.1% (SD ±9.8%, N=5), and 33.4% (SD ± 15.1, N=5) of the applied dose was recovered as unchanged cediranib in the faeces. Because the excretion of cediranib was fast (majority excreted the first 72 hours) while the plasma elimination half-life is 24 hours, this indicates that cediranib is not completely absorbed. A smaller proportion of cediranib radioactive material was excreted in urine: 20.8% (SD± 7.1%). The proportion of unchanged cediranib excreted in urine was low (<2% of the administered dose). Excretion of cediranib in urine and faeces has been investigated sufficiently.

Table 4. Recovery of radioactive material following a single oral administration of ^{14}C-cediranib to 6 patients with solid metastatic tumours (study 19)

	Per cent of administered dose (± SD)	
	Total radioactivity	Cediranib
Urine	20.8 ± 7.1	1.9 ± 0.8
Faeces	68.1 ± 9.8	33.4 ± 15.1

Metabolism:

In vitro studies showed that cediranib is unlikely to be metabolised by CYPP450 enzymes. Two metabolites were formed in vitro: cediranib-pyrrolidine N-oxide and a N-glucuronic acid conjugate of cediranib. Using selective enzymes it was shown that cediranib-pyrrolidine N-oxide could be formed by FMO1 and FMO3. UGT1A4 was responsible for the formation of the N-glucuronic acid conjugate. The two metabolites were not present in non-clinical species.

The metabolic profile of cediranib in vivo was evaluated in the mass balance study 19 in six subjects following administration a single oral 45 mg dose of [14C]-cediranib. Metabolic profile was evaluated in plasma, urine and faeces.

Figure 2 shows that maximum plasma concentration of cediranib was observed between 2 and 6 h post-dose, with a plateau observed around these times, followed by a decline in levels. The concentration profiles of radioactive material in plasma were similar, but the concentrations were typically 2 to 3 times higher than concentrations of cediranib. The difference is already apparent during the absorption phase indicating a considerable first-pass metabolism.

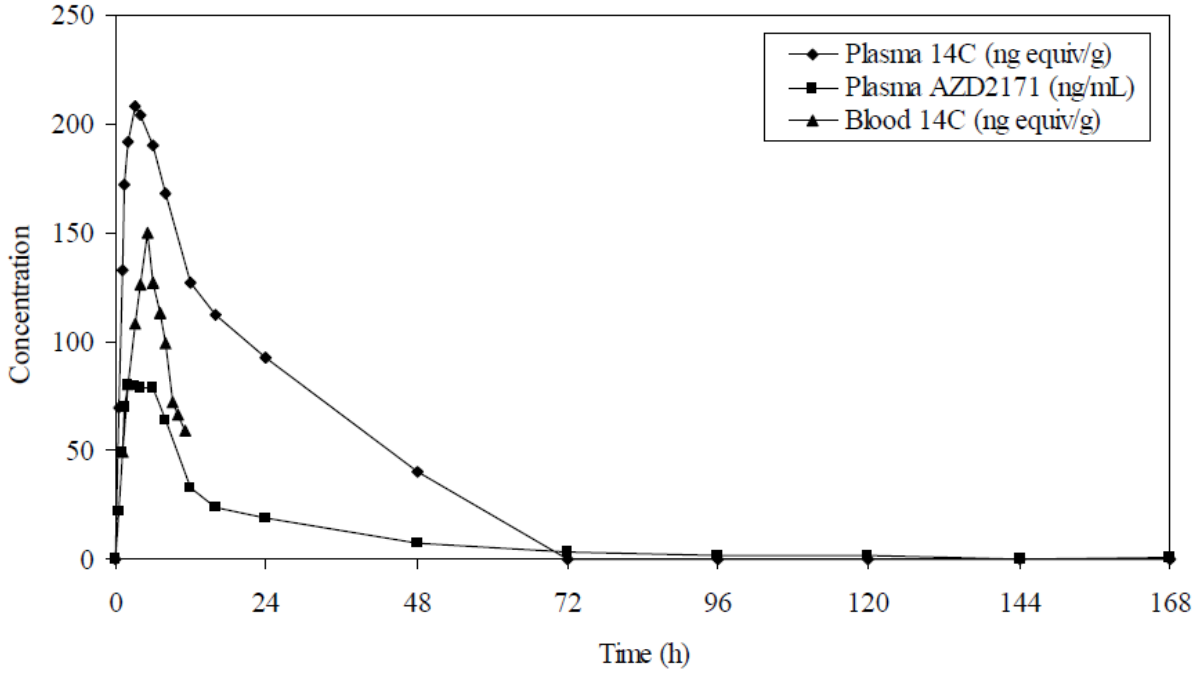

Figure 2. Mean concentrations of cediranib (AZD2171) in plasma and radioactive material in plasma and blood following a single oral administration of 14C-cediranib to patients with solid metastatic tumours (study 19)

Cediranib is the major circulating substance 31.7±12.1% in plasma. Radioactivity concentrations were higher for *N*-propyl pyrrolidine oxidised cediranib (27.5±22.5%) than for N-glucuronide cediranib (9.7±6.6%). No plasma time profiles for *N*-propyl pyrrolidine oxidised cediranib and *N*-glucuronide conjugate has been determined, thus, the exposures of the metabolites are only estimates. The mean percentage of the individual subjects did not correspond to the values of the reported pool values.

Cediranib, *N*-propyl pyrrolidine oxidised cediranib and *N*-glucuronide cediranib were excreted in urine in low amounts <2% of the administered dose. In the majority of faeces profiles, cediranib was the largest component and contained between 19.4-52.3% of the administered dose. *N*-glucuronide–cediranib accounted for between of 7.6 to 38.3% of dose. *N*-propyl pyrrolidine oxidised cediranib was only excreted in low amounts <2% of dose in faeces.

Pharmacological activity and pharmacokinetics of N-propyl pyrrolidine oxidised cediranib and N-glucuronide-cediranib have not been investigated.

Dose dependency: Dose proportionality of cediranib pharmacokinetics following single and multiple dosing over the dose range 0.5 mg to 60 mg was evaluated in studies 01, 03, 23 (Japanese population) and 60 (Chinese population). There was no deviation from dose proportional pharmacokinetics apparent following single dose of cediranib over the dose range 0.5 to 60 mg.

Following multiple dosing, there was a trend for less accumulation at doses > 20 mg. In study 01, the incidence of dose interruptions and dose reductions was higher at higher dosing. Only patients with continuous dosing for 7 days prior to day 28 were included in the analysis and this dose was noted as the allocated dose. This may cause selection bias comparing single vs multiple dose and this may have caused the less than dose proportional increase in cediranib following multiple dosing.

Time dependency: Following multiple daily dosing, the accumulation index ranged from 1-3 fold, mean accumulation index for cediranib 20 mg was 1.85. Steady-state plasma concentrations are attained at ≤7 days of repeated once daily dosing. Time to reach steady-sate and accumulation are

consistent with the observed elimination half-life of ~22h. There is no indication of time dependent pharmacokinetics of cediranib.

Inter- and intrasubject variability: Inter- and intraindividual variability was evaluated in the popPK analysis. The interindividual variability (coefficient of variation (CV%)) for CL/F and Vc/F were estimated to be 53.7% and 61.5%, respectively. Intra-individual variability was estimated to 44.6%.

Pharmacokinetics in the target population: The applicant did not present pharmacokinetic data specifically in target ovarian cancer population. In the pivotal study ICON6, no pharmacokinetic data were collected but some patients with ovarian carcinoma were included in the clinical studies.

Special populations: Special populations was evaluated by popPK analysis and a study (study 32) in patients with impaired hepatic function.

In the popPK analysis, no intrinsic factors were found to impact cediranib pharmacokinetic parameters to a clinically significant relevant extent. Body weight and age were found to impact cediranib pharmacokinetics to a small extent (<25% of median), with higher exposure in patients with low body weight or elderly patients. There is a downward trend in CL/F with increasing degree of renal impairment. Median of the individual CL/F estimates were 28.6, 24.7 and 20.7 L/h for no, mild, and moderate renal impairment respectively. No pharmacokinetic data in patients with severe renal impairment are available. Race and gender had no effect on cediranib pharmacokinetics when taken into account the difference in body weight.

Pharmacokinetic data in patients with hepatic impairment were somewhat contradictory: following single dose administration exposure of cediranib in patients with moderate hepatic was 1.6-fold higher than in patients with normal/mild hepatic impairment. In the patients who continued multiple dose administration, there was no difference between patients with moderate and normal/mild hepatic impairment.

Interactions: The potential of cediranib to interact by means of CYPP450 enzymes has been investigated sufficiently in vitro. Cediranib is no substrate for CYP P450 enzymes, does not inhibit any CYPP450 enzymes at systemic and intestinal relevant concentrations, and does not induce any CYP450 enzymes at systemic relevant concentrations. Induction of intestinal CYP3A4 cannot be excluded based in the in vitro data. This should be indicated in the SmPC.

In vitro studies evaluating the potential of cediranib to interact with transporters showed that cediranib is a substrate for Pglycoprotein but not for BCRP, OATP1B1, and OATP1B3. Inhibitory data indicated that cediranib can inhibit many transporters i.e. Pgp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1, though not at clinical systemic concentrations. . Cediranib is an inhibitor of MAT2-K and OATP1A2 at clinical systemic concentrations. *In vivo* Cediranib is a substrate for Pglycoprotein. When cediranib was co-administered with 400 mg ketoconazole qd, steady-state exposure to cediranib increased by 21% AUC and 26% for Cmax.

Rifampicin, a potent but relatively non-specific inducer of CYPP450 enzymes, P-glycoprotein and UGT, decreased the exposure of cediranib by 39% of AUC (90% CI: 34% to 43%) and 23% of Cmax (90% CI: 16% to 30%). Metabolites of cediranib were not evaluated in this study, therefore, it is not known by which mechanism rifampicin decreased cediranib exposure.

Hypertension is a common AE of cediranib and other VEGFR inhibitors, which is in general manageable by co-administration of anti-hypertensive medications. The effects of co-administration of various anti-hypertensive agents on cediranib PK was examined in a non-crossover Phase II study (study 38) to determine the effect of differing hypertension management strategies. Patients who received anti-hypertension prophylaxis (variously, beta blocker, ACE inhibitor, calcium channel blocker, AII

antagonist, diuretic, or vasodilator) had a 40% and 70% higher geometric mean cediranib AUCss, compared with patients who had not.

In a cross study comparison, the steady-state plasma PK parameters of 20, 30, and 45 mg cediranib when given in combination with a number of standard chemotherapy regimens, were comparable with those reported for cediranib monotherapy following multiple once daily oral doses Table 5.

Table 5. Steady-state PK parameters of cediranib when given in combination with various chemotherapy (Studies 01, 08, 09 and 22)

Treatment	N	PK parameter and summary statistic			
		$C_{ss,max}$ (ng/mL) gmean (CV%)	t_{max} (h) median (range)	$C_{ss,min}$ (ng/mL) gmean (CV%)	AUC_{ss} (ng*h/mL) gmean (CV%)
Cediranib monotherapy 20 mg	11	78 (58)	4.7	23 (56)	958 (50)
Cediranib monotherapy 30 mg	12	44 (24)	2.1	13.3 (19)	489 (34)
Cediranib monotherapy 45 mg	6	73.9 (87.5)	3.0	24.3 (92)	1060 (66)
mFOLFOX6 + cediranib 20 mg	5	65.3 (86.2)	4.0	21.7 (114)	986 (98.8)
Irinotecan + cediranib 20 mg	5	76.0 (57.6)	2.1	15.1 (43.5)	1014 (54.8)
Irinotecan+cetuximab+cediranib 20 mg	3	50.9 (126)	4.0	13.1 (148)	668 (124)
Cediranib monotherapy 30 mg	12	69.6 (49.5)	2.1	19.4 (54.7)	741 (48.7)
mFOLFOX6 + cediranib 30 mg	4	73.7 (31.6)	2.1	14.4 (70.1)	842 (42.0)
Docetaxel + cediranib 30 mg	8	62.5 (53.3)	5.0	29.0 (74.8)	1099 (59.2)
Irinotecan + cediranib 30 mg	5	84.5 (52.7)	6.0	35.8 (48.4)	1385 (38.3)
Pemetrexed + cediranib 30 mg	4	74.9 (31.6)	3.95	38.1 (59.6)	1206 (35.3)
Carboplatin/paclitaxel + cediranib 30 mg	2	41.6	3.2	19.1	676
Carboplatin/paclitaxel + cediranib 45 mg	9	90.8 (36)	9.3	69.3 (72)	1410 (31)

AUC_{ss} = area under the plasma concentration-time curve at steady state; $C_{ss,max}$ = maximum (peak) steady-state drug concentration in plasma during dosing interval; $C_{ss,min}$ = minimum (trough) steady-state drug concentration in plasma during dosing interval; CV = coefficient of variation; FOLFOX = 5-fluorouracil, leucovorin and oxaliplatin; gmean = geometric mean; PK = pharmacokinetic; t_{max} = time to reach maximum concentration.

In the pivotal study cediranib was co-administered with platin/paclitaxel in most patients. Data from study 09 in NSCLC patients suggest that co-administration of carboplatin/paclitaxel influences the pharmacokinetics of cediranib (slower absorption and higher Css,min).

The effect of cediranib on the exposure of carboplatin, cisplatin and paclitaxel has been investigated in a cross-over design. No effect of cediranib on pharmacokinetics of carbo- and cisplatin was observed (Table 6). Paclitaxel exposure increased with 35% when given in combination with cediranib, and the effect of 30 mg and 45 mg cediranib on paclitaxel exposure was comparable.

Table 6. Mean chemotherapy clearance before and after coadministration of cediranib (study 09)

Chemotherapy	PK parameter	Cediranib 30 mg		Cediranib 45 mg	
		Before cediranib (N)	With cediranib (N)	Before cediranib (N)	With cediranib (N)
Carboplatin	CL (L/h)	6.4 ± 0.9 (N=8)	6.4 ± 1,3 (N=8)	9.9 ± 3.5 (N=10)	8.8 ± 3.9 (N=10)
Paclitaxel	CL (L/h)	19.5 ± 2.9 (N=8)	14.3 ± 4.2 (N=8)	22.4 ±4.6 (N=10)	18.2 ± 6.0 (N=10)
Cisplatin	CL (L/h)	21.9 ± 2.5 (N=4)	21.1 ± 6.1 (N=4)	17.2 ± 1.7 (N=3)	19.0 ± 3.6 (N=3)
Gemcitabine	CL (L/h)	124 ± 14.4 (N=2)	93.4 ± 8.0 (N=2)	123 ± 25.1 (N=6)	114 ± 37.1 (N=6)

3.3.2. Pharmacodynamics

Cediranib is a potent tyrosine kinase inhibitor of all three VEGF receptors (VEGFR-1, -2, and -3) at nanomolar concentrations. Cediranib inhibits activation of VEGF Receptor 2 and its downstream intracellular signaling components, leading to inhibition of angiogenesis. Receptor specificity and binding of cediranib has been characterised in vitro.

Ovarian cancer is associated with the activation of the VEGFR signalling axis. Both VEGF-A and VEGF-C are up-regulated in the serum of ovarian cancer patients and are associated with poor prognosis. VEGF-A and VEGF-C are also expressed at high levels in ovarian tumours. Bevacizumab, inhibiting binding of VEGF-A to VEGFR receptor, has proven beneficial in ovarian cancer.

Pharmacodynamic evidence of biological activity was demonstrated by demonstrated increased levels of VEGF and decreased levels of VEGFR2 with cediranib treatment, which is in agreement with an effect on VEGF signalling. These effects were already apparent at doses <20 mg. A decrease in the iAUC60 for the gadolinium curve as measured by DCE-MRI was observed. The effects were related with cediranib concentration. Because of the overlap in cediranib exposure between 20, 30 and 45 mg, decrease in the iAUC60 was not dose dependent. Phase I studies identified cediranib 20 mg as the lowest dose with clear evidence of anti-tumour activity. Clinical activity of cediranib 20 mg, 30 mg and 45 mg dose was assessed in Study 01 in patients with solid tumours and liver metastases refractory to standard therapies. Statistical analyses showed that cediranib doses of 30 mg and 45 mg resulted in greater reductions in tumour size compared with cediranib 20 mg (one sided p=0.02 and 0.03, respectively).

In the pivotal study ICON6, the initial cediranib dose of 30 mg was reduced during the study to 20 mg because the treatment was not well tolerated. Even with the 20 mg dose, 32.2% of the population discontinued treatment with cediranib due to AEs. Exposure-safety relationships were explored for hypertension and diarrhoea based on cediranib monotherapy studies.

Exposure-blood pressure relationship

Hypertension is a well-known AE of VEGFR inhibitors. The diastolic and systolic blood pressures (DBP, SBP) were simultaneously modelled with an indirect response model using the predicted cediranib concentrations from the cediranib population PK model as a driver of effect. An Emax type of relationship with a delayed DBP and SBP effect was found between cediranib plasma concentration and blood pressure elevation as a proportional increase from baseline (see Figure 3). The estimated population typical maximum DBP and SBP (Emax) corresponds to an absolute increase of 20 mmHg and 26 mmHg from the baseline for DBP and SBP, respectively. The estimated typical cediranib concentration to reach the half of Emax of DBP and SBP (EC50) was 62.9 ng/mL (confidence interval [CI] 95%: 50.8 to 75). Typical increases in DBP and SBP for 20 mg cediranib concentration range is predicted to be 7 and 8 mmHg respectively, (CI 95%:3 to 13 and 3 to 16 respectively). Maximum blood pressure was observed after a few days of repeated dosing. During the first 6 weeks, 50.4% of patients had received their first intervention and a rapid effect of anti-hypertensive medication could be estimated from these early data. SBP and DBP decreased by 8 mmHg (CI 95%: 7 to 9) and 5 (CI 95%: 4 to 5) following anti-hypertensive medication. No covariates were identified to impact the Emax for the E-R relationship of DBP or SBP and exposure.

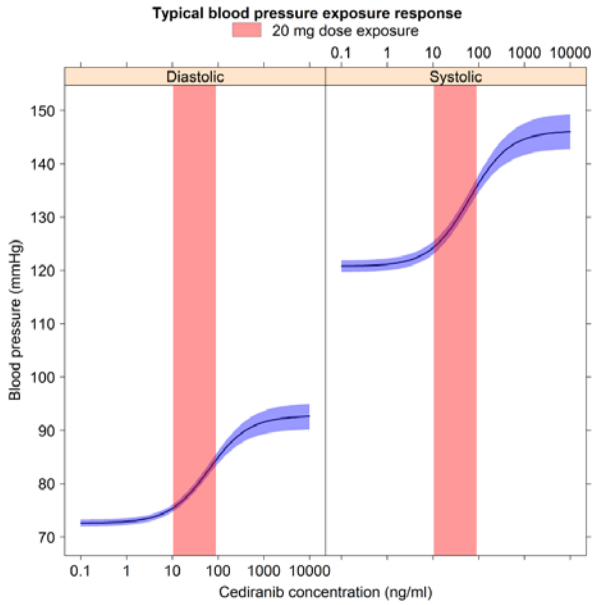

Figure 3. Typical blood pressure exposure response plot

Exposure-diarrhoea relationship

Diarrhoea is also a common AE for VEGFR inhibitors. Relation between diarrhoea and exposure data was modelled through an ordered categorical proportional odds model predicting the probabilities of observing none, mild, moderate or severe diarrhoea on a given day with the average cediranib concentration on the day of observation as the predictor.

The proportion of patients experiencing diarrhoea was increasing with dose and over time (see Figure 4). A dose and concentration dependent relationship was found between the average cediranib plasma concentration and the probability of observing higher grade diarrhoea. Probability of observing none or any grade diarrhoea was highly dependent on the grade on the previous day.

The exposure relationship was found to follow an Emax shape which reaches half of maximum effect at an average cediranib concentration of 28.4 ng/mL (CI 95%: 15.3 to 41.4) which is within the observed range of a 20 mg dose exposure. There was a strong correlation between the probability of severe diarrhoea and average cediranib concentration. No covariates were identified to impact the diarrhoea and average cediranib concentration relationship.

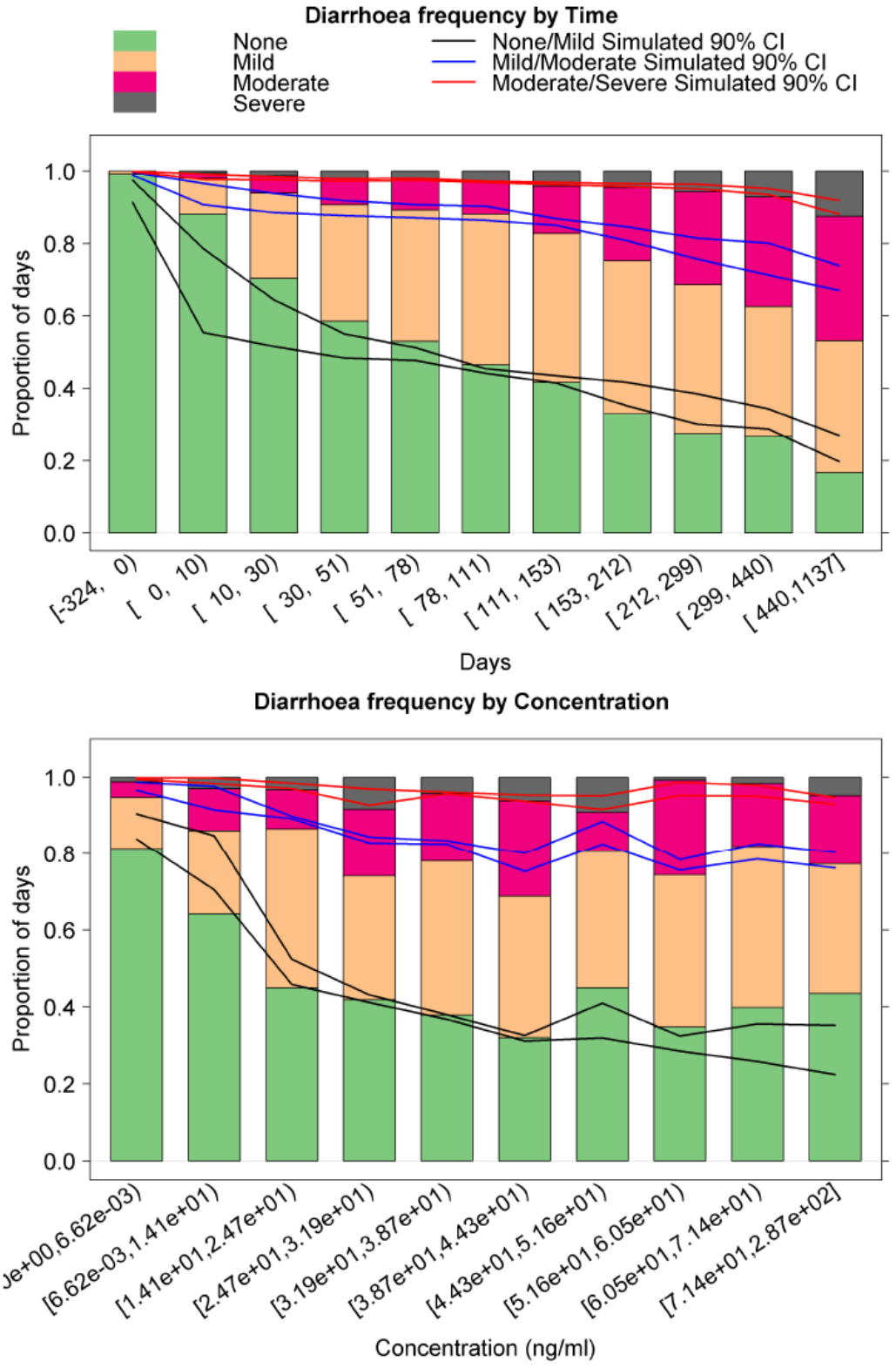

Figure 4. Visual predictive check for diarrhoea model (estimated mean Cmax,ss and Cmin,ss were 49.9 ng/ml (63%CV) and 17.5 ng/ml (74% CV), respectively, for cediranib 20 mg by popPK modelling)

Effect of cediranib on QTc prolongation

Digital ECGs were collected from 4 studies in the cediranib clinical program at doses ranging from 0.5 to 60 mg and used for a concentration-QTc analysis. Studies 01, 02, 04 and 21 were utilized to obtain data from 242 patients with approximately 2000 plasma samples and over 5000 QTc assessments. There was no evidence of QTc prolongation with increasing cediranib plasma concentrations.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics: Basic pharmacokinetic characteristics such as absorption, dose- and time dependency, distribution, excretion have been sufficiently investigated. Cediranib is moderately (between 20-70%) absorbed. Pharmacokinetics of cediranib do not show dose (0.5-60 mg) of time-dependent behaviour. Inter- and intrasubject variability of cediranib pharmacokinetics is high. Cediranib is mainly cleared by metabolism, only a low fraction (<2%) of cediranib was excreted unchanged in the urine. In the popPK analysis, no intrinsic factors were found to impact cediranib pharmacokinetic parameters to a clinically relevant extent. Body weight and age were found to impact cediranib pharmacokinetics to a small extent (<25% of median), with higher exposure in patients with low body weight or elderly patients. No dose adjustments are considered necessary. Clearance of cediranib was approximately 30% reduced in patients with moderate renal impairment compared to patients with normal function. Patients with moderate renal impairment had an increased incidence of discontinuation of cediranib treatment. As only a low fraction of cediranib is excreted unchanged in the urine, no effect of creatinine clearance on cediranib pharmacokinetics is anticipated. The relation for cediranib exposure seen with CLCR is likely related to body weight and age but as cediranib is metabolised by FMO1, decreased metabolism cannot be ruled out. No pharmacokinetic data in patients with severe renal impairment are available. Information regarding moderate and severe renal impairment have been included in the SmPC. Further, pharmacokinetic data in patients with hepatic impairment were somewhat contradictory: following single dose administration exposure of cediranib in patients with moderate hepatic was higher than in patients with normal/mild hepatic impairment. It seemed that subjects with high cediranib exposure dropped out. Thus, cediranib seems poorly tolerated in this population. Patients with moderate and severe hepatic impairment were not included in ICON6, and safety experience with cediranib in this group of patients is very limited. This has been acknowledged in the SmPC.

Cediranib is mainly cleared by metabolism. The metabolic fate of cediranib has not been characterised sufficiently. Poor HPLC separation of metabolites prevented quantification of metabolic pathways but two metabolites *N*-propyl pyrrolidine oxidised cediranib and N-glucuronide-cediranib have tentatively been identified. FMO3 (FMO1) and UGT1A4 are the main enzymes involved in formation of these two metabolites. The limited data on metabolite formation in the mass balance study suggest that variability might be high due to differences in metabolism of cediranib.

N-propyl pyrrolidine oxidised cediranib has been synthesised and the pharmacological activity of N-propyl pyrrolidine oxidised cediranib the potential of N-propyl pyrrolidine oxidised cediranib for DDI in vitro will be investigated as a post approval measure. It should be noted that it is not entirely sure if the synthesised N-propyl pyrrolidine oxidised cediranib is the metabolite formed in vivo. If N-propyl pyrrolidine oxidised cediranib is pharmacological active, the pharmacokinetics should be evaluated. Attempts to synthesise N-glucuronide cediranib failed, but for most substances N-glucuronidation results in loss of pharmacological activity. As the exposure of the N-glucuronide cediranib seems lower than the exposure of cediranib and N-propyl pyrrolidine oxidised cediranib, significant contribution of N-glucuronide cediranib to pharmacological activity seems unlikely. N-glucuronide cediranib is a human specific metabolite but as already discussed in non-clinical part, in line with ICH S9 guidance no further non-clinical toxicology studies are considered necessary as cediranib is indicated for patients with late

stage or advanced cancer and N-glucuronic conjugates of drugs are generally not pharmacological active or toxic to humans or non-clinical species.

Interactions: The potential of cediranib to interact by means of CYPP450 enzymes is considered low because cediranib is no substrate, inhibitor or inducer of CYP P450 enzymes at systemic concentrations. Cediranib did not inhibit UGT enzymes at clinically relevant concentrations. Potential drug drug interactions involving FMO1 and FMO3, however, have not been explored. H2-antagonists cimetidine and ranitidine are substrates for FMO3 and have been used to phenotype FMO3 in vivo (reviewed in Cashman 2002, Hisamuddin 2007). Cimetidine or ranitidine are recommended to be administered prior to paclitaxel administration and may thus interact with the pharmacokinetics of cediranib.

Further, the potential of cediranib to interact with transporters was investigated for Pgp, BCRP and the hepatic uptake transporters OATP1B1 and OATP1B3. Cediranib is a substrate for Pglycoprotein but not for BCRP, OATP1B1, OATP1B3 and OCT1. An in vivo interaction study with ketoconazole increased cediranib exposure by 21%. As cediranib is no substrate for CYP P450 enzymes, it can be assumed that the increase is d ue to inhibition of intestinal absorption. Because of the small effect, no dose recommendations are considered necessary when cediranib is co-administered with P-glycoprotein inhibitors. Inhibitor transporter studies revealed that cediranib has the potential to inhibit many transporters Pgp, BCRP, OATP1B1, OATP1B3, OCT2, MATE1 albeit at higher than systemic concentrations. Cediranib is a potent inhibitor of MATE2K and OATP1A2 at clinical relevant concentrations. The applicant committed to investigate the potential of cediranib to inhibit MRP2. The results can be submitted post-approval.

In the pivotal study, cediranib was co-administered with platin/paclitaxel in 85% of the patients. No pharmacokinetic data have been collected in the pivotal study and only limited information on the effect of cediranib on the pharmacokinetics of carboplatin, cisplatin and paclitaxel and vice versa is available from study 09 in NSCLC patients. Evaluation of the potential interaction is further hampered because study 09 had no cross-over data for the effect of carboplatin/paclitaxel on cediranib and no individual pharmacokinetic data were submitted in study 09. The summarised data, however, suggest that co-administration of carboplatin/paclitaxel does not affect the AUC of cediranib. This should be further substantiated.

The effect of cediranib on the exposure of carboplatin, cisplatin and paclitaxel has been investigated in a cross-over design and the results are therefore more reliable. No effect of cediranib on pharmacokinetics of carboplatin and cisplatin was observed. Paclitaxel clearance, when given in combination with cediranib, decreased by approximately 20% compared with paclitaxel alone. This was confirmed in another study in NSCLC in which patients co-administered 20 mg cediranib had a 30% higher paclitaxel AUC compared to patients without cediranib. Mechanism for this effect is not entirely clear because cediranib does not inhibit CYP enzymes or OATP1B3. The potential higher exposure of paclitaxel when co-administered with cediranib did not lead to more discontinuations or dose reductions of chemotherapy in the combination arms with cediranib compared to chemotherapy only arm in the pivotal study ICON6. The increase in paclitaxel when co-administered with cediranib has been described adequately in the SmPC.

Cediranib has shown significant effects on all stages of female reproduction in rats. No interaction studies with oral contraceptives have been conducted. A warning in the SmPC section 4.4 has been issued that the efficacy of hormonal contraceptives may be reduced if co-administered with cediranib because of decreased absorption due to diarrhoea. In addition, induction of intestinal enzymes by cediranib cannot be excluded. As effectiveness of oral contraceptives is uncertain, it should be mentioned in section 4.6 to use an additional non-hormonal contraceptive method should be

considered during cediranib treatment. Further, concomitant use of anthracyclines was not allowed in ICON6 in order to avoid potential cardiac toxicity when administered in combination with cediranib. Further, cediranib is an anti-angiogenic agent and may have the potential to increase the risk of severe bleeding or clotting. Patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medications that increase the risk of bleeding are at risk for these interactions. These interactions have been described in the SmPC.

Pharmacology: Cediranib is a potent tyrosine kinase inhibitor of all three VEGF receptors (VEGFR-1, -2, and -3) at nanomolar concentrations. The pharmacological activity of the metabolites of cediranib need further investigation. Various pharmacodynamic markers for VEGFR inhibitors, show a dose dependent response. For some markers i.e. VEGF an sVEGFR plasma concentrations the effects were already apparent at doses < 20 mg cediranib, while effects on blood pressure and iAUC60 were significant at doses of 20 mg and higher. The role of these biomarkers in relation to clinical outcome is unclear.

Dose – dose recommendations: Anti-tumour activity of cediranib in phase 1 studies was observed at ≥ 20 mg doses; anti-tumour response seemed better at higher doses of cediranib (30 and 45 mg). The selection of 20 mg dose of cediranib for ICON6 is understood from efficacy and tolerability experiences with other studies. In ICON6, there is the option for a dose reduction to cediranib 15 mg. There are no clinical data with the 15 mg dose from phase 1 or 2 studies.

Dose recommendations have been proposed with regard to food intake and co-administration of strong enzyme inducers. Co-administration of cediranib with a high fat meal reduced cediranib AUC by 24%. In order to obtain the highest exposure, the applicant recommends cediranib be taken on an empty stomach at least 1 hour before or 2 hours after a meal. This is the same dosing recommendation as in the pivotal study

Co-administration with the strong inducer rifampicin resulted in a 39% decrease in exposure of cediranib. The applicant proposes a dose increase of cediranib to 30 mg qd when co-administration with strong inducers of Pglycoprotein/UGTs cannot be avoided. These dose recommendations can be accepted.

Exposure effect: Hypertension and diarrhoea are common AEs of VEGFR inhibitors. Exposure-safety relationships were explored for hypertension and diarrhoea based on cediranib monotherapy studies. A Emax type of relationship was found between cediranib plasma concentration and blood pressure elevation and diarrhoea. Cediranib plasma concentrations obtained with 20 mg dose are in the steep part of the exposure-effect relationships.

It should be noted that these relationships have been established for cediranib monotherapy. Co-administration with platin/paclitaxel is likely to change the relationship. Support for this is that the MTD for cediranib was lower when given in combination with chemotherapy compared to monotherapy. Furthermore, pharmacokinetics suggested an interaction between platin/paclitaxel co-administration and cediranib. The absence of pharmacokinetic data in ICON6 hampers evaluation of what effective but safe exposure of cediranib is when co-administered with platin/paclitaxel.

3.3.4. Conclusions on clinical pharmacology

Pharmacokinetic data showed an interaction between paclitaxel co-administration and cediranib resulting in a 30% higher paclitaxel exposure. The underlying pharmacokinetic data from study D8483C00002 should be provided. There were no more discontinuations or dose reductions of paclitaxel/carboplatin in the combination arms with cediranib compared to chemotherapy only arm in

the pivotal study ICON6. Therefore, no start dose adjustment for paclitaxel when combined with cediranib is considered necessary.

Relationships between cediranib exposure and probability of hypertension and diarrhoea were established for cediranib monotherapy studies. The absence of pharmacokinetic data in ICON6 hampers evaluation of what effective but safe exposure of cediranib is when co-administered with platin/paclitaxel. The applicant committed to evaluate exposure-response relationship from ongoing trials D8485C00002, D8486C00001, D8487C00001, and D8488C00001 in patients with ovarian cancer as a post approval measure.

Another important issue is characterisation of metabolic fate of cediranib. Two major metabolites N-propyl pyrrolidine oxidised cediranib and N-glucuronide-cediranib have been tentatively identified, however, the contribution of each pathway to the overall elimination of cediranib is not clear. The exposure of cediranib and metaboltes will be evaluated in plasma samples from study D8480C00098. The results will be submitted as a post approval measure. Depending on the results, additional (in vitro) interaction studies with the metabolites may be required. The applicant commits to evaluate the inhibitory potential of cediranib on human MRP2 in vitro.

N-propyl pyrrolidine oxidised cediranib has been synthesised and the pharmacological activity of N-propyl pyrrolidine oxidised cediranib the potential of N-propyl pyrrolidine oxidised cediranib for DDI in vitro will be investigated. The results will be submitted as a post approval measure.

3.3.5. Efficacy

3.3.6. Main study – ICON6

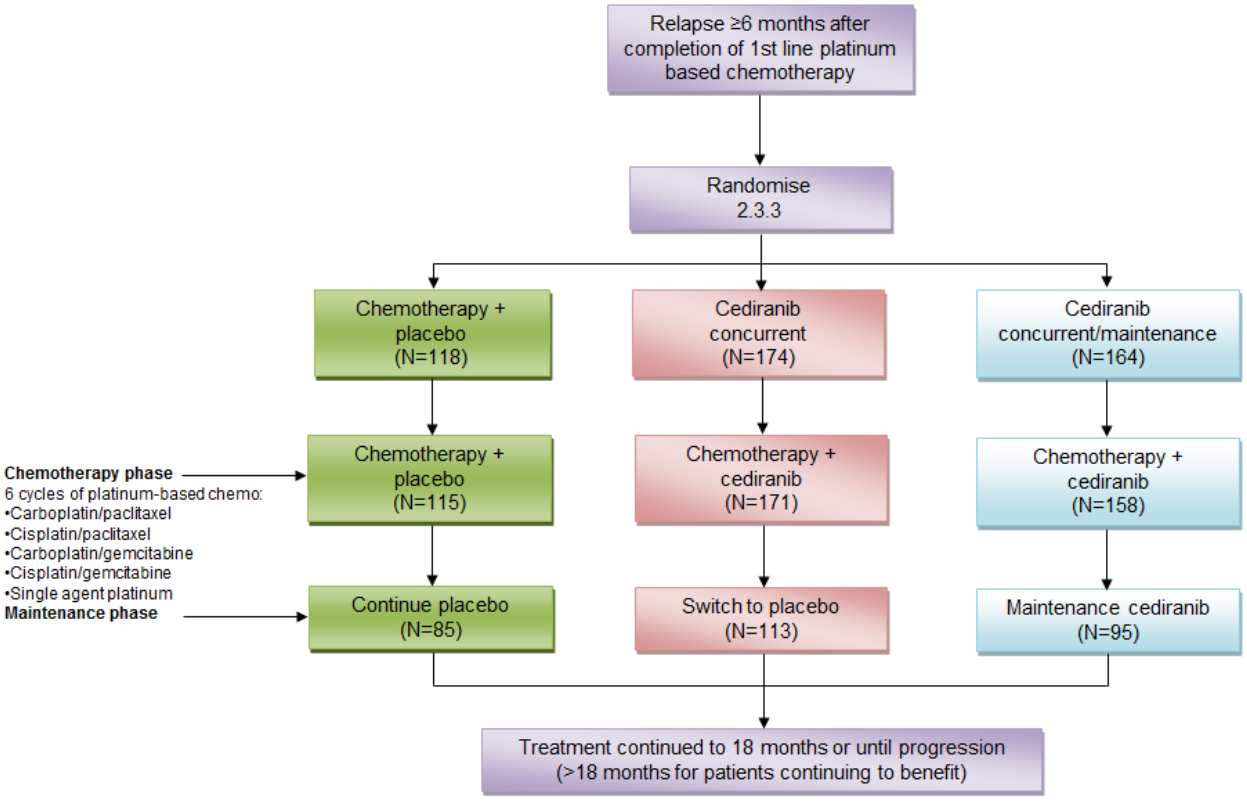

Figure 5. Design of the ICON6 study

This submission is supported by the results of one pivotal study (ICON6), sponsored by the Medical Research Council (MRC) and conducted by the MRC Clinical Trials Unit.

Study participants

In this study, eligible patients had epithelial ovarian, fallopian tube or serous primary peritoneal carcinoma relapsing ≥6 months after first-line platinum-based chemotherapy. Previous maintenance treatment with a biological therapy (eg, bevacizumab) was permitted (provided this was stopped >6 weeks before inclusion of the study. Previous chemotherapy maintenance treatment was not allowed. Patients were required to have Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1 and without any severe uncontrolled medical condition or disease.

Treatments

All patients, regardless of the arm they were randomised to, were to receive 6 cycles of platinum-based chemotherapy, which is widely used in patients with PSR ovarian cancer across all geographic regions. The recommendation in ICON6 was that patients were to be treated with carboplatin area under the concentration-time curve 6 (AUC6; calculated dose) or AUC5 (glomerular filtration rate measured) over 30 to 60 minutes, in combination with paclitaxel 175 mg/m2 over 3 hours, once every 3 weeks (1 cycle) for 6 cycles. This regimen was selected based on the findings from ICON4/AGO-OVAR-2.2 (Parmar et al. Lancet. 2003 Jun 21; 361).

Patients were randomised to 1 of 3 arms in a 2:3:3 ratio to:

- Chemotherapy + placebo (Arm A): Patients were to receive a platinum-based chemotherapy regimen, as described above, plus a daily oral placebo tablet for the duration of the chemotherapy (18 weeks) and then as maintenance for up to 18 months from randomisation or until progression.
- Cediranib concurrent (arm B) patients were to receive a platinum-based chemotherapy regimen, as described above, plus daily oral cediranib (20 mg during chemotherapy only, and then an oral daily placebo tablet as maintenance for up to 18 months from randomisation or until progression.
- Cediranib concurrent/maintenance (Arm C): Patients were to receive a platinum-based chemotherapy regimen, as described above, plus oral cediranib (20 mg) daily during chemotherapy and then continued cediranib as maintenance for up to 18 months from randomisation or until progression.

After the first 30 patients had been recruited, the cediranib starting dose was reduced to 20 mg QD. The selection of this dose was based on the emerging clinical data from the ongoing cediranib programme (other Phase II/III cediranib studies, rather than any specific tolerability issue in ICON6). This dose was consistent with the 20 mg dose that was being progressed concurrently in the colorectal cancer (Studies 51 and 13), glioblastoma (Study 55), and NSCLC (Study BR.29) development programmes with cediranib in combination with chemotherapy.

Outcomes/endpoints

The primary outcome was investigator assessed PFS, defined as:

Tumour assessment data will be used to determine each subject's visit response according to a modified (see Section 3.1.1.3.4) version of RECIST 1.0 (Therasse 2000). Endpoints determined from RECIST data will be based on the investigator's assessment on the CRF, which is the primary assessment, as well as a programmatic determination using tumour measurements provided by the

investigator on the tumour assessment CRF. Baseline radiological tumour assessments were to be performed no more than 28 days before the start of randomised treatment; however, a 6-week window was considered after discussion with the chief investigator. Tumour assessments were then performed after 6 cycles of chemotherapy, and at 12 and 18 months from day 1 of cycle 1 or until disease progressed. Baseline values recorded after randomisation were not to be used as the baseline assessment; although such assessments could be used in the calculation of progressive disease (PD).

Patients will be assessed by radiographic tumour assessments using CT or MRI, which were performed at baseline, after 6 cycles of chemotherapy and then at clinical progression or 12 and 18 months after randomisation (if not progressed previously). Patients will be clinically assessed and CA 125 measured at the start of every chemotherapy cycle, then every six weeks until the end of the 18 months from randomisation and three monthly thereafter, until protocol defined disease progression. Additional unscheduled assessments of progression were triggered by suspicion of clinical progression or rises in CA125. Once patients had progressed, no further scans were performed.

Secondary outcomes were: Overall survival (OS), HRQoL, Objective response, Duration of response, Change in tumour size, Time to first/second subsequent chemotherapy or death, Time to discontinuation of trial drug or death.

The primary comparison was cediranib concurrent/maintenance versus chemotherapy + placebo. Other comparisons between arms were made in an exploratory manner.

Randomisation

Patients were randomised to placebo or one of the two treatment groups (cediranib concurrent or cediranib concurrent/maintenance) in a 2:3:3 ratio, in order to maximise the number of patients who could receive active drug, whilst maintaining statistical power, and stratified by five stratification factors:

• Gynaecological Cancer InterGroup (GCIG group)

• Planned chemotherapy regimen (carboplatin/cisplatin versus carboplatin/cisplatin + paclitaxel versus carboplatin/cisplatin + gemcitabine)

• First-line chemotherapy (paclitaxel versus no paclitaxel)

• Duration of relapse-free interval (6 to 12 months versus >12 months)

Randomisation was conducted using a computer software program that incorporates a standard procedure (using an Interactive voice response system) for generating random numbers, which is considered adequate.

Baseline characteristics

Baseline characteristics were generally equally distributed across the study arms. However, imbalances in baseline characteristics were observed (CA-125 level, % moderately or poorly differentiated) that favoured the cediranib arms (Table 7 and Table 8).

Table 7. Demographics and other patient characteristics Baseline characteristics (Full Analysis Set)

Demographic characteristic		Chemotherapy + placebo (N=118)	Cediranib concurrent (N=174)	Cediranib concurrent/ maintenance (N=164)	Total (N=456)
Age (years)	n	118	174	164	456
	Mean	60.1	61.0	61.1	60.8
	StDev	9.13	10.25	10.65	10.11
	Median	62.0	62.0	62.0	62.0
	Minimum	37	30	32	30
	Maximum	77	85	86	86
Age group (years) n (%)	<35	0	2 (1.1)	2 (1.2)	4 (0.9)
	35 to <50	18 (15.3)	22 (12.6)	26 (15.9)	66 (14.5)
	50 to <55	21 (17.8)	23 (13.2)	16 (9.8)	60 (13.2)
	55 to <65	36 (30.5)	54 (31.0)	54 (32.9)	144 (31.6)
	65 to <75	38 (32.2)	62 (35.6)	52 (31.7)	152 (33.3)
	75 to <85	5 (4.2)	10 (5.7)	13 (7.9)	28 (6.1)
	≥85	0	1 (0.6)	1 (0.6)	2 (0.4)
BMI (kg/m^2)	n	115	173	164	452
	Mean	27.7	28.0	27.6	27.8
	StDev	5.43	5.71	5.98	5.73
	Median	26.9	27.2	26.3	26.8
	Minimum	18	18	17	17
	Maximum	50	47	49	50
BMI group (kg/m^2) n (%)	<18.5	1 (0.8)	2 (1.1)	4 (2.4)	7 (1.5)
	18.5 to <30	85 (72.0)	119 (68.4)	113 (68.9)	317 (69.5)
	≥30	29 (24.6)	52 (29.9)	47 (28.7)	128 (28.1)
	Unknown	3 (2.5)	1 (0.6)	0	4 (0.9)
ECOG PS n (%)	0	63 (53.4)	107 (61.5)	88 (53.7)	258 (56.6)
	1	50 (42.4)	64 (36.8)	72 (43.9)	186 (40.8)
	2	2 (1.7)	2 (1.1)	1 (0.6)	5 (1.1)
	3	0	0	1 (0.6)	1 (0.2)
	4	0	0	1 (0.6)	1 (0.2)
	Unknown	3 (2.5)	1 (0.6)	1 (0.6)	5 (1.1)
Cancer antigen 125 (U/mL)	n	117	174	160	451
	Mean	1521.2	801.4	1111.2	1098.0
	StDev	8343.65	1726.89	4111.28	5014.47
	Median	264.0	284.5	282.9	276.0
	Minimum	7	7	8	7
	Maximum	88770	15726	49472	88770

Note: Percentages are based on the number of patients in the analysis population.
BMI body mass index; ECOG PS Eastern Cooperative Oncology Group performance status; N, n number of patients; StDev standard deviation.

Table 8. Baseline disease characteristics (Full Analysis Set)

		Number (%) of patients			
Baseline disease characteristics		**Chemotherapy + placebo (N=118)**	**Cediranib concurrent (N=174)**	**Cediranib concurrent/ maintenance (N=164)**	**Total (N=456)**
Disease origin	Ovary	98 (83.1)	139 (79.9)	131 (79.9)	368 (80.7)
	Fallopian	1 (0.8)	6 (3.4)	6 (3.7)	13 (2.9)
	Peritoneal	19 (16.1)	29 (16.7)	27 (16.5)	75 (16.4)
Histology	Serous	96 (81.4)	140 (80.5)	126 (76.8)	362 (79.4)
	Mixed epithelial	1 (0.8)	1 (0.6)	1 (0.6)	3 (0.7)
	Endometroid	7 (5.9)	13 (7.5)	11 (6.7)	31 (6.8)
	Clear cell	5 (4.2)	8 (4.6)	6 (3.7)	19 (4.2)
	Undifferentiated	3 (2.5)	1 (0.6)	2 (1.2)	6 (1.3)
	Mucinous	1 (0.8)	5 (2.9)	2 (1.2)	8 (1.8)
	Transitional cell carcinoma	1 (0.8)	0	1 (0.6)	2 (0.4)
	Other	14 (11.9)	18 (10.3)	25 (15.2)	57 (12.5)
	Unknown	1 (0.8)	1 (0.6)	1 (0.6)	3 (0.7)
Tumour grade	Well differentiated	1 (0.8)	6 (3.4)	5 (3.0)	12 (2.6)
	Moderately differentiated	18 (15.3)	20 (11.5)	24 (14.6)	62 (13.6)
	Poorly differentiated	97 (82.2)	132 (75.9)	117 (71.3)	346 (75.9)
	Unknown	2 (1.7)	16 (9.2)	18 (11.0)	36 (7.9)
Previous VEGF therapy	No	112 (94.9)	162 (93.1)	154 (93.9)	428 (93.9)
	Yes	6 (5.1)	12 (6.9)	10 (6.1)	28 (6.1)
First-line chemotherapy	Carboplatin/cisplatin alone	13 (11.0)	20 (11.5)	14 (8.5)	47 (10.3)
	Carboplatin/cisplatin + gemcitabine	0	0	1 (0.6)	1 (0.2)
	Carboplatin/cisplatin + paclitaxel	103 (87.3)	149 (85.6)	148 (90.2)	400 (87.7)

Outcomes and estimation

Following the primary analysis of the ICON6 data performed by the MRC, AstraZeneca undertook extensive source data verification (SDV) and quality control checks to validate the ICON6 study database. The outcomes presented are based on the validated ICON6 study database (after SDV).

Overall, 118 patients were randomised to the chemotherapy + placebo arm, 174 patients to the cediranib concurrent arm and 164 patients to the cediranib concurrent/maintenance arm. In total, PFS events were reported for 113 (95.8%) patients in the chemotherapy + placebo arm, 156 (89.7%) patients in the cediranib concurrent arm and 140 (85.4%) patients in the cediranib concurrent/maintenance arm. There was a statistically significant improvement in PFS for the cediranib concurrent/maintenance arm (median 11.0 [95% CI 10.4-11.8] months) compared with the chemotherapy + placebo arm (median 8.7 [CI 7.8-9.4] months) with a HR of 0.57 (95% CI: 0.44, 0.73; p<0.001) (Figure 6). There was also a statistically significant improvement in PFS for the cediranib concurrent arm (median 9.9 [CI 9.4-10.7] months) compared with the chemotherapy + placebo arm (median 8.7 months) with a HR of 0.70 (95% CI: 0.55, 0.89; p=0.004).

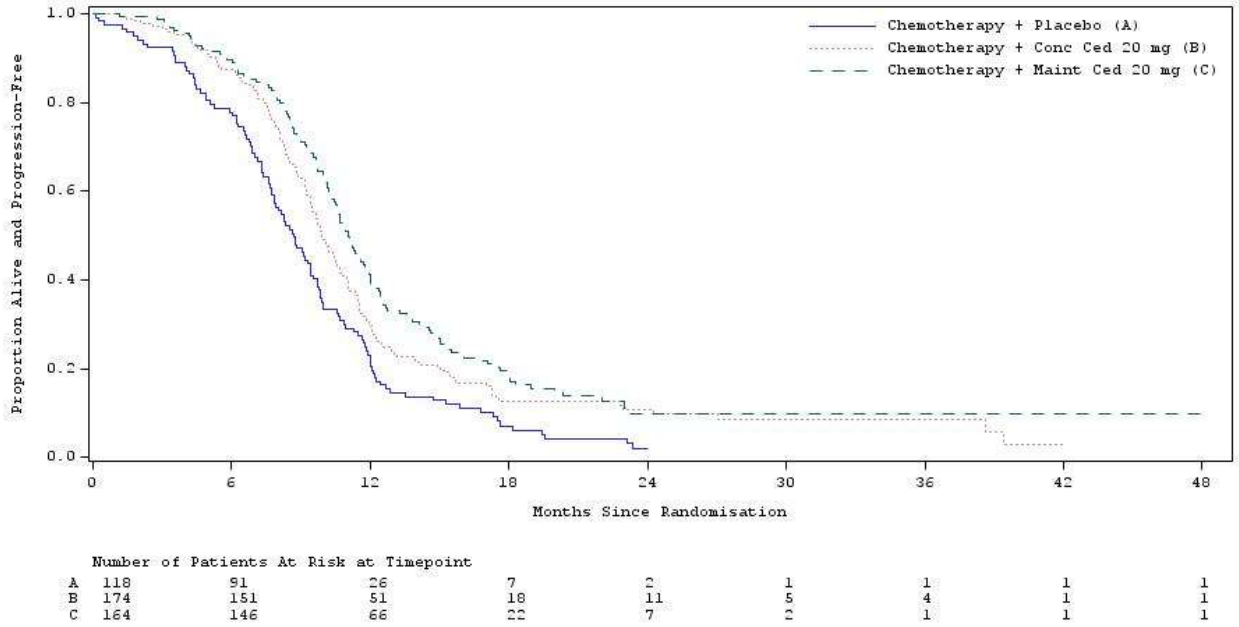

Figure 6. Kaplan-Meier plot for progression-free survival – Investigator's assessment (Full Analysis Set study ICON6)

A number of sensitivity analyses were conducted, which confirmed the robustness of the PFS results. Among these was an analysis excluding progressive disease without radiologic confirmation and an analysis in which blinded independent review of radiographic (MRI or CT scans was used to assess progression. Patients for which scans were unavailable were excluded from this analysis (95% of patients had at least 1 scan available).

Table 9. ICON6: Summary of progression-free survival analyses (Full Analysis Set)

Analyses	Median PFS, months (No. events, n [%])			Comparison, HR (95%CI), p-value	
	Chemotherapy + placebo arm (N=118)	Cediranib concurrent arm (N=174)	Cediranib concurrent/ maintenance arm (N=164)	Cediranib concurrent/ maintenance arm versus Chemotherapy + placebo arm	Cediranib concurrent arm versus Chemotherapy + placebo arm
Primary					
Investigator's assessment[a]	8.7 (113 [95.8%])	9.9 (156 [89.7%])	11.0 (140 [85.4%])	0.57 (0.44, 0.73), p<0.001	0.70 (0.55, 0.89), p=0.004
Secondary					
Investigator's assessment (covariate adjusted)[b]				0.52 (0.41, 0.67), p<0.001	0.70 (0.54, 0.89), p=0.004
Sensitivity[a]					
Exclude progressive disease without radiologic confirmation	8.8 (112 [94.9%])	10.1 (153 [87.9%])	11.3 (139 [84.8%])	0.59 (0.46, 0.76), p<0.001	0.71 (0.55, 0.90), p=0.007
Evaluation time bias[c]	8.3 (113 [95.8%])	9.5 (156 [89.7%])	10.5 (140 [85.4%])	0.58 (0.45, 0.75), p<0.001	0.71 (0.56, 0.91), p=0.007
Attrition bias[d]	9.1 (93 [78.8%])	9.9 (124 [71.3%])	11.1 (115 [70.1%])	0.57 (0.43, 0.75), p<0.001	0.74 (0.57, 0.97), p=0.033
Ascertainment bias (incorporates BICR)[e]	9.4 (102 [90.3%])	10.5 (134 [82.7%])	11.2 (128 [81.0%])	0.64 (0.49, 0.83), p<0.001	0.75 (0.58, 0.97), p=0.036

a Calculated using an unadjusted Cox regression model including treatment as a covariate, p-value from unstratified log-rank test.
b Calculated using a Cox model including factors used to stratify randomisation as covariates: GCIG (Australia and New Zealand, Canada, Spain, United Kingdom), previous paclitaxel use (yes, no), planned chemotherapy (platinum alone, platinum+gemcitabine, platinum+paclitaxel), time since last chemotherapy (<12 months, >12 months), and prior VEGF therapy (yes, no).
c Time to progression was revised to the midpoint between the time of progression and the previous visit where the patient was evaluated by the Investigator.
d Patients who took subsequent anticancer therapy prior to progression and patients who missed >1 visit were censored.
e The Investigator's assessment of PFS was adjusted using the assessment of PFS by BICR. Patients who were not evaluated by BICR due to unavailable scans have been excluded. The evaluable population for this analysis was 113, 162, and 158 patients in the chemotherapy + placebo arm, cediranib concurrent arm and cediranib concurrent/maintenance arm, respectively.

BICR blinded independent central review; CI confidence interval; GCIG Gynaecologic Oncology InterGroup; HR hazard ratio; N number of patients; n number of events; VEGF vascular endothelial growth factor.

Additional sensitivity analyses

The requested sensitivity analysis, censoring patients who discontinued cediranib due to AE but proceeded to other anticancer treatment before progression, also revealed a statistically significant PFS benefit (10.9 vs. 8.7 months; p<0.001), which is considered supporting for the primary analysis.

Another post hoc sensitivity analysis was initiated by the Applicant for the subset of 293 patients who entered the ICON6 maintenance phase (Maintenance Analysis Set). This analysis showed a statistically borderline significant improvement for the cediranib concurrent/maintenance arm compared with the cediranib concurrent arm (median PFS 11.8 vs. 10.2 months; p=0.045), although the clinical relevance of the 1.6 months difference can be disputed.

Subgroup analyses

The forest plot of PFS comparing cediranib concurrent/maintenance with chemotherapy+placebo showed a consistent benefit for most subgroups except for CGIG group other than UK or Canada (HR 1.09; CI 0.29-4.11), but this estimate was based only on 13 patients (Figure 7). The forest plot of PFS comparing cediranib concurrent with chemotherapy+placebo also showed a consistent PFS benefit across subgroups. The exception here was in other than serous histology (HR 1.10; CI 0.62-1.95). The point estimate for patients who received prior VEGF therapy suggested a benefit (HR 0.34; CI 0.11-1.09), but this result pertained only to 16 patients and was accompanied by a large confidence interval.

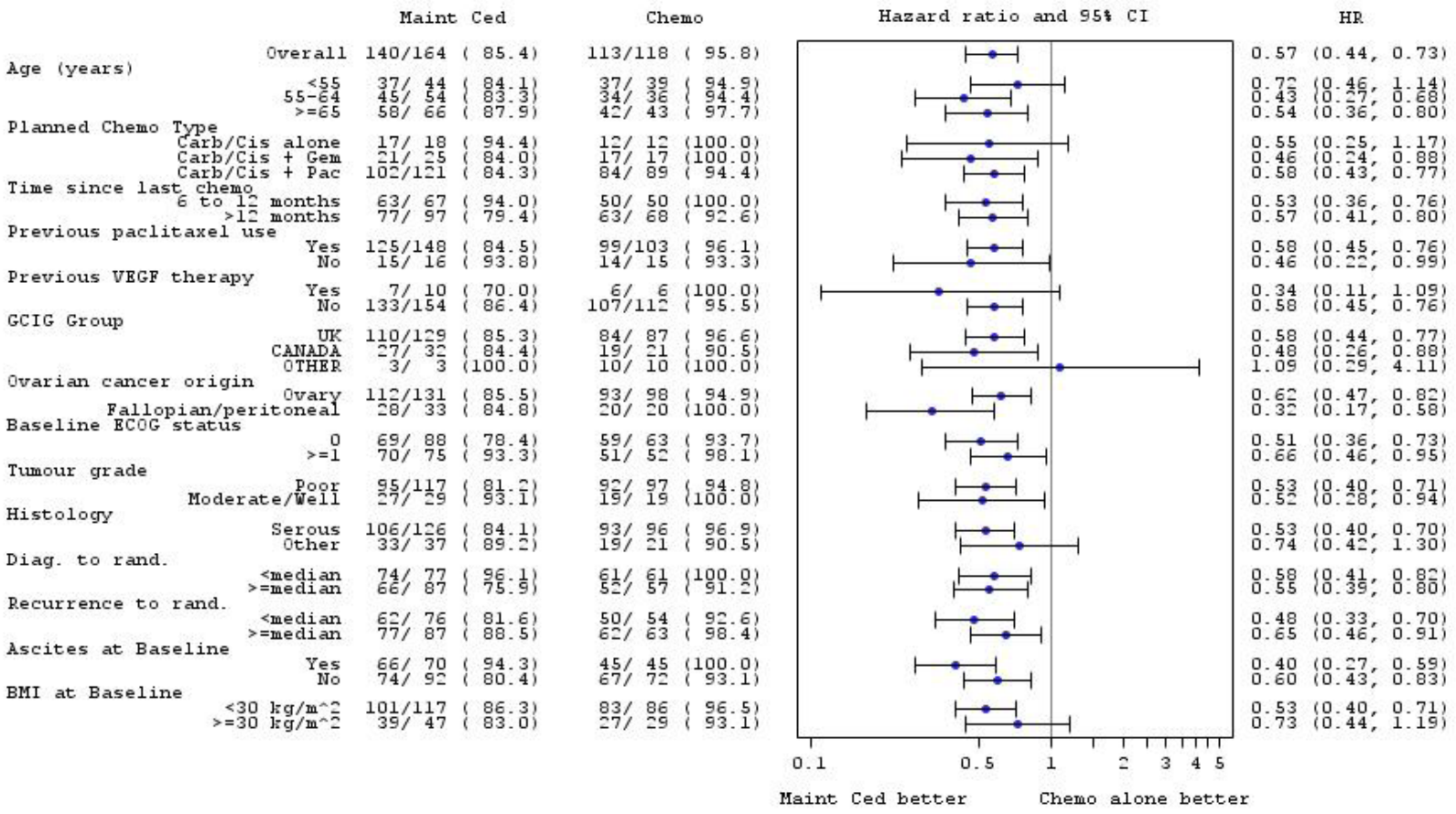

Figure 7. Forest plot for progression-free survival (Inv) cediranib concurrent/maintenance versus chemotherapy + placebo (study ICON6).

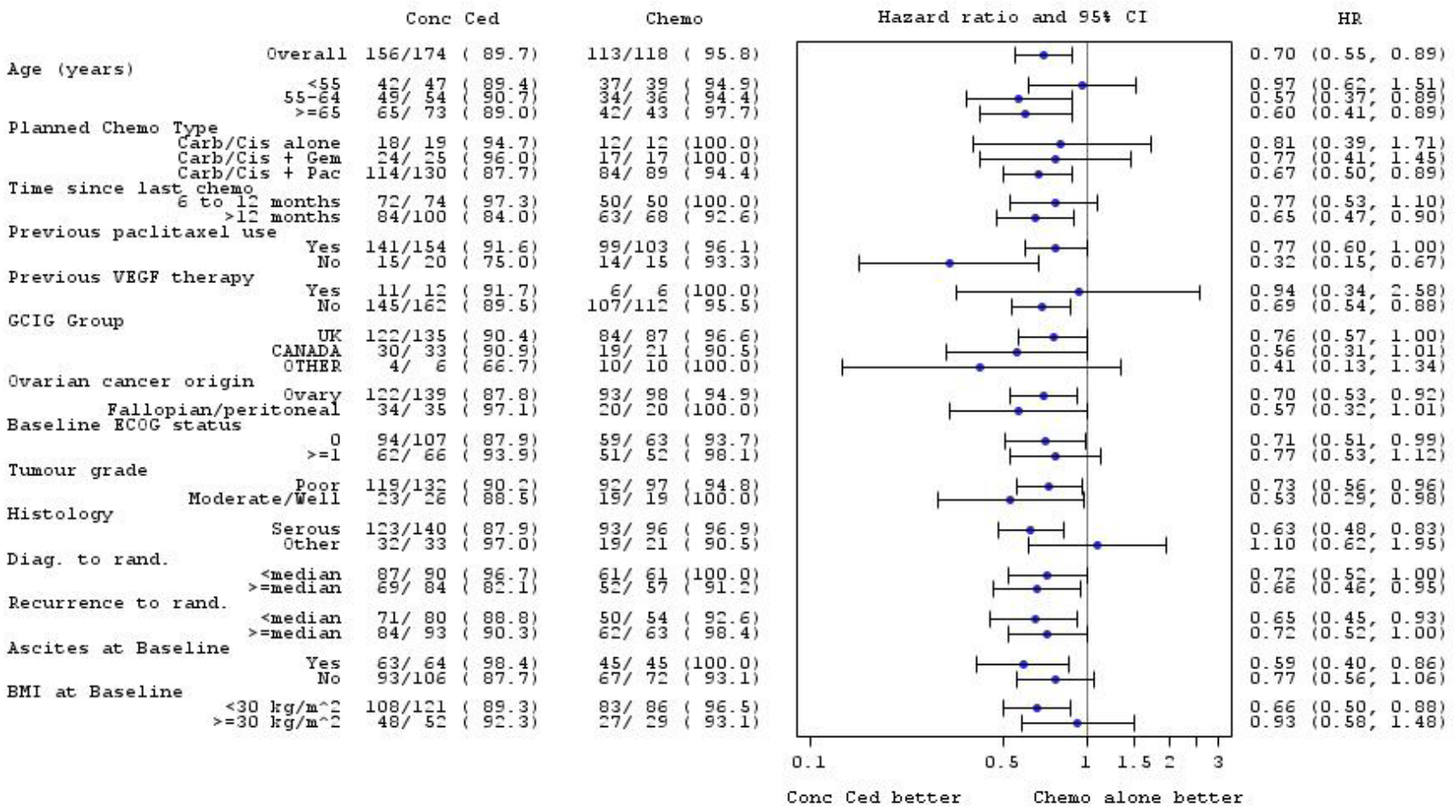

Figure 8. Forest plot for progression-free survival (Inv) cediranib concurrent versus chemotherapy + placebo(study ICON6).

Overall survival

Overall, 51.3% of patients had died at the time of data cut-off (19 April 2013). Results at that moment of efficacy analysis suggested an improvement in OS for the cediranib concurrent/maintenance arm compared with the chemotherapy + placebo arm (26.5 months versus 21.0 months, respectively. An improvement was also suggested for the cediranib concurrent arm (25.3 vs. 21.0 months; p=0.285).

Upon CHMP request, the applicant provided an updated OS analysis (data cut-off 1 November 2014; 74% maturity) suggested a benefit in OS for the cediranib concurrent/maintenance arm (median OS 27.9 months) compared with the chemotherapy + placebo arm (median 19.9 months) (Figure 9). Nevertheless, this improvement was not statistically significant (HR 0.84 (95% CI: 0.63, 1.11, p=0.209). Likewise, OS was lasting longer for the cediranib concurrent arm compared with the chemotherapy + placebo arm (median 26.7 months versus median 19.9 months) (HR 0.95; 95% CI: 0.72, 1.24; p=0.682) but this result was also not statistically significant (Table 10). No conclusions on OS can be made at this stage.

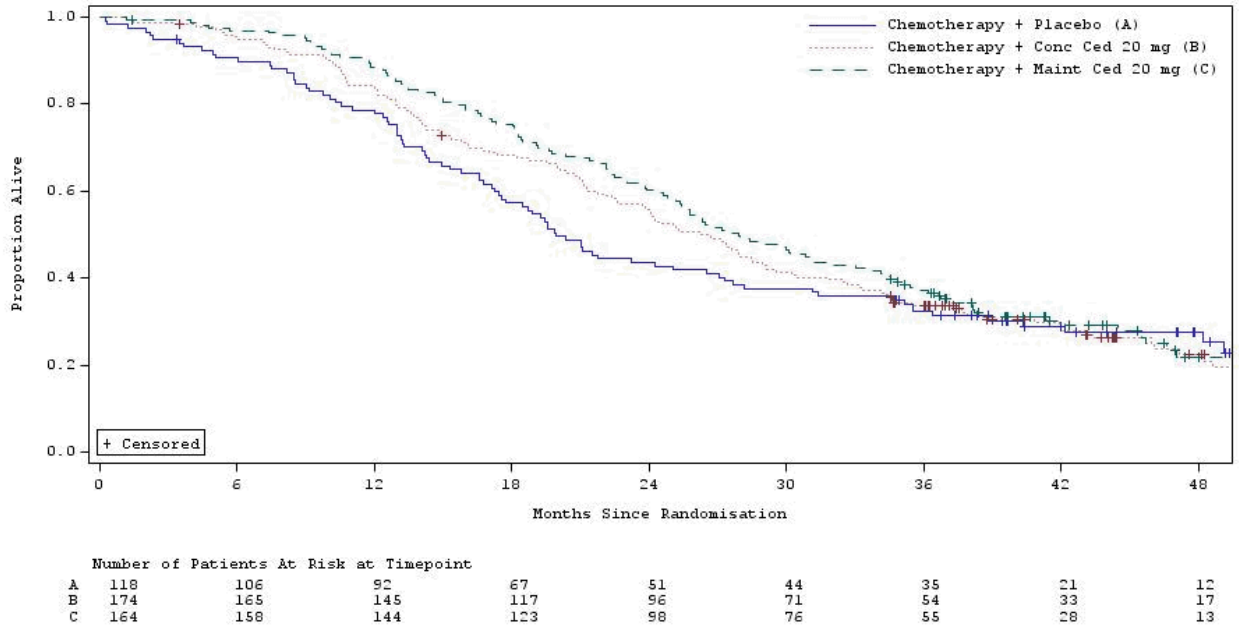

Figure 9. Kaplan-Meier plot for overall survival, updated analysis after survival sweep (Full Analysis Set)

Table 10. Overall survival, updated analysis after survival sweep – unstratified log-rank (Full Analysis Set study ICON6)

	Chemotherapy + placebo (N=118)		Cediranib concurrent (N=174)		Cediranib concurrent/ maintenance (N=164)	
Patients with events	86	(72.9)	133	(76.4)	119	(72.6)
Death	86	(72.9)	133	(76.4)	119	(72.6)
Patients censored[a]	32	(27.1)	41	(23.6)	45	(27.4)
Patients prematurely censored[b]	4	(3.4%)	5	(2.9%)	3	(1.8%)
Median overall survival in months (95% CI)[c]	19.9	(17.4, 26.5)	26.7	(22.5, 29.1)	27.9	(25.2, 33.0)
Comparison to chemotherapy + placebo						
Unadjusted hazard ratio (95% CI)[d]			0.95	(0.72, 1.24)	0.84	(0.63, 1.11)
Unstratified log-rank p-value			0.682		0.209	
Test of proportionality assumption					<0.001	
Restricted mean survival time at 3 yrs	22.3		24.7		26.2	
Difference in restricted mean survival time (95% CI)			2.4	(-0.29, 5.17)	3.9	(1.17, 6.56)

[a] Patients were censored at the last date known alive or at the data cut-off (01 November 2014) date if they recorded a visit subsequent to the data cut-off.
[b] Premature censoring was defined as censoring that occurred more than 1 month prior to the data cut-off date.
[c] Calculated using the Kaplan-Meier technique.
[d] Calculated using an unstratified Cox regression model including treatment as a covariate.
CI confidence interval; N number of patients.

The forest plot of overall survival comparing cediranib concurrent/maintenance with chemotherapy+placebo showed a consistent benefit across subgroups except for age group <55 years (HR 1.17; CI 0.63-2.21) and time from recurrence to randomization ≥median (HR 1.14; CI 0.72-1.81). (Figure 10). The forest plot comparing the cediranib concurrent arm with chemotherapy+placebo revealed similar results (Figure 10). In addition, no benefit was suggested for patients receiving prior platinum-based therapy in combination with gemcitabine (HR 1.33; CI 0.53-3.34).

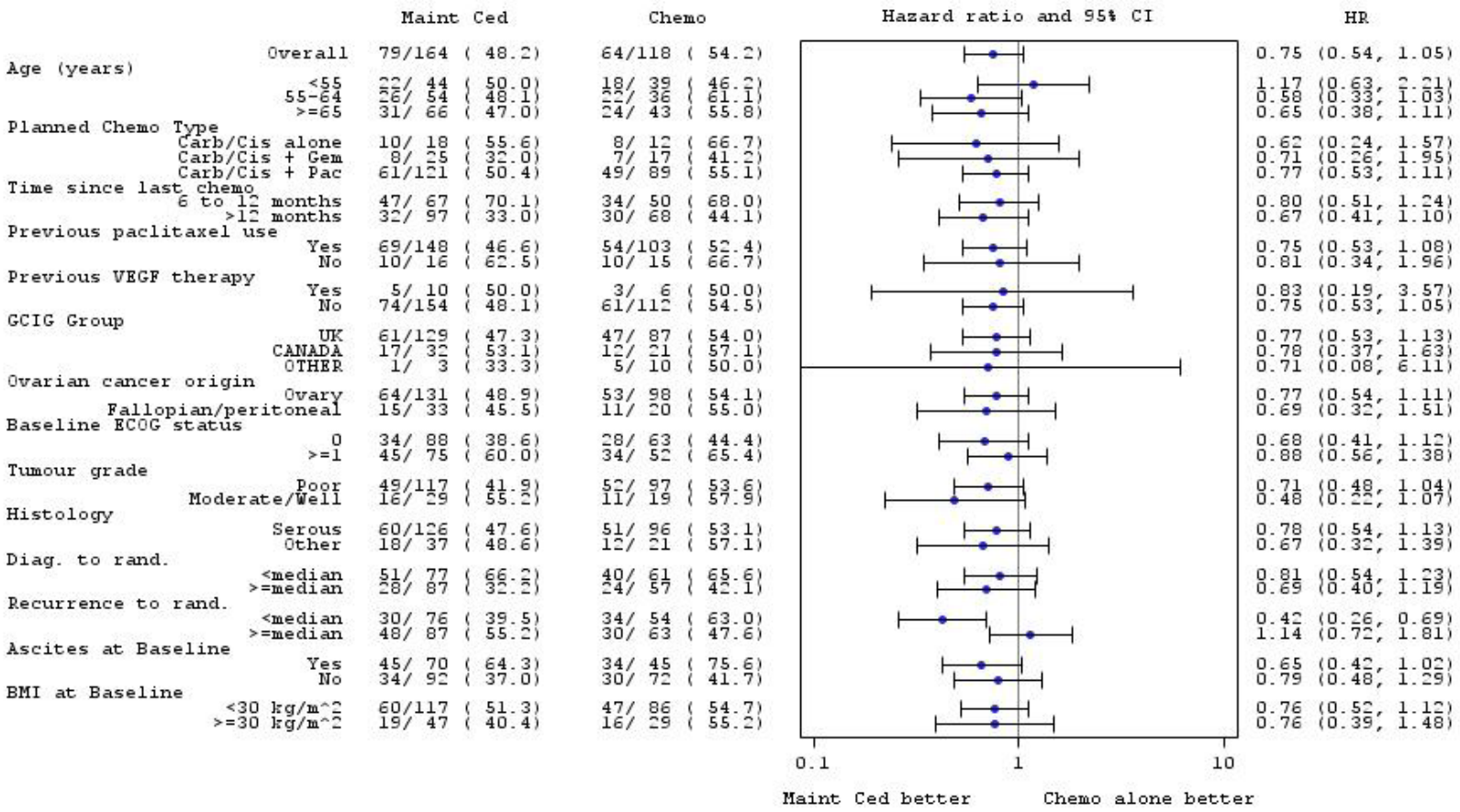

Figure 10. Forest plot for overall survival, cediranib concurrent/maintenance versus chemotherapy + placebo.

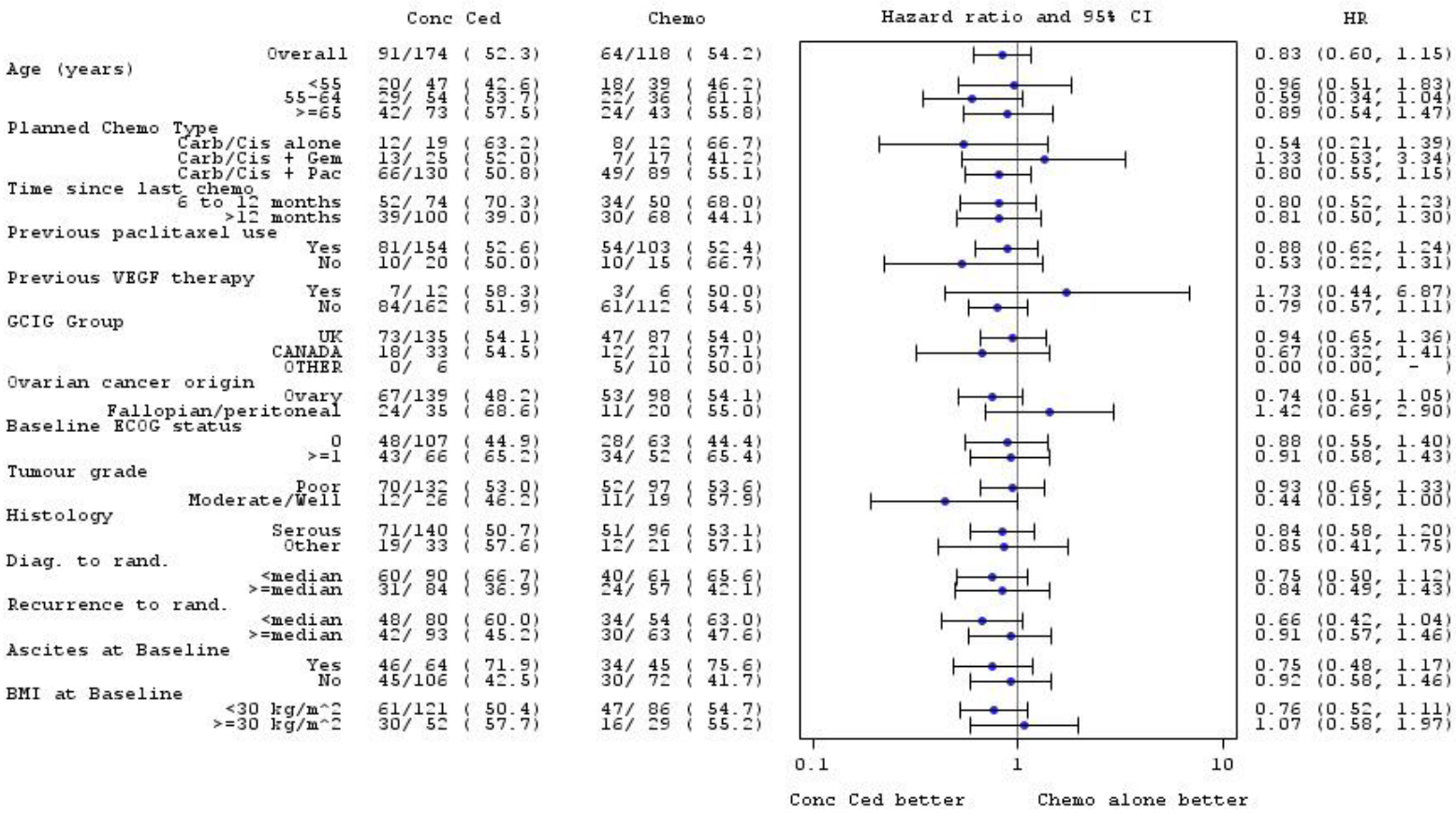

Figure 11. Forest plot for overall survival, cediranib concurrent versus chemotherapy + placebo (Full Analysis Set)

There was little difference in the proportion of patients who received a first or second subsequent chemotherapy comparing the cediranib concurrent arm (78.2% and 54.6%, respectively) and the cediranib concurrent/maintenance arm (75.0% and 52.4%, respectively) compared with the chemotherapy + placebo (78.0% and 53.4%, respectively). No information was provided on the type of chemotherapy or on the distribution of these between the study arms.

Quality of life

Cediranib treatment was not associated with a decline in HRQoL at 12 months, as measured by the QLQ-C30 and QLQ-OV28 instruments in ICON6. In the primary analysis of HRQoL, the QLQ-C30 global health status score at 12 months from baseline appeared higher for cediranib in combination with chemotherapy followed by maintenance monotherapy compared with chemotherapy + placebo, although no significant difference was observed (least square mean difference 5.6; 95% CI: -0.73, 12.00; p=0.082) (Table 11). Comparing the cediranib concurrent arm (70.9 ± 1.98) with the chemotherapy + placebo arm, a statistically significant treatment difference in favour of the cediranib concurrent arm was observed (7.6; 95% CI: 1.31, 13.95; p=0.018). The compliance rate (proportion responding of those alive at the start of the 12-month window) for the primary HRQoL analysis was consistent across the arms: 64.3%, 63.5% and 62.2% in the chemotherapy + placebo, cediranib concurrent and cediranib concurrent/maintenance arm respectively.

Table 11. QLQ-C30 global health status score at 12 months after baseline – (Full analysis set)

	Global health status score						Difference versus chemotherapy + placebo		
Treatment group	**n**	**Mean**	**StDev**	**Min**	**Max**	**LSMean (SE)**	**LSMean**	**95% CI**	**p-value**
Chemotherapy + placebo (N=118)	63	62.2	22.54	0	100	63.3 (2.52)			
Cediranib concurrent (N=174)	101	71.3	21.65	0	100	70.9 (1.98)	7.6 (3.21)	(1.31, 13.95)	0.018
Cediranib concurrent/maintenance (N=164)	97	69.2	19.63	17	100	68.9 (2.02)	5.6 (3.23)	(-0.73, 12.00)	0.082

Note: The analysis includes patients who completed the QLQ-C30 at Baseline and within 3 months (92 days) of the Month 12 (Day 365) timepoint. There were 98, 159 and 156 patients who were alive at the start of the Month 12 interval in the Chemotherapy + Placebo, Chemotherapy + Conc Ced 20 mg, and Chemotherapy + Maint Ced 20 mg groups, respectively.

ANCOVA analysis of covariance; CI confidence interval; LSMean least squares mean; n number of patients; Max maximum; Min minimum; SE standard error; StDev standard deviation.

At 12 months from baseline, the LS mean QLQ-C30 diarrhoea symptom scale score was statistically significantly worse for the cediranib concurrent/maintenance arm (p<0.001) but not the cediranib concurrent arm (p=0.544) compared with the chemotherapy + placebo arm. The median time from randomisation to deterioration in the diarrhoea symptom scale score was statistically significantly shorter for the cediranib concurrent/maintenance arm (1.7 months) and cediranib concurrent arm (1.5 months) compared with the chemotherapy + placebo arm (4.2 months) (p=0.002 and p<0.001, respectively). For all other QLQ-C30 sub-scales analysed, there was no statistically significant (p<0.01) difference in LS mean scale scores at 12 months from baseline for the 2 cediranib treatment arms compared with the chemotherapy + placebo arm. The compliance rate was generally high while patients remained on treatment but declined when patients were off treatment.

ORR

The ORR (programmatic assessment) showed that a higher proportion of patients in the cediranib concurrent/maintenance arm (65.1%) and cediranib concurrent arm (63.2%) achieved a best overall response of either CR or PR compared with the chemotherapy + placebo arm (53.4%) (Table 12). For ORR, there was a trend in favour of the cediranib concurrent/maintenance arm compared with the chemotherapy + placebo arm, which did not reach statistical significance (odds ratio 1.63; 95% CI: 0.97, 2.72; p=0.065).

Table 12. Objective response rate – programmatic assessment (Full Analysis Set study ICON6 –patients with measurable disease at Baseline).

	Chemotherapy + placebo (N=103)		Cediranib concurrent (N=155)		Cediranib concurrent/maintenance (N=146)	
Responders	55	(53.4)	98	(63.2)	95	(65.1)
Partial response	48	(46.6)	81	(52.3)	75	(51.4)
Complete response	7	(6.8)	17	(11.0)	20	(13.7)
Nonresponders	48	(46.6)	57	(36.8)	51	(34.9)
Stable disease	24	(23.3)	20	(12.9)	25	(17.1)
Progressive disease	13	(12.6)	16	(10.3)	10	(6.8)
Non-evaluable	11	(10.7)	21	(13.5)	16	(11.0)
Comparison with chemotherapy + placebo						
Odds ratio (95% CI)[a]			1.50	(0.90, 2.49)	1.63	(0.97, 2.72)
p-value			0.116		0.065	
Median time (months) to response (95% CI)	5.3	(4.7, 10.2)	4.8	(4.6, 5.1)	4.7	(4.6, 5.1)
First Quartile - Third Quartile	4.5	–	4.4	–	4.2	–
Median duration (months) of response (95% CI)[b]	5.4	(4.4, 6.7)	6.5	(5.6, 7.2)	7.6	(6.6, 8.7)
First Quartile - Third Quartile	3.6 –	7.8	4.7 –	10.6	5.6 –	13.4

Note: Percentages are based on the number of patients in the analysis set in each treatment group.
Note: The programmatic assessment of the overall visit response was used to identify patients who had an objective response to treatment. Confirmation of response was not required.
[a] Odds ratio and p-value were from a logistic regression model with treatment as the factor.
[b] Duration of response was defined as the time from the date of first documented response until date of documented progression or death in the absence of disease progression.
CI confidence interval; N number of patients.

Duration of response

There was a 2.2 month improvement in the median duration of response for the cediranib concurrent/maintenance arm (7.6 months) compared with the chemotherapy + placebo arm (5.4 months). In addition, the median duration of response was 1.1 months longer for the cediranib concurrent arm (6.5 months) compared with the chemotherapy + placebo arm (5.4 months). These results were consistent with the improvements in PFS observed for the 2 cediranib arms compared with the chemotherapy + placebo arm.

Other secondary endpoints:

Change in lesion size

At Baseline, the median tumour size (sum of longest diameters of targets lesions) differed notably at baseline and was 5.40, 7.20 and 6.45 cm for the chemotherapy + placebo arm, the cediranib concurrent arm, and the cediranib concurrent/maintenance arm, respectively. The median reduction in tumour size at 18 weeks was 47.00%, 58.01% and 55.56% for the chemotherapy + placebo arm, the cediranib concurrent arm and the cediranib concurrent/maintenance arm, respectively.

The time to *first* subsequent chemotherapy or death was significantly longer ($p<0.001$) for the cediranib concurrent/maintenance arm (median: 12.0 months) compared with the chemotherapy + placebo arm (median: 10.2 months), with an HR=0.65 (95% CI: 0.50, 0.83). The time to first subsequent chemotherapy or death in the cediranib concurrent arm (10.5 months) was not significantly different ($p=0.241$) from the chemotherapy + placebo arm.

The median time to *second* subsequent chemotherapy or death was statistically significantly longer for the cediranib concurrent/maintenance arm compared with the chemotherapy + placebo arm (17.0 months versus 14.0 months; $p=0.002$). For the cediranib concurrent arm, there was no

statistically significant difference in the median time to second subsequent chemotherapy or death compared with the chemotherapy + placebo arm (13.9 months versus 14.0 months; p=0.214).

Summary of main efficacy results

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 13. Summary of efficacy for trial ICON6

Title: A Randomised, Placebo-Controlled, Trial of Concurrent Cediranib [AZD2171] (with Platinum-Based Chemotherapy) and Concurrent and Maintenance Cediranib in Women with Platinum-Sensitive Relapsed Ovarian Cancer			
Study identifier	D8480C00037		
Design	Randomised controlled trial		
	Duration of main phase (chemotherapy phase – 6 cycles): Duration of Extension phase (maintenance phase):		18 weeks 18 months or until progression
Hypothesis	The primary hypothesis was to only test the cediranib concurrent/maintenance arm against the chemotherapy+ placebo arm		
Treatments groups	Placebo arm		chemotherapy (6 cycles of of platinum based chemotherapy (mainly carboplatin+paclitaxel)) + placebo for 18 weeks. n=187
	Cediranib concurrent		chemotherapy+cediranib (n=174) for 18 weeks
	Cediranib concurrent/maintenance		chemotherapy+cediranib for 18 weeks, followed by 18 months cediranib maintenance treatment (n= 164)
Endpoints and definitions	Primary endpoint	PFS	progression free survival
	Secondary	OS	Overall survival (updated analysis at 74% maturity)
	Secondary	HRQOL	Health related quality of life
		ORR	Objective response rate
			Change in lesion size.
			Duration of response
Database lock	19 April 2013		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	<Intent to treat> <time point>			
Primary endpoint	Treatment group	Chemotherapy + placebo	Cediranib concurrent	Cediranib concurrent/ maintenance

	Number of subject	118	174	164
	Median PFS	8.7	9.9	11.0
	95% CI	7.8-9.4	9.4-10.7	10.4-11.8
	Hazard ratio	1 (ref)	0.70	0.57
	95% CI	-	0.55-0.89	0.44-0.73
Secondary endpoint	Median OS	19.9	26.7	27.9
	95% CI	17.4-26.5	22.5-29.1	25.2-33.0
	Hazard ratio	1 (ref)	0.95	0.84
	95% CI	-	0.72-1.24	0.63-1.11
Secondary endpoint	Mean QLQ-C30 global health status score	62.2	71.3	69.2
	Least square mean difference	1 (ref)	7.6	5.6
	95% CI		1.31, 13.95	-0.73, 12.00
	p-value		0.018	0.082
Secondary endpoint	ORR	53.4%	63.2%	65.1%
	Odds ratio	1 (ref)	1.50	1.63
	95% CI		0.90-2.49	0.97-2.72
	p-value		0.116	0.065
Secondary endpoint	Duration of response (mo)	5.4	6.5	7.6
Secondary endpoint	Median reduction in tumour size at 18 weeks	47.0%	58.01%	55.56%
Secondary endpoint	Median time (mo)to first subsequent chemotherapy or death	10.2	10.5	12.0
	p-value		0.241	<0.001

Secondary endpoint	Median time (mo) to second subsequent chemotherapy or death	14.0	13.9	17.0
	p-value		0.214	0.002

Supportive study(ies)

Data from the Phase I/II study NCI 8348 are presented to provide supportive evidence for the efficacy of cediranib. In this study, the efficacy of cediranib in combination with olaparib for the treatment of recurrent papillary-serous ovarian, fallopian tube, or peritoneal cancer or for treatment of recurrent triple-negative breast cancer was investigated. This was a Phase I/II, multicentre, 2-stage open-label, randomised study. In Phase I, 28 patients with ovarian cancer or triple-negative breast cancer were enrolled to a standard 3+3 dose escalation protocol to determine the MTD of cediranib in combination with olaparib. The MTD for Phase II of the study was determined to be cediranib 30 mg od + olaparib. The primary objective of phase II was to determine the PFS of the combination of cediranib 30 mg od/olaparib 200 mg twice daily versus single agent olaparib 400 mg twice daily.

Study participants

In the Phase II study, 90 patients (median age 58.1 years) with histologically or cytologically Grade 2 or 3 (high-grade) epithelial ovarian cancer, primary peritoneal serous cancer, or fallopian tube cancer were recruited to US sites. Patients with high-grade disease of any histology were allowed as long as the patient was positive for a BRCAm, otherwise the histology was required to be papillary-serous or endometrioid (BRCAm positive or negative).

Unlike ICON6, which was in the second line setting, patients in NCI 8348 were permitted to have had multiple prior lines of platinum-based chemotherapy. In total, 52.2% of patients in NCI 8348 had received ≥2 lines of platinum-based chemotherapy, suggesting that just over half the NCI 8348 study population had disease that was more advanced compared with patients in ICON6

It is noted that only patients with other histology were required to be positive for BRCAm.

Patients were randomized in a 1:1 ratio to one of the two following arms:

Arm A: Olaparib 400 mg BID (dose level 1A)

Arm B: Cediranib and olaparib at the recommended phase 2 dose of cediranib 30 mg QD and olaparib 200 mg BID (dose level 2) derived from the phase 1 portion of this study. Patient randomization in this unblinded study was stratified based upon:

1. Prior receipt of anti-angiogenic therapy.

2. BRCA mutation status (carrier, non-carrier, unknown).

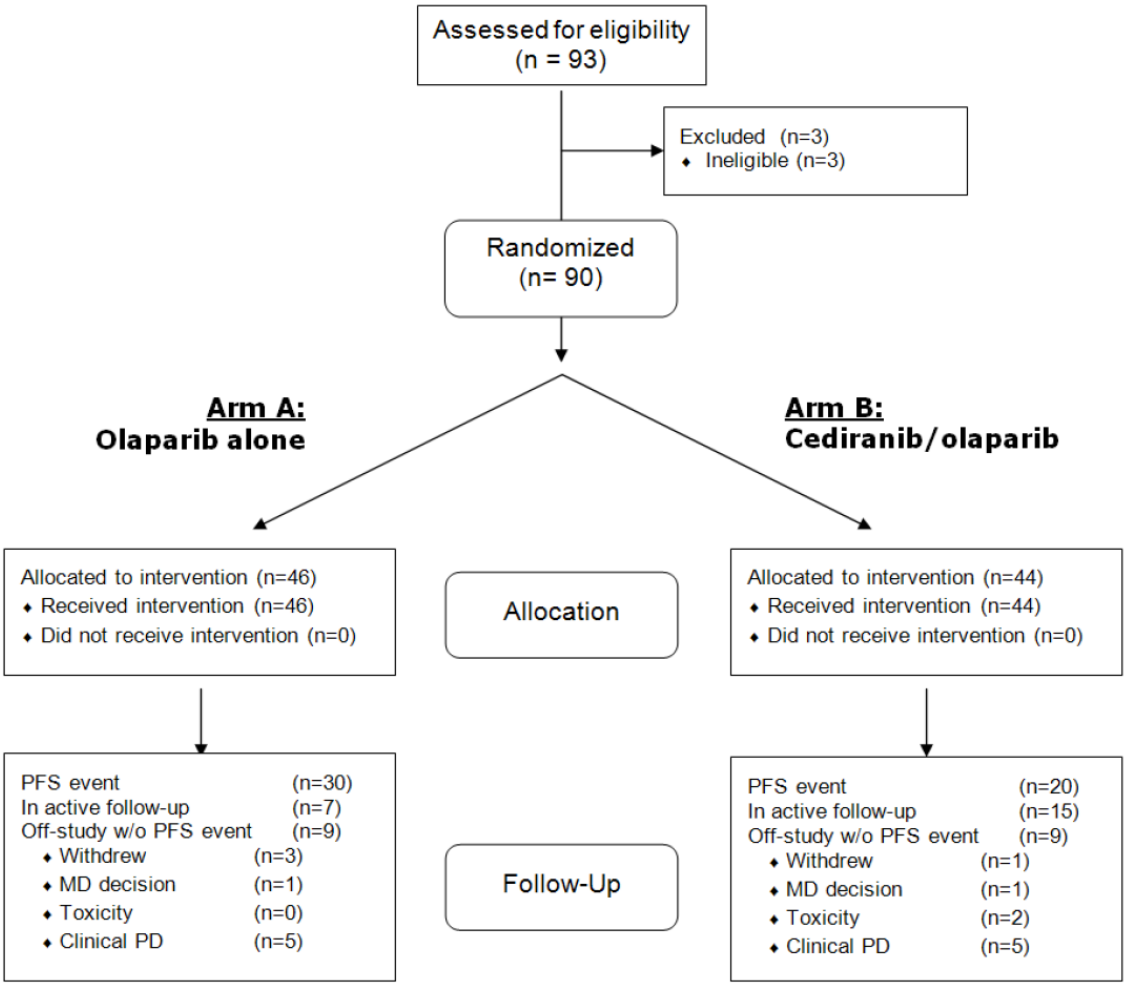

Figure 12. Disposition of patients in phase II of the NCI 8348 study.

Baseline demographics and disease characteristics were generally balanced between the 2 treatment groups except for the number of prior lines of platinum-based chemotherapy and baseline median CA125 levels, both of which were higher for the olaparib alone arm compared with the cediranib/olaparib arm. Prior anti-angiogenic therapy was not frequently reported (13.3% of patients overall)

Table 14. Baseline characteristics of patients in phase II of the NCI 8348 study

	Treatment Arm				Overall	
	Arm A (Olaparib)		Arm B (Olaparib/Cediranib)			
	N	%	N	%	N	%
Number of patients randomized	46	100.0	44	100.0	90	100.0
Ethnicity						
Ethnicity Not Known	1	2.2	1	2.3	2	2.2
Hispanic or Latino	1	2.2	-	-	1	1.1
Non-Hispanic	44	95.7	43	97.7	87	96.7
Race						
Asian	1	2.2	0	0	1	1.1
Black or African American	1	2.2	1	2.3	2	2.2
Other	2	4.3	0	0	2	2.2
White	42	91.3	43	97.7	85	94.4
ECOG performance status						
Fully active	34	73.9	31	70.5	65	72.2
Restricted	12	26.1	13	29.5	25	27.8
***BRCA* mutation status**						
Carrier	24	52.2	23	52.3	47	52.2
Non-Carrier	11	23.9	12	27.3	23	25.6
Unknown	11	23.9	9	20.5	20	22.2
Prior anti-angiogenic therapy						
No	40	87.0	38	86.4	78	86.7
Yes	6	13.0	6	13.6	12	13.3
Prior lines of platinum-based therapy						
1	17	37.0	26	59.1	43	47.8
2	18	39.1	10	22.7	28	31.1
≥3	11	23.9	8	18.2	19	21.1
Prior platinum-free interval (PFI)						
6-12 mo	26	56.5	23	52.3	48	53.3
>12 mo	20	43.5	21	47.7	42	46.7

	Treatment Arm	N	N Miss-ing	Mean	SD	Min	Q1	Median	Q3	Max	*P*-value
Age, Years	Olaparib	46	0	57.6	9.0	32.7	52.2	58.1	62.9	81.9	0.33
	Olaparib/ Cediranib	44	0	60.1	9.0	41.9	53.3	57.8	67.0	85.6	
	overall	90	0	58.8	9.0	32.7	52.9	58.1	63.8	85.6	
Weight, Kg	Olaparib	46	0	70.7	16.7	51.1	58.8	65.9	77.2	126.1	0.45
	Olaparib/ Cediranib	44	0	74.4	20.0	50.8	57.6	69.8	87.7	130.9	
	overall	90	0	72.5	18.4	50.8	58.8	67.3	81.7	130.9	
CA125, U/ml	Olaparib	46	0	654.2	1959.8	10.9	60.8	115.3	327.5	11512.0	0.083
	Olaparib/ Cediranib	44	0	172.9	262.2	4.0	34.9	68.0	169.7	1351.0	
	overall	90	0	418.9	1426.1	4.0	47.0	100.0	258.2	11512.0	

Results

The results (Table 14) are consistent with a statistically significant superior PFS on the combination arm: 16.5 months vs. 8.2 months in patients receiving olaparib alone (P=0.0028; HR 2.44,* 95% CI: 1.36-4.38).

Table 15. PFS Analysis of the NCI 8348 study (Stratified Log-Rank)

	Arm A (olaparib)	Arm B (olaparib/cediranib)
PFS events	30	20
Median PFS (95% CI)	8.2 months (5.7–14.9)	16.5 months (12.7–NA)
***P*-value**	**0.0028**	
Hazard ratio (95% CI)	2.44 (1.36-4.38)	

* 2 For the NCI 8348 study, hazard ratios were calculated such that HR>1 favours the cediranib combination arm.

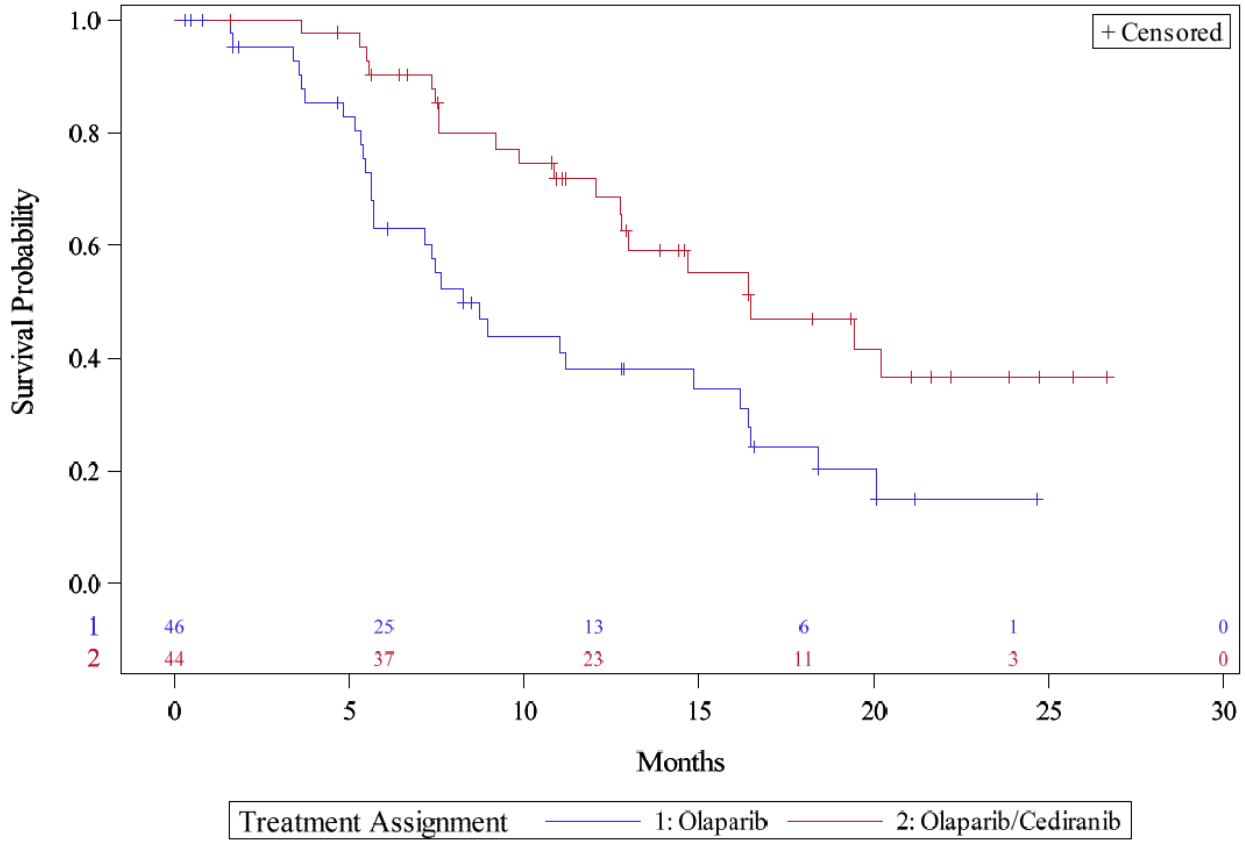

Figure 13. Kaplan-Meier plot of PFS estimates by treatment arm of phase II of the NCI 8348 study (clinical progression events censored. NCI 8348 study).

Outcome Stratified by BRCA Mutational Status (Phase 2)

In an unplanned analysis, the comparison between arms was tested using a stratified log-rank test based upon BRCA mutation status.

Table 16 summarizes PFS outcome results for patients stratified by BRCA status. Around 50% of patients in both arms of the phase 2 portion were known BRCA mutation carriers (BRCAm), with the remaining patients in each arm evenly split between known BCRA wild-type (BRCAwt) and patients of unknown mutational status. For BRCAwt or unknown patients, the margin of benefit of combination therapy (Arm B) over Arm A appears significant whether the clinical progression events are censored (PFS 16.5 months vs. 5.7 months, P=0.0025) or included (PFS 12.8 months vs. 5.6 months, P=0.0026). For known BRCAm carriers, cediranib/olaparib combination therapy shows no significant advantage over olaparib alone, although the observed medians point into the direction of a beneficial effect (P>0.1) (Table 16).

Table 16. PFS Analysis of Known BRCA Mutation Carriers vs. Non- Carriers/Unknown (Univariate Log-Rank)

	BRCAm		*BRCAwt* or Unknown	
	Arm A (Olaparib) N=24	Arm B (Cediranib / Olaparib) N=22	Arm A (Olaparib) N=22	Arm B (Cediranib / Olaparib) N=22
Clinical progression events censored				
PFS events	13	11	17	9
Median PFS (95% CI)	16.5 months (7.5–20.1)	19.4 months (12.0–NA)	5.7 months (3.7–9.0)	16.5 months (7.6–NA)
***P*-value**	0.23		**0.0025**	
Hazard ratio (95% CI)	1.64 (0.73–3.71)		3.53 (1.56–7.99)	
Clinical progression events included				
PFS events	16	14	19	11
Median PFS (95% CI)	11.0 months (7.2–20.1)	16.4 months (9.9–24.7)	5.6 months (3.6–9.0)	12.8 months (7.5–NA)
***P*-value**	0.15		**0.0026**	
Hazard ratio (95% CI)	1.72 (0.82–3.61)		2.18 (1.50–6.74)	

3.3.7. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy of cediranib was evaluated in one phase 3, double-blind, placebo controlled, randomized study (ICON6; n=456) and a supportive study randomized unblinded study (NCI8348; n= 90)

Study design of ICON6

The recruitment of patients with epithelial ovarian, fallopian tube or serous primary peritoneal carcinoma that have encountered PD after 1st line platinum-containing chemotherapy is considered acceptable. Epithelial ovarian, fallopian tube or serous primary peritoneal carcinoma are commonly regarded as comparable with epithelial ovarian cancer (EOC) as tumours from these three locations exhibit similar clinical characteristics and behaviour. Initial (first line) treatment with platinum-based chemotherapy is considered acceptable.

It is noted that only 6.1% of the participants had received prior VEGF therapy and that BRCA mutation status was not reported.

The Applicant has undertaken several activities to validate the ICON6 database. All sites including at least one patient were subjected to a post-SDV by an independent third-party, which were able to verify data from 97% of the patients. All sensitivity analyses performed (including planned analyses by the Applicant as well as post-hoc analyses, some of which requested by the CHMP) were all consistent with the primary analysis of PFS. However, after unblinding, an extensive monitoring process was initiated to verify data collected in the CRF and transferred to the database against real source data. The applicant performed a retrospective source data verification and quality control process together with a Blinded Independent Central Review (BICR) of all available radiographic scans to support a sensitivity analysis of PFS.

The BICR included scans from 91.9% of the patients. This analysis confirmed the findings of the primary analysis. Concordance with investigator assessed PFS was 80.7%, which is considered acceptable and in line with other studies in the same patient population. However, this was not confirmed, since it was seen that Investigators review and the BICR review varied. Based on an initial concordance analysis, at one site 6 out of 13 subjects had different RECIST outcome comparing the investigator and BICR review of scans. At a second site in 6 out of 14 subjects had different RECIST outcome when comparing the Investigator and the BICR review. Thus, there seems to be extensive differences between investigator assessed PFS and PFS by BICR for these patients. This introduces a large uncertainty about the high concordance rate reported by the Applicant. The Applicant is asked to discuss this issue.

Treatments

The backbone treatment of carboplatin and paclitaxel every 3 weeks for 6 cycles is considered adequate, as this constitutes standard treatment for patients with relapsed platinum sensitive EOC.

Justification of proposed dose

Initially, patients were randomised to cediranib received 30 mg QD. After the first 30 patients had been recruited, the cediranib starting dose was reduced to 20 mg QD. The selection of this dose was based on the emerging clinical data from the ongoing cediranib programme (other Phase II/III cediranib studies, rather than any specific tolerability issue in ICON6) and was consistent with the 20 mg dose that was being used concurrently in the colorectal cancer (Studies 51 and 13), glioblastoma (Study 55), and NSCLC (Study BR.29) development programmes with cediranib in combination with chemotherapy. This is considered acceptable.

Outcomes

The primary outcome was PFS assessed by the investigator, whereas OS was a secondary outcome. According to the EMA Guideline on the evaluation of anticancer medicinal products in man (2013), when OS is reported as secondary endpoint, the estimated treatment effect on OS should ensure that there are no relevant negative effects on this endpoint, in most cases by showing trends towards superiority. In situations where there is a large effect on PFS, or if there is a long expected survival after progression, and/or a clearly favourable safety profile, precise estimates of OS may not be needed for approval. Radiological progression criteria followed widely adopted standards based on the Response Evaluation Criteria in Solid Tumours (RECIST). Note that in this population median OS was not particularly long (median around 18 months), therefore OS would have been feasible and preferably the primary endpoint. In fact, the original design of the trial had OS as primary endpoint (with PFS as secondary endpoint) for the planned but not executed third stage of the trial. Due to discontinuation of development of cediranib by the Applicant (disappointing results in other cancer applications), the trial was shortened and was redesigned to have PFS as primary endpoint and OS as secondary (with consultation of the UK

regulatory agency). Only radiographic scans were used for PFS assessments. However, the number of planned scans was rather limited: at baseline, after 6 cycles of chemotherapy (18 weeks) and then at clinical progression or 12 and 18 months after randomisation. Since the risk of unblinding is not negligible due to typical AEs of VEGF targeting agents such as hypertension, a difference in the timing and frequency of additional scans may have occurred, potentially introducing a bias.

Three statistical sensitivity analyses were performed to assess the impact of any imbalance in tumour assessment timing, 'evaluation time bias', 'interval-censored approach' and the requested 'unscheduled scan reassignment approach', the results of which were consistent with the primary analysis

The interval-censored approach and the 'unscheduled scan reassignment approach are considered convincing to show that the difference in PFS is robust. The first because it reflects that a PD can only be determined as having occurred between the scan that shows PD and the previous scan that did not; the second because it reflects the situation that PD detected in between planned scans would be observed in the first following planned scan.

Therefore, the results of these approaches suggest that the PFS results can be considered robust with respect to differences in the number of unscheduled scans.

Design and conduct of NCI 8348 study

In the supportive randomized unblinded NCI8348 study patients years) were randomized to olaparib alone or olaparib in combination with cediranib. Of note, only 50% of the patients were identified to be a BRCA mutation carrier, the population in which olaparib is expected to have a beneficial effect. In total, 52.2% of patients in NCI 8348 had received ≥ 2 lines of platinum-based chemotherapy, suggesting that just over half the NCI 8348 study population had disease that was more advanced compared with patients in ICON6.

Efficacy data and additional analyses

In ICON6, a statistically significant improvement (of 2.3 months) in median PFS for the cediranib concurrent/maintenance arm) was observed compared with the chemotherapy + placebo arm. There was also a statistically significant improvement (of 1.3 months) in median PFS for the cediranib concurrent arm. No statistically significant add-on effect is demonstrated for concurrent/maintenance cediranib treatment vs. cediranib concurrent therapy (exploratory analysis). As mentioned above, the number of planned radiographic scans was limited and additional scans were scheduled by the investigator. Since side effects of TKIs and in particular of substances with VEGF signalling inhibition activity have a typical pattern, the investigator may have been unblinded to the assigned treatment. This could have compromised the validity of the PFS results, as discussed above.

Analyses of overall survival suggested a benefit (of 8.0 months) in median OS for the cediranib concurrent/maintenance arm, although this improvement was not statistically significant. Likewise, a benefit in median OS (of 6.8 months) was observed for the cediranib concurrent arm. It is noted that about 75% of patients received a first and about 50% a second subsequent chemotherapy. More information on the type and the distribution of subsequent chemotherapy could help to elucidate the mechanism by which cediranib has a beneficial effect on OS which could help in specific recommendations regarding subsequent therapy in cediranib-treated patients. As illustrated in

Table 17, the largest differences between arms were observed after the start of 2nd subsequent therapy. The median survival of 10.9 and 12.8 months (in the cediranib concurrent/maintenance

and the cediranib concurrent arm, respectively) after the start of 2nd subsequent therapy is exceptional and remains unexplained.

Several secondary endpoints were included as part of the AstraZeneca analysis of the ICON6 study database. The Applicant is asked to justify why these retrospectively defined endpoints, although exploratory in nature, should be taken into consideration. These analyses seem to be defined after the MRC analyses had shown a PFS gain in favour of cediranib.

In NCI8348, a statistically significant superior PFS was observed for the combination arm. However, in an analysis stratified for BRCA mutation status, efficacy of cediranib was only demonstrated in patients with wild type or unknown BRCA status), but not for BRCA carriers, although the results for BRCA-m carriers point to a beneficial effect as well.

Table 17. Differences in time (months) to subsequent therapy in relation to overall survival.

Outcome	Chemotherapy+placebo	Cediranib concurrent	Cediranib concurrent/maintenance
PFS	8.7	9.9	11.0
Time to 1st subsequent therapy	10.2	10.5	12.0
Gain in median (PFS-1st subsequent therapy)	1.5	0.6	1.0
Time to 2nd subsequent therapy	14.0	13.9	17.0
Gain in median (time between 1st and 2nd subsequent therapy)	3.8	3.4	5.0
Median to death	19.9	26.7	27.9
Gain in median (2nd subseq. therapy-death)	5.9	12.8	10.9

3.3.8. Conclusions on clinical efficacy

A significant improvement in investigator assessed PFS compared to placebo treatment was observed for cediranib used as concurrent treatment added to platinum-based chemotherapy and a further benefit was obtained when continued as maintenance treatment in the ICON6 study. Although a retrospective blinded independent central review (BICR) of radiographic scans was conducted, questions remain regarding the validity of the PFS results. A more pronounced benefit on OS was observed for both comparisons, although these results were not statistically significant. Patients were treated for up to 18 months with cediranib in the maintenance phase of Arm C. Comparing Arm B (concurrent cediranib) with Arm C shows a no statistically significant difference, and the clinical relevance of the numerical difference is not clear. Taking into consideration the

high risk of AEs/SAEs, discontinuations due to AEs, etc., related to the use of cediranib, its use as maintenance therapy needs further justification.

In the supportive NCI8348 study, a benefit of cediranib was only shown, albeit only statistically significant in patients with wild type or unknown BRCA mutation status.

3.3.9. Clinical safety

Patient exposure

As of March 2015, approximately 5800 patients have been treated with cediranib in a broad clinical programme that includes both monotherapy and combination studies, in multiple tumour types: PSR ovarian cancer (the sought indication), colorectal cancer (CRC), glioblastoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma. A large number of signal-searching studies in a range of other tumour types have also been conducted. Studies were sponsored by AstraZeneca and/or by collaborative groups.

The focused safety evaluation in the proposed indication is based on data from 1272 cediranib-treated patients and is presented as follows:

- ICON6 – A Phase III, randomised, double-blind, placebo-controlled Gynaecologic Cancer InterGroup study sponsored by the Medical Research Council (MRC), in which 444 patients with PSR ovarian cancer received cediranib 20 mg od (n=329) or placebo (n=115) in combination with platinum-based chemotherapy then as a maintenance therapy. This pivotal study (ICON6) provided comparative safety data

- Pooled safety data from 4 AstraZeneca-sponsored/collaborative group studies of cediranib administered at the proposed dose of 20 mg od in combination with platinum-based chemotherapy, including ICON6 (combination therapy pool hereafter). In these supportive studies, 769 patients received cediranib 20 mg (n=501, including 329 patients from ICON6) or placebo (n=268) in combination with carboplatin- or cisplatin-containing chemotherapy as treatment for ovarian cancer or lung cancer. AstraZeneca considers the strategy of pooling data from all patients treated with cediranib in combination with platinum-based chemotherapy at the proposed 20 mg od dose to be relevant to the indication being sought (Table 18).

Table 18. Number of patients included in each combination therapy group (cediranib 20 mg od) by study – combination therapy pool

	Treatment in chemotherapy phase/maintenance phase		
Study	**Chemotherapy+ placebo**	**Cediranib concurrent[a]**	**Cediranib concurrent/ maintenance[b]**
D8480C00040			3
D8480C00054			18
D8480C00037 (ICON6)	115	171	158
D8483C00002 (BR.29)	153		151
Total	**268**	**171**	**330**

[a] Cediranib was taken in combination with platinum-based chemotherapy during chemotherapy and then cediranib placebo was taken as maintenance therapy after completion of chemotherapy.

[b] Cediranib was taken in combination with platinum-based chemotherapy during chemotherapy and then cediranib continued to be taken as maintenance therapy after completion of chemotherapy.

Pooled safety data from 15 AstraZeneca-sponsored studies of cediranib as monotherapy (monotherapy pool hereafter), in which 789 patients received cediranib at doses ranging from 0.5 mg to 90 mg (n=771) or placebo (n=18) for the treatment of various tumour types. Of the 771 cediranib-treated patients, 96 patients received the starting 20 mg od dose and 640 patients received a starting dose of ≥30 mg od. These studies allowed more precise assessment of infrequent adverse events (AEs) reported with cediranib (Table 19).

Table 19. Number of patients included in each monotherapy dose group by study – monotherapy pool

Study	Cediranib						Placebo
	≤5 mg	10 mg	20 mg	30 mg	≥45 mg	All doses	
D8480C00001	12[a]	4	19	21	27[b]	83	
D8480C00002		4	9	22		35	
D8480C00003	9[c]	3	10	4		26	
D8480C00015				19		19	
D8480C00019[d]				6		6	
D8480C00020			46			46	
D8480C00021[e]				14	40	54	
D8480C00023		3	3	27	7	40	
D8480C00029					64	64	
D8480C00030					67[f]	67	18[g]
D8480C00032[d]				30		30	
D8480C00038				59	60	119	
D8480C00046					34	34	
D8480C00055[h]				128		128	
D8480C00060			9	11		20	
Total	**21**	**14**	**96**	**341**	**299**	**771**	**18**

[a] 3 patients each at 0.5 mg, 1.0 mg, 2.5 mg and 5.0 mg.
[b] 19 patients at 45 mg and 8 patients at 60 mg.
[c] 3 patients each at 1.0 mg, 2.5 mg and 5.0 mg.
[d] A single dose of 45 mg was administered to patients first and was followed by a wash-out period and then a period of continuous dosing with 30 mg.
[e] Patients were assigned to dose group based on maximum dose in Study Part B or the Part A dose (45 mg) for patients who only participated in Part A.
[f] Includes 53 patients who received cediranib in the double-blind period and 14 placebo patients who switched to cediranib after the double-blind period
[g] Placebo Patient D8480C00030/E2001009 received cediranib starting on Study Day 28 for 1 week.
[h] Patients who received lomustine in combination with 20 mg cediranib or placebo were not included in the pool.

Three other studies (study 13, 51 and 41) provide additional safety data for cediranib in combination with chemotherapy (oxaliplatin-based), to support the findings from ICON6 and the combination therapy pool. To further characterise the safety profile of cediranib, data from these studies have been included in the discussion of CTCAE grade ≥3 AEs, AEs leading to discontinuation across cediranib studies and selected adverse drug reactions (ADRs). These studies are not included in either the combination therapy pool or the monotherapy pool because of the non-carboplatin or cisplatin chemotherapy combination used in these studies (Table 20).

Study 13 (896 patients received cediranib) was a Phase II/III, randomised, double-blind, multi-centre study to compare the efficacy of cediranib in combination with 5-fluorouracil, leucovorin,

and oxaliplatin (FOLFOX), to the efficacy of bevacizumab in combination with FOLFOX in patients with previously untreated metastatic CRC.

Study 51 (714 patients received cediranib) was a Phase III, randomised, double-blind study to compare the efficacy and safety of cediranib when added to FOLFOX or capecitabine and oxaliplatin (XELOX) with the efficacy and safety of placebo when added to FOLFOX or XELOX in patients with previously untreated metastatic CRC.

Study 41 (143 patients received cediranib) was a Phase II, randomised, double-blind, multi-centre study to compare the efficacy and safety of cediranib in combination with FOLFOX vs. bevacizumab in combination with FOLFOX in patients with previously-treated metastatic CRC.

Table 20. Duration of exposure to cediranib, cediranib placebo and placebo (days) – Studies 13 and 51 (safety set).

	Study 13				Study 51			
	Cediranib 20 mg (N=705)		Bevacizumab 5 mg/kg[a] (N=704)		Cediranib 20 mg (N=500)		Placebo (N=358)	
	Intended exposure[b]	Actual exposure[c]	Intended exposure[b]	Actual exposure[c]	Intended exposure[b]	Actual exposure[c]	Intended exposure[b]	Actual exposure[c]
n	705	705	704	704	500	500	358	358
Mean (StDev)	234.0 (154.2)	220.1 (147.2)	255.9 (157.0)	246.1 (152.2)	273.0 (202.7)	261.0 (195.1)	261.6 (183.8)	253.8 (178.7)
Median	211.0	200.0	251.5	231.5	238.5	225.0	230.5	220.0
Min, max	1, 875	1, 861	1, 967	1, 940	4, 1036	4, 1022	1, 924	1, 924
Total number of treatment days[d]	164979	155168	180125	173266	136517	130521	93659	90877

[a] Investigators made dose reductions while blinded to study medication; hence, patients in the bevacizumab arm may have received dummy reductions or pauses in their placebo tablets.
[b] Intended exposure = (last dose date [where dose >0 mg] minus first dose date) +1.
[c] Actual exposure = Intended exposure minus total duration of dose pauses.
[d] If a patient had not discontinued treatment then last dose date was the date of data cut-off.
max maximum; min minimum; StDev standard deviation.

In ICON6, the overall median total treatment duration (actual) of cediranib/placebo treatment was slightly shorter in the cediranib concurrent/maintenance (32.6 weeks) and cediranib concurrent (34.0 weeks) arms compared with the chemotherapy+placebo arm (35.1 weeks) (Table 22), which is most likely a reflection of the higher proportion of dose pauses in the cediranib arms as compared with the chemotherapy+placebo arm (Table 21). In the chemotherapy phase, median total treatment duration (actual) of cediranib/placebo treatment was only marginally shorter in the cediranib concurrent/maintenance (18.4 weeks) and cediranib concurrent (18.6 weeks) arms compared with the chemotherapy+placebo arm (20.6 weeks), suggesting that there was no significant effect of chemotherapy on cediranib treatment duration.

Table 21. Duration of exposure to cediranib/placebo – ICON6 (safety analysis set)

	Number (%) of patients					
	Chemotherapy+placebo (N=115)		Cediranib concurrent (N=171)		Cediranib concurrent/maintenance (N=158)	
	Intended[a] (weeks)	Actual[b] (weeks)	Intended[a] (weeks)	Actual[b] (weeks)	Intended[a] (weeks)	Actual[b] (weeks)
Chemotherapy phase						
N	115	115	171	171	157	156
Mean (StDev)	18.4 (5.57)	17.8 (5.72)	16.5 (7.60)	15.3 (7.38)	16.6 (7.23)	15.4 (7.09)
Median	20.9	20.6	20.0	18.6	20.0	18.4
Min, max	1 - 23	1 - 23	0 - 30	0 - 26	0 - 29	0 - 28
Total treatment weeks	2111	2048	2822	2621	2605	2404
Maintenance phase						
N	85	85	113	113	95	95
Mean (StDev)	26.5 (22.60)	25.9 (22.50)	29.6 (23.53)	29.0 (23.35)	33.9 (23.53)	32.2 (22.82)
Median	19.7	19.3	23.9	22.6	28.0	26.3
Min, max	4 - 138	3 - 137	1 - 151	1 - 149	1 - 116	1 - 110
Total treatment weeks	2256	2198	3347	3282	3219	3055
Overall						
N	115	115	171	171	157	156
Mean (StDev)	38.0 (25.24)	36.9 (25.20)	36.1 (28.15)	34.5 (27.76)	37.1 (29.02)	35.0 (27.99)
Median	37.0	35.1	35.1	34.0	34.4	32.6
Min, max	1 - 157	1 - 156	0 - 171	0 - 168	0 - 136	0 - 130
Total treatment weeks	4366	4247	6169	5902	5825	5459

[a] Intended exposure was calculated as last dose date – first dose date + 1, where last dose date was the earliest of the cediranib/placebo discontinue date, date the patient completed 81 weeks of treatment, and the data cut-off date.
[b] Actual exposure was calculated as the intended exposure minus the total duration of dose pause(s).
max maximum; min minimum; StDev standard deviation.

Adverse events

All patients (except 1 patient in the chemotherapy + placebo arm) had at least 1 AE during the study. Larger proportions of patients in the cediranib arms had CTCAE grade ≥3 AEs (77.2% and 78.9% in the cediranib concurrent/maintenance and cediranib concurrent arms, respectively) compared with the chemotherapy+placebo arm (67.8%) (Table 22). The proportions of patients reported with CTCAE grade ≥3 AEs, SAEs and SAEs leading to hospitalisation were higher in the cediranib groups than the placebo group. The proportion of patients reported with AEs leading to death was low and similar across the treatment arms (1.9%, 1.8% and 2.6%, respectively). The proportions of patients with AEs leading to cediranib/placebo discontinuation, AEs leading to cediranib dose reduction or dose pauses were higher in the cediranib treatment arms compared to the chemotherapy+placebo arm and was highest in the cediranib concurrent/maintenance arm. In section 4.2 of the SmPC, it is stated that, the dose may be reduced to 15 mg once a day to manage toxicity, if required. Approximately half of the AEs leading to discontinuation of cediranib/placebo occurred during the first 3 months of starting treatment (30/62, 33/55 and 9/16 patients in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms, respectively.

According to the Applicant, this perhaps reflects under-recognition and under-treatment of common AEs. The early discontinuation of cediranib/placebo was associated with discontinuation of chemotherapy in two thirds of patients in the chemotherapy+placebo arm and only in one third of patients in the cediranib arms, providing more evidence that early discontinuation of cediranib did not adversely affect the ability of patients to continue chemotherapy. The most frequent reasons for discontinuation were diarrhoea (7.0% and 10.8% in the cediranib concurrent and cediranib concurrent/maintenance arm, respectively) and fatigue (4.7% and 6.3%), among various other AEs) (Table 23).

Table 22. Number (%) of patients who had at least 1 AE in any category during the maintenance phase (safety analysis set)

	Chemotherapy+ placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/ maintenance (N=158)
Any AE	114 (99.1)	171 (100.0)	158 (100.0)
Any AE with outcome of death	3 (2.6)	3 (1.8)	3 (1.9)
Any CTCAE grade ≥3 AE	78 (67.8)	135 (78.9)	122 (77.2)
Any SAE	39 (33.9)	63 (36.8)	60 (38.0)
SAEs related to cediranib/cediranib placebo	14 (12.2)	39 (22.8)	30 (19.0)
SAEs related to chemotherapy	19 (16.5)	40 (23.4)	37 (23.4)
AEs leading to permanent discontinuation of cediranib/cediranib placebo	16 (13.9)	55 (32.2)	62 (39.2)
AEs leading to dose reduction in cediranib/cediranib placebo	27 (23.5)	56 (32.7)	72 (45.6)
AEs leading to dose pause in cediranib/cediranib placebo	64 (55.7)	117 (68.4)	123 (77.8)
AEs leading to permanent discontinuation of chemotherapy	30 (26.1)	40 (23.4)	46 (29.1)
SAEs leading to dose reduction of chemotherapy	0	5 (2.9)	5 (3.2)

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events; SAE serious adverse event.

The most frequent AEs leading to discontinuation of cediranib were diarrhoea, fatigue and dyspnoea. According to the protocol, these AEs were not mentioned as reasons to discontinue cediranib. The Applicant argues that these discontinuations may reflect under-recognition and under-treatment of common AEs. Data regarding resolution of fatigue in the ICON6 study are not available. In Studies 13 and 51, the majority of AEs of fatigue resolved without requiring dose manipulation (50.3% overall in Study 13 and 64.5% overall in Study 51).

Table 23. Number (%) of patients who had at least 1 AE leading to discontinuation (reported in ⩾1% of patients in any treatment group) during the overall study period – ICON6 (safety analysis set)

Preferred term[a]	Chemotherapy+ placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/ maintenance (N=158)
Patients with any AE leading to discontinuation	**16 (13.9)**	**55 (32.2)**	**62 (39.2)**
Diarrhoea	2 (1.7)	**12 (7.0)**	**17 (10.8)**
Fatigue	1 (0.9)	**8 (4.7)**	**10 (6.3)**
Dyspnoea	1 (0.9)	2 (1.2)	**7 (4.4)**
Hypersensitivity	1 (0.9)	1 (0.6)	**5 (3.2)**
Hypertension	0	**5 (2.9)**	**4 (2.5)**
Abdominal pain	1 (0.9)	2 (1.2)	**5 (3.2)**
Nausea	0	**5 (2.9)**	**4 (2.5)**
Hypomagnesaemia	0	1 (0.6)	3 (1.9)
Transient ischaemic attack	0	1 (0.6)	3 (1.9)
Vomiting	1 (0.9)	**8 (4.7)**	2 (1.3)
Pulmonary embolism	1 (0.9)	3 (1.8)	2 (1.3)
Headache	0	3 (1.8)	2 (1.3)
Febrile neutropenia	1 (0.9)	1 (0.6)	2 (1.3)
Dizziness	0	1 (0.6)	2 (1.3)
Rash	0	1 (0.6)	2 (1.3)
Transaminases increased	1 (0.9)	0	2 (1.3)
Abdominal pain upper	0	0	2 (1.3)
Mucosal inflammation	0	0	2 (1.3)
Stomatitis	0	0	2 (1.3)
White blood cell count decreased	0	0	2 (1.3)
Platelet count decreased	0	2 (1.2)	1 (0.6)
Dehydration	0	**4 (2.3)**	0
Neutrophil count decreased	0	**4 (2.3)**	0
Proteinuria	0	3 (1.8)	0
Depressed mood	0	2 (1.2)	0
Epistaxis	0	2 (1.2)	0
Hyponatraemia	0	2 (1.2)	0
Tinnitus	0	2 (1.2)	0
Abdominal distension	2 (1.7)	0	0

[a] Number (%) of patients with AEs, sorted by PT in decreasing order of frequency (sorted by frequency in the

The 5 most commonly reported AEs in the chemotherapy + placebo arm, cediranib concurrent arm and cediranib concurrent/maintenance arm were: fatigue (91.3%, 91.2%, 97.5%); diarrhoea (65.2%, 87.1%, 93.0%); nausea (76.5%, 80.7%, 79.7%); alopecia (77.4%, 71.9%, 71.5%) and constipation (74.8%, 65.5%, 66.5%). In addition to diarrhoea, the most commonly reported AEs with a difference in reporting rate of ≥10% for the chemotherapy + placebo arm compared with either the cediranib concurrent arm or cediranib concurrent/maintenance arm were: neutrophil count decreased (49.6%, 69.0%, 70.3%); hypertension (37.4%, 62.0%, 59.5%); abdominal pain (65.2%, 43.9%, 56.3%) and decreased appetite (37.4%, 36.8%, 51.3%). Besides hypertension, other typical AEs associated with VEGF targeting agents, occurring with a higher frequency in the cediranib arms were proteinuria (12.2%, 21.1% and 28.5% in the chemotherapy+placebo arm, cediranib concurrent and cediranib concurrent/maintenance arm, respectively), peripheral oedema

(3.45%, 7.6% and 9.9%), bleeding/haemorrhage (13.0%, 22.8% and 31.6% Arterial thromboembolism (0.9%, 2.3%, 3.2%), gastrointestinal perforation (0.9%, 1.2% [2 SAE], 0%). Fistula were not reported with a higher frequency in the cediranib arms (0.9%, 0.6%, 0%), nor were wound healing complications (2.6%, 1.2%, 1.3%).

Of the AEs reported for a greater proportion (≥5% difference) of patients in either the cediranib concurrent/maintenance arm or cediranib concurrent arm compared with the chemotherapy+placebo arm, the following PTs have not been previously identified or reported at a higher incidence than comparator: dyspnoea (31.3%, 36.8% and 38.0%, resp), pain in extremity (15.7%, 21.6%, 22.8%), dysgeusia (taste disorder) (8.7%, 15.2%, 16.5%), blood ALP increased, mucosal inflammation, pruritus and peripheral oedema (Table 24).

Table 24. Number (%) of patients with most common AEs (⩾10% in any treatment group) by PT during the overall study period – ICON6 (safety analysis set)

Preferred term[a]	Chemotherapy+ placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/ maintenance (N=158)
Patients with any AE	**114 (99.1)**	**171 (100.0)**	**158 (100.0)**
Fatigue	105 (91.3)	156 (91.2)	**154 (97.5)**
Diarrhoea	75 (65.2)	**149 (87.1)**	**147 (93.0)**
Nausea	88 (76.5)	138 (80.7)	126 (79.7)
Alopecia	**89 (77.4)**	123 (71.9)	113 (71.5)
Peripheral sensory neuropathy	80 (69.6)	106 (62.0)	113 (71.5)
Neutrophil count decreased	57 (49.6)	**118 (69.0)**	**111 (70.3)**
Constipation	**86 (74.8)**	112 (65.5)	105 (66.5)
Hypertension	43 (37.4)	**106 (62.0)**	**94 (59.5)**
Abdominal pain	**75 (65.2)**	75 (43.9)	89 (56.3)
Haemoglobin decreased	**70 (60.9)**	95 (55.6)	87 (55.1)
Decreased appetite	43 (37.4)	63 (36.8)	**81 (51.3)**
Platelet count decreased	42 (36.5)	**84 (49.1)**	**76 (48.1)**
Vomiting	54 (47.0)	**92 (53.8)**	75 (47.5)
White blood cell count decreased	48 (41.7)	**86 (50.3)**	**75 (47.5)**
Transaminases increased	43 (37.4)	66 (38.6)	65 (41.1)
Stomatitis	28 (24.3)	**63 (36.8)**	**65 (41.1)**
Dyspnoea	36 (31.3)	**63 (36.8)**	**60 (38.0)**
Rash	38 (33.0)	46 (26.9)	55 (34.8)
Headache	29 (25.2)	**58 (33.9)**	**52 (32.9)**
Hypomagnesaemia	25 (21.7)	**51 (29.8)**	**52 (32.9)**
Dysphonia	10 (8.7)	**40 (23.4)**	**50 (31.6)**
Hypersensitivity	37 (32.2)	48 (28.1)	49 (31.0)
Proteinuria	14 (12.2)	**35 (20.5)**	**45 (28.5)**
Arthralgia	35 (30.4)	48 (28.1)	43 (27.2)
Back pain	24 (20.9)	36 (21.1)	**43 (27.2)**
Epistaxis	7 (6.1)	**29 (17.0)**	**39 (24.7)**
Pain in extremity	18 (15.7)	**37 (21.6)**	**36 (22.8)**
Weight decreased	11 (9.6)	**28 (16.4)**	**35 (22.2)**
Cough	26 (22.6)	31 (18.1)	33 (20.9)
Dry mouth	21 (18.3)	25 (14.6)	33 (20.9)
Hypothyroidism	10 (8.7)	18 (10.5)	**33 (20.9)**
Muscular weakness	16 (13.9)	22 (12.9)	29 (18.4)

Preferred term[a]	Chemotherapy+ placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/ maintenance (N=158)
Dizziness	15 (13.0)	25 (14.6)	27 (17.1)
Hypokalaemia	16 (13.9)	30 (17.5)	26 (16.5)
Dysgeusia	10 (8.7)	**26 (15.2)**	**26 (16.5)**
Abdominal pain upper	14 (12.2)	15 (8.8)	25 (15.8)
Urinary tract infection	17 (14.8)	**35 (20.5)**	24 (15.2)
Dehydration	8 (7.0)	**23 (13.5)**	**24 (15.2)**
Insomnia	20 (17.4)	36 (21.1)	23 (14.6)
Dyspepsia	19 (16.5)	27 (15.8)	21 (13.3)
Palmar-plantar erythrodysaesthesia syndrome	14 (12.2)	22 (12.9)	19 (12.0)
Abdominal distension	26 (22.6)	35 (20.5)	17 (10.8)
Myalgia	23 (20.0)	32 (18.7)	17 (10.8)
Blood alkaline phosphatase increased	5 (4.3)	**22 (12.9)**	**17 (10.8)**
Blood magnesium decreased	8 (7.0)	**22 (12.9)**	16 (10.1)
Oropharyngeal pain	11 (9.6)	14 (8.2)	16 (10.1)
Mucosal inflammation	5 (4.3)	13 (7.6)	**16 (10.1)**
Abdominal pain lower	13 (11.3)	12 (7.0)	16 (10.1)
Nasopharyngitis	11 (9.6)	11 (6.4)	16 (10.1)
Febrile neutropenia	4 (3.5)	7 (4.1)	**16 (10.1)**
Peripheral motor neuropathy	**18 (15.7)**	15 (8.8)	15 (9.5)
Musculoskeletal pain	10 (8.7)	22 (12.9)	14 (8.9)
Hypocalcaemia	3 (2.6)	**19 (11.1)**	**14 (8.9)**
Anxiety	14 (12.2)	13 (7.6)	12 (7.6)
Hot flush	12 (10.4)	12 (7.0)	8 (5.1)

[a] Number (%) of patients with AEs, sorted by PT in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance arm).

Note: Bold numbers are presented in this table for PTs where there was a ≥5% higher incidence of an AE in either the cediranib concurrent/maintenance arm or cediranib concurrent arm vs. the chemotherapy+placebo arm. Bold numbers are also presented for PTs where there was a ≥5% higher incidence of an AE in the chemotherapy+placebo arm vs. both cediranib arms.

AE adverse event; PT preferred term.

Larger proportions of patients in the cediranib arms had CTCAE grade ≥3 AEs (77.2% and 78.9% in the cediranib concurrent/maintenance and cediranib concurrent arms, respectively) compared with the chemotherapy+placebo arm (67.8%) (Table 25). The 3 most common CTCAE grade ≥3 AEs reported on cediranib treatment were neutrophil count decreased (27.2%, 26.9% and 24.3% of patients in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms, respectively), fatigue (22.2%, 14.0% and 8.7% of patients, respectively) and diarrhoea (19.0%, 8.8% and 2.6% of patients, respectively). The most common CTCAE grade ≥3 AEs that were reported at a ≥2% higher incidence in either the cediranib concurrent/maintenance arm or cediranib concurrent arm compared with the chemotherapy+placebo arm included neutrophil count decreased, fatigue and diarrhoea (as described above), as well as platelet count decreased (10.1%, 8.2% and 2.6% of patients in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms,

respectively), hypertension (9.5%, 16.4% and 5.2% of patients, respectively), febrile neutropenia (8.2%, 2.9% and 2.6%) and nausea (3.8%, 5.8% and 3.5%, respectively).

Table 25. Number (%) of patients with most common AEs of CTCAE grade 3 or higher (reported in ≥5% of patients in any treatment group) during the overall study period – ICON6 (safety analysis set)

Preferred term[a]	Chemotherapy+placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/ maintenance (N=158)
Any CTCAE grade ≥3 AE	**78 (67.8)**	**135 (78.9)**	**122 (77.2)**
Neutrophil count decreased	28 (24.3)	**46 (26.9)**	**43 (27.2)**
Fatigue	10 (8.7)	**24 (14.0)**	**35 (22.2)**
Diarrhoea	3 (2.6)	**15 (8.8)**	**30 (19.0)**
Platelet count decreased	3 (2.6)	**14 (8.2)**	**16 (10.1)**
Hypertension	6 (5.2)	**28 (16.4)**	**15 (9.5)**
Hypersensitivity	13 (11.3)	10 (5.8)	15 (9.5)
White blood cell count decreased	9 (7.8)	10 (5.8)	14 (8.9)
Febrile neutropenia	3 (2.6)	5 (2.9)	**13 (8.2)**
Vomiting	**11 (9.6)**	13 (7.6)	8 (5.1)
Abdominal pain	**12 (10.4)**	13 (7.6)	7 (4.4)
Nausea	5 (4.3)	10 (5.8)	6 (3.8)
Hypomagnesaemia	4 (3.5)	9 (5.3)	6 (3.8)
Dyspnoea	5 (4.3)	10 (5.8)	4 (2.5)
Haemoglobin decreased	**6 (5.2)**	4 (2.3)	4 (2.5)

[a] Number (%) of patients with AEs, sorted by PT in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance arm).

Note: Bold numbers are presented in this table for PTs where there was a ≥2% higher incidence of an AE in either the cediranib concurrent/maintenance arm or cediranib concurrent arm vs. the chemotherapy+placebo arm. Bold numbers are also presented for PTs where there was a ≥2% higher incidence of an AE in the chemotherapy+placebo arm vs. both cediranib arms.

AE adverse event; CTCAE Common Terminology Criteria for Adverse Events; PT preferred term.

The adverse events pattern in the other studies included in the safety database was largely similar to that observed in ICON6.

Serious adverse events and deaths

ICON6 – serious adverse events: overall study period

Serious adverse events were reported with a higher frequency in the cediranib arms (38.0%, 36.8% and 33.9% in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms, respectively), in the overall study period. The 3 most common SOCs for reported SAEs in the cediranib arms were GI disorders (8.9%, 15.2% and 13.0% of patients, in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms, respectively), infections and infestations (8.2%, 8.2% and 7.0% of patients, respectively) and immune system disorders (6.3%, 4.7% and 8.7%, respectively). The 5 most common SAEs by PT reported in the cediranib arms were hypersensitivity (5.1%, 2.9% and 6.1% of patients in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms, respectively), febrile neutropenia (3.8%, 2.3% and 2.6% of patients, respectively), neutropenic

sepsis (3.8%, 1.8% and 1.7%, respectively), diarrhoea (2.5%, 3.5% and 2.6% of patients, respectively) and vomiting (1.9%, 5.8% and 4.3% of patients, respectively). A summary of the most common SAEs (≥1%) reported in ICON6 is presented by PT in (Table 27).

Table 26. Number (%) of patients who had at least 1 SAE (reported in ≥1% of patients in any treatment group) during the overall study period, ICON6 (safety analysis set)

Preferred term[a]	Chemotherapy+placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/ maintenance (N=158)
Patients with any SAE	**39 (33.9)**	**63 (36.8)**	**60 (38.0)**
Hypersensitivity	7 (6.1)	5 (2.9)	8 (5.1)
Febrile neutropenia	3 (2.6)	4 (2.3)	6 (3.8)
Neutropenic sepsis	2 (1.7)	3 (1.8)	**6 (3.8)**
Diarrhoea	3 (2.6)	6 (3.5)	4 (2.5)
Vomiting	5 (4.3)	10 (5.8)	3 (1.9)
Pulmonary embolism	1 (0.9)	4 (2.3)	3 (1.9)
Anaphylactic reaction	1 (0.9)	2 (1.2)	3 (1.9)
Neutropenia	0	1 (0.6)	3 (1.9)
Transient ischaemic attack	0	1 (0.6)	3 (1.9)
Abdominal pain	2 (1.7)	6 (3.5)	2 (1.3)
Intestinal obstruction	2 (1.7)	2 (1.2)	2 (1.3)
Hypertension	0	2 (1.2)	2 (1.3)
Hypomagnesaemia	0	2 (1.2)	2 (1.3)
Thrombocytopenia	0	2 (1.2)	2 (1.3)
Chest pain	0	1 (0.6)	2 (1.3)
Dyspnoea	0	1 (0.6)	2 (1.3)
Lower respiratory tract infection	1 (0.9)	0	2 (1.3)
Embolism	0	0	2 (1.3)
Dehydration	1 (0.9)	3 (1.8)	1 (0.6)
Pyrexia	1 (0.9)	2 (1.2)	1 (0.6)
Convulsion	0	2 (1.2)	1 (0.6)
Nausea	0	3 (1.8)	0
Constipation	1 (0.9)	2 (1.2)	0
Epistaxis	0	2 (1.2)	0
Pneumonia	0	2 (1.2)	0
Drug hypersensitivity	**3 (2.6)**	1 (0.6)	0

[a] Number (%) of patients with SAEs, sorted by PT in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance arm).

Note: Bold numbers are presented in this table for PTs where there was a ≥5% higher incidence of an AE in either the cediranib concurrent/maintenance arm or cediranib concurrent arm vs. the chemotherapy+placebo arm. Bold numbers are also presented for PTs where there was a ≥5% higher incidence of an AE in the chemotherapy+placebo arm vs. both cediranib arms.

PT preferred term; SAE serious adverse event.

Deaths

Table 30 Summary of cause of death (Full Analysis Set)

Cause of death	Number (%) of patients		
	Chemotherapy + placebo (N=118)	Cediranib concurrent (N=174)	Cediranib concurrent/maintenance (N=164)
Chemotherapy phase	2 (1.7)	0	0
Disease related	1 (0.8)	0	0
Treatment related	0	0	0
Disease and treatment related	0	0	0
Other	1 (0.8)	0	0
Maintenance phase	0	0	0
Disease related	0	0	0
Treatment related	0	0	0
Disease and treatment related	0	0	0
Other	0	0	0
Post-treatment follow-up	62 (52.5)	91 (52.3)	79 (48.2)
Disease related	47 (39.8)	59 (33.9)	51 (31.1)
Treatment related	0	0	0
Disease and treatment related	1 (0.8)	0	1 (0.6)
Other	14 (11.9)	32 (18.4)	27 (16.5)
Overall	64 (54.2)	91 (52.3)	79 (48.2)
Disease related	48 (40.7)	59 (33.9)	51 (31.1)
Treatment related	0	0	0
Disease and treatment related	1 (0.8)	0	1 (0.6)
Other	15 (12.7)	32 (18.4)	27 (16.5)

Note: All deaths are summarised.
Note: "Other" was everything other than treatment related and/or disease related.
N number of patients.
Data source Table 11.3.3.1.1.

The majority of deaths seems to occur in the Post-treatment follow-up period and the majority seems to be related to the underlying disease, where there is a clear difference in favor of Arm B and C. There is a small difference between Arm B and C, but it is not considered substantial (33.9% vs. 31.1%).

However, a considerable number of deaths are classified as "Other", where there is a considerable higher frequency in the cediranib arms. The Applicant is asked to clarify what is meant by "Other". Furthermore, the Applicant is asked to present data (incl. reasons) on non-PD deaths <90 days post-treatment, and discuss any difference.

Table 31 Summary of patients who had an adverse event with a fatal outcome – overall study period (Safety Analysis Set)

System Organ Class Preferred term	Number (%) of patients[a] Chemotherapy + placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/maintenance (N=158)
Patients with any adverse event with fatal outcome[b]	3 (2.6)	3 (1.8)	3 (1.9)
Infections and infestations	1 (0.9)	1 (0.6)	0
Bronchopneumonia	1 (0.9)	0	0
Pneumonia	0	1 (0.6)	0
Blood and lymphatic system disorders	0	1 (0.6)	0
Neutropenia	0	1 (0.6)	0
Nervous system disorders	1 (0.9)	0	0
Depressed level of consciousness	1 (0.9)	0	0
Cardiac disorders	0	1 (0.6)	0
Acute myocardial infarction	0	1 (0.6)	0
Arteriosclerosis coronary artery	0	1 (0.6)	0
Myocardial ischaemia	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders	0	0	2 (1.3)
Dyspnoea	0	0	2 (1.3)
Hypoxia	0	0	1 (0.6)
Gastrointestinal disorders	1 (0.9)	1 (0.6)	2 (1.3)
Nausea	0	0	1 (0.6)
Pancreatitis	0	0	1 (0.6)
Gastrointestinal obstruction	1 (0.9)	0	0
Intestinal perforation	0	1 (0.6)	0

[a] Number (%) of patients with adverse events with a fatal outcome, sorted by international System Organ Class order followed by Preferred Term in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance group).

[b] Patients could have more than 1 event with a fatal outcome.

MedDRA version 16.1.

MedDRA Medical Dictionary for Regulatory Activities; N number of patients.

Data source Table 11.3.3.1.2.

Three patients died in each arm as a consequence of an AE with a fatal outcome. A closer look at these fatal cases (data not shown, please see table 32 in the CSR) show no clear pattern. The Applicant mentions that there are some inconsistencies between table 30 and 31 due to differences in CRF pages. The Applicant is invited to elaborate more on reason(s) these inconsistencies.

Laboratory findings

Haemoglobin

In ICON6, no clinically meaningful differences in haemoglobin levels were observed between the 3 treatment arms throughout the chemotherapy and maintenance phases (ICON6 Table 11.3.7.1.1). Across all 3 arms median haemoglobin levels decreased from Cycles 1 to 6 during the chemotherapy phase, dropping to slightly below the lower limit of the normal range in all 3 arms from Cycles 4 to 6 (Figure 26). During the maintenance phase, median haemoglobin levels increased from Week 21 to Week 87 in all 3 arms, with median levels returning to within the normal range from Week 33 onwards. There were slight differences between the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms in the proportions of patients with shifts to CTCAE grade ≥3 for low haemoglobin (5.1%, 1.8% and 3.6%, respectively), but these were not clinically relevant. In addition, the incidence of CTCAE grade ≥3 anaemia (grouped term) varied slightly between the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms (2.5%, 2.3% and 5.2%, respectively), but these differences were not clinically important.

Increased transaminases

There were largely no differences between the ICON6 treatment arms in the incidence of transaminases increased AEs (PT) (41.1%, 38.6% and 37.4% of patients in the cediranib concurrent/maintenance, cediranib concurrent and chemotherapy+placebo arms, respectively). These events occurred more often during the chemotherapy phase (38.3% and 35.7% of patients in the combined cediranib arms and chemotherapy+placebo arms, respectively) than the maintenance phase (25.3% and 21.2% of patients in the cediranib concurrent/maintenance and chemotherapy+placebo arms, respectively). Liver function test abnormal (PT) was reported in only 1 patient (cediranib concurrent arm).

Safety in special populations

The elderly population

The proportions of patients in the 65-<75 and ≥75 years subgroups reporting AEs, SAEs, grade ≥3 AEs and AEs leading to discontinuation in ICON6 were not markedly different to the overall population, with the exception of the proportion of patients in the cediranib concurrent/maintenance arm within the ≥75 years subgroup who had AEs leading to discontinuation (84.6% vs. 39.2% overall) (Table 28). The most frequently reported AEs, SAEs, grade ≥3 AEs and AEs leading to discontinuation were similar between the 65-<75 and the ≥75 years subgroups and were consistent with the overall data. The most frequently reported SAEs were generally similar for the 65-<75 years age subgroup compared to the overall data, with the exception of nausea and abdominal pain, which were reported more frequently as SAEs in the 65-<75 year subgroup of the cediranib concurrent/maintenance group than the overall population (4.5% vs. 0% [nausea]; 3.6% vs.1.3% [abdominal pain]). A similar increase was not observed in this age subgroup in the chemotherapy+placebo group.

Table 27. Number (%) of patients who had at least 1 AE in any category during the overall study period by age – ICON6 (safety analysis set).

	Age subgroups (years)	Chemotherapy +placebo	Cediranib concurrent	Cediranib concurrent/ maintenance
Any AE	<35	0/0	2/2 (100.0)	2/2 (100.0)
	35-<50	17/17 (100.0)	22/22 (100.0)	25/25 (100.0)
	50-<55	21/21 (100.0)	23/23 (100.0)	16/16 (100.0)
	55-<65	34/35 (97.1)	53/53 (100.0)	51/51 (100.0)
	65-<75	37/37 (100.0)	61/61 (100.0)	51/51 (100.0)
	≥75	5/5 (100.0)	10/10 (100.0)	13/13 (100.0)
	Overall	114/115 (99.1)	171/171 (100.0)	158/158 (100.0)
Any SAE	<35	0/0	0/2	2/2 (100.0)
	35-<50	6/17 (35.3)	9/22 (40.9)	8/25 (32.0)
	50-<55	4/21 (19.0)	9/23 (39.1)	5/16 (31.3)
	55-<65	15/35 (42.9)	19/53 (35.8)	21/51 (41.2)
	65-<75	13/37 (35.1)	21/61 (34.4)	19/51 (37.3)
	≥75	1/5 (20.0)	5/10 (50.0)	5/13 (38.5)
	Overall	39/115 (33.9)	63/171 (36.8)	60/158 (38.0)
Any CTCAE grade ≥3 AE	<35	0/0	2/2 (100.0)	1/2 (50.0)
	35-<50	12/17 (70.6)	18/22 (81.8)	22/25 (88.0)
	50-<55	14/21 (66.7)	16/23 (69.6)	12/16 (75.0)
	55-<65	26/35 (74.3)	42/53 (79.2)	38/51 (74.5)
	65-<75	22/37 (59.5)	49/61 (80.3)	39/51 (76.5)
	≥75	4/5 (80.0)	8/10 (80.0)	10/13 (76.9)
	Overall	78/115 (67.8)	135/171 (78.9)	122/158 (77.2)
AEs leading to permanent discontinuation[a]	<35	0/0	0/2	1/2 (50.0)
	35-<50	2/17 (11.8)	4/22 (18.2)	5/25 (20.0)
	50-<55	1/21 (4.8)	8/23 (34.8)	4/16 (25.0)
	55-<65	7/35 (20.0)	19/53 (35.8)	21/51 (41.2)
	65-<75	5/37 (13.5)	21/61 (34.4)	20/51 (39.2)
	≥75	1/5 (20.0)	3/10 (30.0)	11/13 (84.6)
	Overall	16/115 (13.9)	55/171 (32.2)	62/158 (39.2)

[a] AEs leading to permanent discontinuation of cediranib/cediranib placebo.
AE adverse event; CTCAE Common Terminology Criteria for Adverse Events; SAE serious adverse event.

Renal impairment

In general, in ICON6 the proportion of patients reporting AEs and grade ≥3 AEs were similar across each estimated CrCl category (<50, 50-<80, ≥80 mL/minute) and were consistent with the overall data. However, larger proportions of patients in the cediranib concurrent/maintenance arm in the subgroup of patients with moderate/severe renal impairment (CrCl <50 mL/minute) compared with the overall data had an SAE (60.0% vs. 38.0%) or an AE leading to discontinuation (60.0% vs. 39.2%). The low number of patients in the moderate/severe renal impairment category, however, means it is difficult to draw conclusions from these data. The same pattern was noted when looking at the same subgroups of patients in the combination therapy pool.

Discontinuation due to AES

Permanent discontinuation

Table 37 Summary of adverse events leading to permanent discontinuation of cediranib/placebo reported for ≥1.0% of patients at the Preferred Term level within a treatment arm – overall study period (Safety Analysis Set)

	Number (%) of patients[a]		
System Organ Class Preferred term	Chemotherapy + placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/maintenance (N=158)
Patients with any adverse event leading to permanent discontinuation of cediranib/placebo	16 (13.9)	55 (32.2)	62 (39.2)
Blood and lymphatic system disorders	1 (0.9)	4 (2.3)	2 (1.3)
Febrile neutropenia	1 (0.9)	1 (0.6)	2 (1.3)
Immune system disorders	2 (1.7)	2 (1.2)	5 (3.2)
Hypersensitivity	1 (0.9)	1 (0.6)	5 (3.2)
Metabolism and nutrition disorders	0	6 (3.5)	4 (2.5)
Hypomagnesaemia	0	1 (0.6)	3 (1.9)
Dehydration	0	4 (2.3)	0
Hyponatraemia	0	2 (1.2)	0
Psychiatric disorders	0	3 (1.8)	0
Depressed mood	0	2 (1.2)	0
Nervous system disorders	4 (3.5)	9 (5.3)	9 (5.7)
Transient ischaemic attack	0	1 (0.6)	3 (1.9)
Dizziness	0	1 (0.6)	2 (1.3)
Headache	0	3 (1.8)	2 (1.3)
Ear and labyrinth disorders	0	2 (1.2)	1 (0.6)
Tinnitus	0	2 (1.2)	0
Vascular disorders	0	8 (4.7)	6 (3.8)
Hypertension	0	5 (2.9)	4 (2.5)
Respiratory, thoracic and mediastinal disorders	3 (2.6)	6 (3.5)	10 (6.3)
Dyspnoea	1 (0.9)	2 (1.2)	7 (4.4)
Pulmonary embolism	1 (0.9)	3 (1.8)	2 (1.3)
Epistaxis	0	2 (1.2)	0
Gastrointestinal disorders	6 (5.2)	21 (12.3)	26 (16.5)
Diarrhoea	2 (1.7)	12 (7.0)	17 (10.8)
Abdominal pain	1 (0.9)	2 (1.2)	5 (3.2)
Nausea	0	5 (2.9)	4 (2.5)
Abdominal pain upper	0	0	2 (1.3)
Stomatitis	0	0	2 (1.3)
Vomiting	1 (0.9)	8 (4.7)	2 (1.3)
Abdominal distension	2 (1.7)	0	0
Skin and subcutaneous tissue disorders	0	2 (1.2)	5 (3.2)
Rash	0	1 (0.6)	2 (1.3)
Renal and urinary disorders	1 (0.9)	3 (1.8)	0
Proteinuria	0	3 (1.8)	0
General disorders and administration site conditions	2 (1.7)	10 (5.8)	16 (10.1)
Fatigue	1 (0.9)	8 (4.7)	10 (6.3)
Mucosal inflammation	0	0	2 (1.3)
Investigations	1 (0.9)	10 (5.8)	4 (2.5)
Transaminases increased	1 (0.9)	0	2 (1.3)
White blood cell count decreased	0	0	2 (1.3)
Platelet count decreased	0	2 (1.2)	1 (0.6)
Neutrophil count decreased	0	4 (2.3)	0

[a] Number (%) of patients with adverse events leading to permanent cediranib/placebo discontinuation, sorted by international System Organ Class order followed by Preferred Term in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance arm).
MedDRA version 16.1.
MedDRA Medical Dictionary for Regulatory Activities; N number of patients.
Data source Table 11.3.5.1.1.

There are clearly more AEs leading to permanent discontinuation in Arm C. The most common AEs leading to discontinuation are diarrhoea and fatigue. The Applicant argues that this "*likely reflects the extended exposure to cediranib for the cediranib concurrent/maintenance in the maintenance phase of the study*". However, no exposure-adjusted analysis has been provided. The Applicant is asked to provide this analysis and discuss the results.

The Applicant is also asked to clarify how many AEs leading to permanent discontinuation resolved with/without sequale, and how many that didn't resolve. Also, the Applicant is asked to present data on the time from discontinuation of cediranib concurrent and cediranib concurrent/maintenance to progression of disease or death.

The majority of discontinuations occurred in the chemotherapy phase (data not shown, see table 38 and table 11.3.3.1.3 in the CSR).

Dose reduction/pauses

Table 39 Summary of adverse events leading to cediranib/placebo dose reduction reported for ≥2.0% of patients at the Preferred Term level within a treatment arm – overall study period (Safety Analysis Set)

System Organ Class Preferred term	Number (%) of patients[a] Chemotherapy + placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/maintenance (N=158)
Patients with any adverse event leading to cediranib/placebo dose reduction	27 (23.5)	56 (32.7)	72 (45.6)
Immune system disorders	3 (2.6)	3 (1.8)	7 (4.4)
Hypersensitivity	2 (1.7)	3 (1.8)	7 (4.4)
Nervous system disorders	3 (2.6)	8 (4.7)	10 (6.3)
Peripheral sensory neuropathy	2 (1.7)	3 (1.8)	6 (3.8)
Vascular disorders	1 (0.9)	6 (3.5)	8 (5.1)
Hypertension	1 (0.9)	6 (3.5)	6 (3.8)
Gastrointestinal disorders	6 (5.2)	29 (17.0)	35 (22.2)
Diarrhoea	3 (2.6)	21 (12.3)	27 (17.1)
Nausea	1 (0.9)	4 (2.3)	4 (2.5)
Abdominal pain	1 (0.9)	5 (2.9)	3 (1.9)
Vomiting	2 (1.7)	5 (2.9)	2 (1.3)
General disorders and administration site conditions	6 (5.2)	10 (5.8)	21 (13.3)
Fatigue	4 (3.5)	10 (5.8)	21 (13.3)
Investigations	10 (8.7)	22 (12.9)	21 (13.3)
Neutrophil count decreased	8 (7.0)	11 (6.4)	11 (7.0)
Platelet count decreased	1 (0.9)	7 (4.1)	9 (5.7)
White blood cell count decreased	3 (2.6)	3 (1.8)	5 (3.2)
Weight decreased	0	1 (0.6)	4 (2.5)
Transaminases increased	2 (1.7)	5 (2.9)	1 (0.6)

[a] Number (%) of patients with adverse events leading to cediranib/placebo dose reductions, sorted by international System Organ Class order followed by Preferred Term in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance arm).
MedDRA version 16.1.
MedDRA Medical Dictionary for Regulatory Activities; N number of patients.
Data source Table 11.3.5.2.1.

Dose pauses

Table 40 Summary of adverse events leading to cediranib/placebo dose pauses reported for ≥5.0% of patients at the Preferred Term level within a treatment arm – overall study period (Safety Analysis Set)

System Organ Class Preferred term	Number (%) of patients[a] Chemotherapy + placebo (N=115)	Cediranib concurrent (N=171)	Cediranib concurrent/maintenance (N=158)
Patients with any adverse event leading to cediranib/placebo dose pause	64 (55.7)	117 (68.4)	123 (77.8)
Blood and lymphatic system disorders	5 (4.3)	4 (2.3)	11 (7.0)
Febrile neutropenia	3 (2.6)	2 (1.2)	8 (5.1)
Immune system disorders	5 (4.3)	4 (2.3)	11 (7.0)
Hypersensitivity	4 (3.5)	3 (1.8)	9 (5.7)
Nervous system disorders	6 (5.2)	13 (7.6)	14 (8.9)
Headache	0	9 (5.3)	0
Vascular disorders	1 (0.9)	17 (9.9)	16 (10.1)
Hypertension	1 (0.9)	13 (7.6)	13 (8.2)
Respiratory, thoracic and mediastinal disorders	5 (4.3)	8 (4.7)	21 (13.3)
Dyspnoea	5 (4.3)	3 (1.8)	10 (6.3)
Gastrointestinal disorders	26 (22.6)	57 (33.3)	69 (43.7)
Diarrhoea	8 (7.0)	32 (18.7)	53 (33.5)
Nausea	7 (6.1)	19 (11.1)	16 (10.1)
Vomiting	12 (10.4)	17 (9.9)	14 (8.9)
Abdominal pain	10 (8.7)	8 (4.7)	6 (3.8)
General disorders and administration site conditions	9 (7.8)	22 (12.9)	40 (25.3)
Fatigue	8 (7.0)	20 (11.7)	34 (21.5)
Investigations	25 (21.7)	43 (25.1)	65 (41.1)
Neutrophil count decreased	16 (13.9)	27 (15.8)	42 (26.6)
Platelet count decreased	6 (5.2)	22 (12.9)	37 (23.4)
Haemoglobin decreased	6 (5.2)	5 (2.9)	12 (7.6)
White blood cell count decreased	7 (6.1)	8 (4.7)	12 (7.6)
Transaminases increased	1 (0.9)	5 (2.9)	9 (5.7)

[a] Number (%) of patients with who reported at least 1 adverse event leading to a cediranib/placebo dose pause, sorted by international System Organ Class order followed by Preferred Term in decreasing order of frequency (sorted by frequency in the cediranib concurrent/maintenance arm).
MedDRA version 16.1.
MedDRA Medical Dictionary for Regulatory Activities; N number of patients.
Data source Table 11.3.5.3.1.

3.3.10. Discussion on clinical safety

Exposure

Of the approximately 5800 patients who have been exposed to cediranib, the Applicant presented safety data on 1272 cediranib-treated patients. These included patients treated with cediranib at the proposed dose of 20 mg OD in combination with platinum-based chemotherapy (combination therapy pool), studies using 20 mg OD as monotherapy (monotherapy pool) and three other studies in which cediranib was given in combination with chemotherapy (oxaliplatin-based).

Adverse events

The safety and tolerability profile of Cediranib observed in ICON6 and other studies is consistent with those known from VEGFR and tyrosine kinase inhibitors, including ramucirumab as well as bevacizumab. AEs related to bone marrow depression, such as neutropenia and thrombopenia, occurred frequently. Besides hypertension, other typical AEs associated with VEGF targeting agents occurring with a substantially higher frequency in the cediranib arms were hypertension (37.4%, 62.0%, 59.5% in the chemotherapy+placebo arm, cediranib concurrent and cediranib concurrent/maintenance arm, respectively); proteinuria (12.2%, 21.1% and 28.5%, peripheral oedema (3.45%, 7.6% and 9.9%), bleeding/haemorrhage (13.0%, 22.8% and 31.6% , Arterial thromboembolism (0.9%, 2.3%, 3.2%) and gastrointestinal perforation (0%, 1.2% [2 SAE], 0.9%).

AE start dates were only collected for SAEs, thus, the study visit on which the AE was reported was used to determine events that were included in summaries. Furthermore, changes in CTCAE grade and AE resolution dates were not recorded for non-serious AEs. This means that it is not possible to assess non-serious AEs duration or outcome. Also, the Applicant claims that there may have been an over-reporting AEs. It seems that when an SAE was reported or an SAE led to treatment discontinuation, all the associated symptoms were also coded as AEs. CTCAE v.3 was also used at the study onset but was changed to CTCAE v.4. This could have an impact and led to inconsistency of allocated AE grades throughout the trial. These issues are together considered a weakness of the safety database.

The proportions of patients reported with CTCAE grade ≥3 AEs (67.8%, 78.9% and 77.2%), SAEs (33.9%, 36.8% and 38.0%) and SAEs leading to hospitalisation (28.7%, 28.7% and 34.8%) were higher in the cediranib groups than the placebo group. The difference in the proportion of AEs and SAEs between the cediranib concurrent arm and the cediranib concurrent/maintenance arm was generally small. However, a number of grade≥3 AEs occurred with a higher frequency in the cediranib concurrent/maintenance arm compared to the cediranib concurrent arm: diarrhoea (19.0% vs. 8.8%), fatigue (22.2% vs. 14.0%), febrile neutropenia (8.2% vs. 2.9%). Furthermore, bleeding/hemorrhage (any grade) was more frequent in the cediranib concurrent/maintenance arm (31.6% vs. 22.8%), as was proteinuria (28.5% vs. 20.5%), abdominal pain (56.3% vs. 43.9%), decreased appetite (51.3% vs. 36.8%), dysphonia (31.6% vs. 23.4%), epistaxis (24.7% vs. 17.0%), hypothyroidism (20.9% vs. 10.5%), muscular weakness (18.4% vs. 12.9%). Therefore, the safety profile of cediranib given concurrent and as maintenance is worse than that of cediranib concurrent only.

The majority of deaths seems to occur in the Post-treatment follow-up period and the majority seems to be related to the underlying disease, where there is a difference in favor of Arm B and C. There is a small difference between Arm B and C, but it is not considered substantial (33.9% vs. 31.1%). However, a considerable number of deaths are classified as “Other”, where there is a considerable higher frequency in the cediranib arms. The Applicant is asked to clarify what is meant by “Other”. Furthermore, the Applicant is asked to present data (incl. reasons) on non-PD deaths <90 days post-treatment, and discuss any difference.

The most frequent AEs leading to discontinuation of cediranib were diarrhoea and fatigue. It is unclear why so many patients with these AEs discontinued treatment, since adherence to management recommendations in ICON6 would have resulted in other actions than discontinuation. The Applicant suggested alternative explanations for the high discontinuation rate due to diarrhoea and fatigue, despite the fact that clear instructions for management were provided during the ICON6 study. Taken together, these data suggest that this toxicity (including the high discontinuation rate) can also be expected when cediranib would be prescribed in clinical practice. A high discontinuation rate due to AE was observed in the age group of 75 years and older: (84.6% vs. 39.2% overall), which was not observed in the cediranib concurrent and chemotherapy and placebo arm (32.2% and 13.9%).

3.3.11. Conclusions on clinical safety

Safety and tolerability profile of Cediranib observed in ICON6 and other studies is consistent with the class effects known for VEGF inhibitors. The frequency of AEs and SAEs was generally not different between the cediranib concurrent and the cediranib concurrent/maintenance arm, although a number of AE (grade≥3 and all grades) was substantially more frequent in the cediranib concurrent/maintenance arm compared to cediranib concurrent. A substantially higher proportion of patients in the cediranib arms discontinued treatment permanently than in the

chemotherapy+placebo arm, raising concern about the tolerability of cediranib treatment in ovarian cancer patients and suggesting that the proposed countermeasures are not effective.

3.4. Risk management plan

The Safety Specification (Part II, SI-SVIII) from RMP version 1, dated 12 June 2015 is assessed below.

Safety Specification

The CHMP considers the data presented in the RMP as follows:

- **Epidemiology of the indications and target population**

(See Overview, section). Ovarian cancer ranks as the 7th most common type of cancer and the 7th most common cause of cancer death in women worldwide (Ferlay et al 2012). In the EU in 2012, ovarian cancer was estimated to be the 6th most common type of female cancer (13.1 new cases per 100 000) and the 5th leading cause of cancer mortality in women (7.6 deaths per 100 000) (Ferlay et al 2013). In recent years there have been 65 500 – 70 000 new cases occurring annually in Europe (Ferlay et al 2012, Ferlay et al 2013 and Ledermann et al 2013). The 2012 ovarian cancer worldwide age standardised rate to the world standard population (ASR-W), as estimated by the IARC, was 6.1 cases per 100 000 woman-years. A higher incidence is seen in well-developed, westernised regions. In Europe, the ASR-W was 9.4 cases per 100 000 woman-years and was particularly elevated in Northern, Central and Eastern Europe where 2012 ASR-W rates were estimated at ≥11.0 per 100 000 woman-years. Data from Europe, Nordic countries (Nordcan 2014) and the US (SEER 2014) suggest a gradual decline in ovarian cancer incidence in developed countries. Survival has also shown a gradual improvement in recent years in Western developed countries.

Ovarian cancer occurs only in females, and the median age at diagnosis according to US registry data is 55-64 years (mean 63 years).

- **Clinical trial exposure**

As of March 2015, approximately 5800 patients have been treated with cediranib in a broad clinical programme that includes both monotherapy and combination studies, in multiple tumour types: PSR ovarian cancer (the sought indication), colorectal cancer (CRC), glioblastoma, non-small cell lung cancer (NSCLC) and renal cell carcinoma. A large number of signal-searching studies in a range of other tumour types have also been conducted. Studies were sponsored by AstraZeneca and/or by collaborative groups.

The focused safety evaluation in the proposed indication is based on data from 1272 cediranib-treated patients (please refer to section 4.2).

- **Populations not studied in clinical trials**

Additional experience is required to determine whether cediranib is associated with less common ADRs. Given the exposure data available for cediranib beyond 2 years, the ability to detect cumulative effects or ADRs due to prolonged exposure is limited. There is no information on the effect of cediranib in patients with uncontrolled hypertension at the time of initiating therapy. Cediranib has not been studied in patients with significant haemorrhage (>30 mL bleeding /episode) in the previous 3 months or in patients with haemoptysis. No formal studies of the effect

of cediranib on wound healing have been conducted, however in the pivotal study there was no evidence of an increase risk of wound healing complications in cediranib treated patients compared to placebo.

Other exclusion criteria:

- Patients with evidence of severe or uncontrolled cardiac disease.

- Women who are pregnant and fertile women of childbearing potential not willing to use adequate contraception for the duration of study treatment and at least 2 weeks after the end of cediranib treatment.

- Gastrointestinal (GI) impairment that could affect the ability to take, or the absorption of, oral medicines, including subacute or complete bowel obstruction.

- Previous radiotherapy within approximately 21 days prior or to anticipated start of treatment.

- Treatment with any other investigational agent within 6 weeks prior to entering the trial or treatment with any other investigational agent within6 weeks prior to entering this study.

- Persisting > Grade 2 CTCAE toxicity (except alopecia and neuropathy) from previous anti-cancer treatments. History or clinical suspicion of brain metastases or spinal cord compression.

- **Post-authorisation experience**

The presentation of above points in the RMP is largely acceptable.

Potential for harm from overdose

Cediranib is intended for use at the dose specified in the SmPC and is intended for use in combination with chemotherapy and monotherapy maintenance treatment in adult patients with PSR ovarian cancer. Cediranib does not have any particular effects or characteristics that might increase the likelihood of intentional overdose. In clinical trials, use of study medication in doses in excess of that specified in the protocol is considered to be an overdose. There is no specific treatment for cediranib overdose. Two patients were treated with 90 mg daily of cediranib in a dose-escalating study. In cases of suspected overdose, the product should be discontinued, blood pressure monitored and supportive care instituted.

Clinical studies with cediranib have reported no relevant cases of overdose.

The risk of (intentional) overdose in the treated population is considered to be low.

Potential for transmission of infectious agents

N.A.

Potential for misuse for illegal purposes

N.A.

Potential for medication errors

N.A.

Potential for off-label use

It is unlikely that cediranib will be used for non-oncologic indications according to the Applicant. Within oncology there is a potential risk that prescribers may opt to use cediranib outside of the approved indication. Such use could involve the use of cediranib as either a monotherapy or in combination with other anticancer agents for the treatment of a range of cancers where the efficacy and safety have not been formally evaluated.

The use of cediranib as monotherapy and combination treatment has been studied in a number of different tumour types. The safety profile of cediranib observed in these studies has been generally consistent with the known safety profile of cediranib 20 mg ovarian cancer maintenance treatment. Therefore, the adverse events experienced with off-label monotherapy and combination therapy use in cancers other than the proposed indication would be expected to be generally consistent with the prescribing information. Off–label use will be assessed during routine pharmacovigilance.

Specific paediatric issues

The Applicant has requested and received confirmation of the applicability of the European Medicines Agency (EMA)/Paediatric Committee (PDCO) class waiver for cediranib in the treatment of ovarian cancer.

- **Identified and potential risks**

Summary of safety concerns	
Important identified risks	Hypertension Diarrhoea Severe neutropenia Severe fatigue Gastrointestinal perforation Fistulae Arterial thromboembolism Posterior reversible encephalopathy syndrome (PRES)
Important potential risks	Symptomatic left ventricular dysfunction and cardiac failure Nephrotic syndrome Renal thrombotic microangiopathy Liver failure Effects on embryofoetal development and survival

The list of safety specifications is quite extensive and should be limited to those risks that are important in the context of RMP (i.e. inclusion of only those risks where the characteristics have not yet been fully explored).

Identified risks:

Many of the risks are class effects of VEGF signalling inhibitors and are already reasonably characterised. This might account for hypertension, severe neutropenia, fistulae and gastrointestinal perforation. For these risks routine risk minimisation via information in the SmPC might be sufficient. The Applicant should discuss this and, if appropriate, the risks should be deleted as important identified risks from the RMP.

Of note, it is agreed to classify severe fatigue and diarrhoea as important identified risks. Both were responsible for a substantial proportion of permanent discontinuations of cediranib treatment. With regard to fatigue, the pivotal ICON6 study does not provide data on the resolution of fatigue; as such, it is uncertain if the proposed management as currently indicated in the SmPC is effective. With regard to diarrhoea, 7.0% and 10.8% (in the cediranib concurrent and concurrent/maintenance arms, respectively) of patients discontinued cediranib due to diarrhoea. In ICON6, patients tended not to start anti-diarrhoeal treatment after the onset of diarrhoea (approximately half of all patients did not receive anti-diarrhoeal treatment), contrary to the recommendation in the proposed SmPC. As such, it is uncertain if the proposed risk minimisation measures (loperamide etc) are effective.

The list of important potential risks is accepted. These risks also represent class effects of VEGF signalling inhibitors; however, either no events have not been reported with cediranib in the ovarian cancer population, or the effect was considered not relevant / asymptomatic (as for left ventricular failure) and/or cases reported other risk factors and/or concomitant disease progression. Further characterisation of these important potential risks in the post-approval period is warranted.

Risks related to a specific formulation, indication or route of administration

N.A.

Risks relating to a specific target population

N.A.

Please see comments on the Summary of the safety concerns.

- **Identified and potential interactions**

Table II-41 Food interactions	
Interacting substance	**Food**
Effect of interaction	Food decreases cediranib C_{max} by 33% (94% CI: 20 to 43%) and AUC by 24% (94% CI: 12 to 34%). There was also a slight delay in the renal T_{max} with administration in the fed state
Evidence source	Study D8480C00021
Possible mechanism	Exact mechanism is not known
Potential health risk	Possible reduction of efficacy when cediranib is administered with food.
Discussion	It is, therefore, recommended that cediranib is administered at least 1 h before or 2 h after food ingestion. Section 4.2 '*Posology and method of administration*' states: "Tradename should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal."

AUC = area under the plasma concentration time curve
C_{max} = maximum plasma concentration
CI = confidence interval
T_{max} = time to maximum plasma concentration

- **Missing information**

Missing information	Use in patients with severe renal impairment Use in patients with significant haemorrhage, within 3 months or any haemoptysis Use in patients with severe uncontrolled cardiac disease Use in patients with poorly controlled hypertension Use in patients with severe hepatic impairment Use in patients with arterial thrombotic events within the previous 12 months Long term exposure to cediranib Off-label use including paediatric use

As for the missing information, although it is acknowledged that in the clinical trials several groups have been excluded, this should not by default lead to inclusion as missing information. It should be considered if the groups for which the information is missing are likely to be treated with the product and if there are plans by the applicant to address these groups in future. If the Applicant only proposes routine pharmacovigilance measures to further characterise the safety in these populations, inclusion as missing information does not seem justified. The Applicant should discuss this, and amend the list of missing information as appropriate. Long term exposure to cediranib is

accepted as missing information considering that the exposure data available for cediranib beyond 2 years is limited. The efficacy of cediranib in patients carrying a BRAC mutation and in patients receiving prior treatment with VEGF is not demonstrated and should therefore also be considered missing information (Please refer to the efficacy section question in this overview and to the list of questions).

Summary of the safety concerns

Table 28. Summary of the Safety Concerns as proposed by the applicant.

Summary of safety concerns	
Important identified risks	Hypertension Diarrhoea Severe neutropenia Severe fatigue Gastrointestinal perforation Fistulae Arterial thromboembolism Posterior reversible encephalopathy syndrome (PRES)
Important potential risks	Symptomatic left ventricular dysfunction and cardiac failure Nephrotic syndrome Renal thrombotic microangiopathy Liver failure Effects on embryofoetal development and survival
Missing information	Use in patients with severe renal impairment Use in patients with significant haemorrhage, within 3 months or any haemoptysis Use in patients with severe uncontrolled cardiac disease Use in patients with poorly controlled hypertension Use in patients with severe hepatic impairment Use in patients with arterial thrombotic events within the previous 12 months Long term exposure to cediranib Off-label use including paediatric use

As mentioned above, the list of safety specifications is quite extensive and should be limited to those risks that are important in the context of RMP (i.e. inclusion of only those risks where the characteristics have not yet been fully explored). Many of the important identified risks are class effects of VEGF signalling inhibitors and are already reasonably characterised. This might account

for hypertension, severe neutropenia, fistulae and gastrointestinal perforation. For these risks routine risk minimisation via information in the SmPC might be sufficient. The Applicant should discuss this and, if appropriate, the risks should be deleted as important identified risks from the RMP.

As for the missing information, although it is acknowledged that in the clinical trials several groups have been excluded, this should not by default lead to inclusion as missing information. It should be considered if the groups for which the information is missing are likely to be treated with the product and if there are plans by the applicant to address these groups in future. If the Applicant only proposes routine pharmacovigilance measures to further characterise the safety in these populations, inclusion as missing information does not seem justified. The Applicant should discuss this, and amend the list of missing information as appropriate. Long term exposure to cediranib is accepted as missing information considering that the exposure data available for cediranib beyond 2 years is limited. The efficacy of cediranib in patients carrying a BRAC mutation and in patients receiving prior treatment with VEGF is not demonstrated and should therefore also be considered missing information (Please refer to the efficacy section question in this overview and to the list of questions).

Pharmacovigilance Plan

Table III-13 On-going and planned additional PhV studies/activities in the Pharmacovigilance 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)
A study of cediranib in combination with standard platinum-based chemotherapy in PSR ovarian cancer patients, comparing continuous dosing with a fixed intermittent schedule, is planned. The primary objective will be to characterise cediranib tolerability, including characterisation of diarrhoea outcome by assessing the proportion of patients discontinuing cediranib treatment due to diarrhoea (Category 3).	Protocol/synopsis is being prepared and will be provided when available	Diarrhoea	Planned	TBC

TBC to be confirmed

The Pharmacovigilance plan has been updated and is considered acceptable.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risk: Diarrhoea	Appropriate wording in the SmPC: Caution advised in Section 4.4 '*Special warnings and precautions for use*' on the risk of diarrhoea, the need to start treatment at the first sign of onset and on the management of diarrhoea while on cediranib treatment. Section 4.8 '*Undesirable effects*' lists Diarrhoea (very common). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Important identified risk: Severe fatigue	Appropriate wording in the SmPC: Caution advised in Section 4.4 '*Special warnings and precautions for use*' on the risk of severe fatigue and on the management of severe fatigue while on cediranib treatment. Section 4.8 '*Undesirable effects*' lists Fatigue (very common). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Important identified risk: Arterial thromboembolism	Appropriate wording in the SmPC: Caution advised in Section 4.4 '*Special warnings and precautions for use*' that cediranib should be used in caution in patients who have a history of, or who are at increased risk of thrombotic events, and on the management of arterial thrombotic events while on cediranib treatment. Section 4.8 '*Undesirable effects*' lists Arterial thromboembolism – cerebrovascular (Common). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Important identified risk: PRES	Appropriate wording in the SmPC: Caution advised in Section 4.4 '*Special warnings*	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	and precautions for use' on the risk of PRES and on the management of PRES while on cediranib treatment. Section 4.8 '*Undesirable effects*' lists PRES (Uncommon). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	
Important potential risk: Symptomatic left ventricular dysfunction and cardiac failure	Appropriate wording in the SmPC: No specific wording on symptomatic left ventricular dysfunction syndrome is provided in Section 4.4 '*Special warnings and precautions for use*', however, caution is advised in Section 4.4 on the need to monitor blood pressure from the start of treatment and frequently throughout, and on the management of hypertension while on cediranib treatment. Section 4.8 '*Undesirable effects*' lists Left ventricular dysfunction (Uncommon). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Important potential risk: Nephrotic syndrome	Appropriate wording in the SmPC: Appropriate wording in the SmPC: No specific wording on nephrotic syndrome is provided in Section 4.4 '*Special warnings and precautions for use*', however caution is advised on the risk of hypertension and its management while on treatment with cediranib. SmPC Section 4.4 states that monitoring of proteinuria before initiation and periodically throughout treatment is recommended; and provides caution that in patients who develop moderate to severe proteinuria, temporary interruption or dose reduction of cediranib treatment should be considered. Section 4.8 '*Undesirable effects*' lists Proteinuria (very common). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk: Renal thrombotic microangiopathy	Appropriate wording in the SmPC: No specific wording on renal thrombotic microangiopathy is provided in Section 4.4 '*Special warnings and precautions for use*', however caution is advised on the risk of hypertension and its management while on treatment with cediranib. SmPC Section 4.4 provides caution that in patients who develop moderate to severe proteinuria, temporary interruption or dose reduction of Zemfirza treatment should be considered. Section 4.8 '*Undesirable effects*' lists Proteinuria (very common). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Important potential risk: Liver failure	Appropriate wording in the SmPC: No specific wording on liver failure is provided in Section 4.4 '*Special warnings and precautions for use*'. However Section 4.8 '*Undesirable effects*' lists Transaminases increased (very common) and Blood ALP increased (very common) and states that modest increases in tranasminases and ALP have been associated with cediranib. Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Important potential risk: Effect on embryofoetal development and survival	Appropriate wording in the SmPC: Caution advised in Section 4.4 '*Special warnings and precautions for use*' that cediranib should not be used during pregnancy and in women of childbearing potential not using reliable contraception; and that absorption of oral contraceptives may be impaired in cases of gastrointestinal symptoms. SmPC Section 4.6 '*Pregnancy and lactation*' provides warning on use during pregnancy and the use of effective contraception; possible impaired efficacy of oral contraceptives and the need for	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	consideration of an additional non-hormonal contraceptive method and pregnancy test during treatment with cediranib.	
Missing information Use in patients with arterial thrombotic events within the previous 12 months	Appropriate wording in the SmPC: No specific guidance relating to use in this population however Section 4.4 '*Special warnings and precautions for use*', Section 4.4 provides a caution and advises that cediranib should be used with caution in patients who are at an increased risk of thrombotic events or who have a history of thrombotic events; that cediranib treatment should be permanently discontinued in patients who develop an arterial thromboembolic event. Section 4.8 '*Undesirable effects*' lists Arterial thrombotic events-cerebrovascular (common). Section 4.2 '*Posology and method of administration*' - Statement on management of AEs.	None
Missing information Long term exposure to cediranib	Appropriate wording in the SmPC: Not applicable	None

The Applicant proposes routine risk minimisation measures for each of the safety concerns. This is considered acceptable.

PRAC Rapporteur's overall conclusion

The RMP is approvable.

Public summary of the RMP

The public summary of the RMP does not require revision.

PRAC Outcome

The PRAC considered that the risk management plan version 2 (dated 17 Feb 2016) could be acceptable if the applicant implements the changes to the RMP as stated in the section 6.

PRAC endorsed the proposed List of Question without any change at PRAC plenary meeting on 14 April 2016.

3.5. Pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

4. Orphan medicinal products

An orphan designation has been granted for this medicinal product on 2014-07-29 based on the criterion of 'significant benefit". Number in the Community Register of Orphan Medicinal Products: EU/3/14/1303.

5. Benefit risk assessment

Benefits

Beneficial effects

The study met its primary endpoint. The median PFS in the maintenance arm is statistically significant compared with the placebo + chemotherapy arm. The investigator's analysis of PFS shows a HR=0.57 (95%CI; 0.44, 0.73) in favour of the cediranib concurrent/maintenance arm (arm C). The median PFS is 8.7 months in the chemotherapy + placebo arm (arm A) compared to 11.0 months in Arm C. There was also a statistically significant improvement in PFS for the chemotherapy + cediranib concurrent arm (arm B: median 9.9 [CI 9.4-10.7] months) compared with arm A (median 8.7 months) with a HR of 0.70 (95% CI: 0.55, 0.89; p=0.004). For both the cediranib concurrent/maintenance arm and the cediranib concurrent arm no conclusions can be drawn regarding efficacy in patients who received prior treatment with VEGF therapy (only comprising 6% of the study population), although no detrimental effect emerged. The results of additionally requested sensitivity analyses, censoring patients who discontinued cediranib due to AE and censoring for the same reason in combination with proceeding to other anticancer treatment before progression, both revealed results that were consistent with the primary PFS estimate.

Analyses of overall survival suggested a benefit in OS for the cediranib concurrent/maintenance arm (median 27.9 months) compared with the chemotherapy + placebo arm (median 19.9 months). Similarly, OS was longer for the cediranib concurrent arm compared with the chemotherapy + placebo arm (median 26.7 months versus median 19.9 months). Neither of these results was statistically significant, but the study was not powered to detect a difference in terms of OS.

To demonstrate the added effect of cediranib in the maintenance phase, the Applicant performed a post-hoc analysis that included only patients that entered the maintenance phase. The PFS results showed a borderline statistically significant benefit of cediranib as maintenance treatment (median difference 1.6 months; HR=0.74, 95%CI: 0.55-1.00, p=0.045). The OS data showed a numerical difference in favour of cediranib maintenance compared to concurrent treatment only (26.5 months vs. 25.3 months).

The median time to first subsequent chemotherapy or death was statistically significantly longer for the cediranib concurrent/maintenance arm compared with the chemotherapy + placebo arm (12.0 months versus 10.2 months) as was the median time to second subsequent chemotherapy or death (17.0 months versus 14.0 months), but no significant difference was observed for the cediranib concurrent arm.

In the supportive randomized unblinded NCI8348 study, a statistically significant superior median PFS was observed for the combination arm (olaparib + cediranib), i.e. 16.5 months compared to 8.2 months in patients receiving olaparib alone.

Uncertainty in the knowledge about the beneficial effects

Initially, patients randomised to cediranib in the pivotal ICON6 study received 30 mg QD. After the first 30 patients had been recruited, the cediranib starting dose was reduced to 20 mg QD. The selection of this dose was based on the emerging clinical data from other Phase II/III cediranib studies rather than any specific tolerability issue in ICON6 and consistent with the dose used in development programmes with cediranib in combination with chemotherapy (colorectal cancer, glioblastoma, NSCLC). In ICON6, there was the option for a dose reduction to cediranib 15 mg. Anti-tumour activity of cediranib in phase 1 studies was observed at ≥ 20 mg doses; statistical analyses showed that cediranib doses of 30 mg and 45 mg resulted in greater reductions in tumour size compared with cediranib 20 mg (one sided p=0.02 and 0.03, respectively). There are no data with the 15 mg dose from the phase 1 studies. The applicant commits to perform and report exposure-response relationship from 4 ongoing trials in patients with ovarian cancer as a post approval measure.

Patients that entered the maintenance phase were younger, in better physical condition and were more likely to have had a platinum-free interval of >12 months. Patients who continued to the cediranib maintenance phase were able to tolerate cediranib long-term treatment. However, whether this is explained by the fact that these patients were in better condition, and/or there were fewer AEs in the concurrent phase, is hard to disentangle. Nonetheless, diarrhoea and fatigue are related to cediranib, and occurred more frequently in the cediranib maintenance phase.

The ICON6 study was an academic study, initiated by the Medical Research Council (MRC). In principle, the results of such a trial could be used for marketing authorisation. A routine inspection revealed issues, the impact of which can still not be fully assessed. The most important remaining issues pertain to the reliability of the data and the integrity of the database. Based on an initial concordance analysis, there were important differences between investigator assessed PFS and PFS by BICR for 15 out of 36 evaluable patients in three inspected sites (i.e. 41% discordance), questioning the reliability of the adjudication of PFS.

Risks

Unfavourable effects

There are more AEs in the cediranib arms, which is expected. The most common AEs in the cediranib arms with a significant difference compared to the chemo + placebo arm are diarrhoea, neutrophil count decreased, hypertension, decreased appetite, platelet count decreased, stomatitis, hypomagnesaemia, dysphonia and proteinuria. Many of these common AEs are recognized as AESI for other VEGF-inhibiting products. These AEs are in general manageable in the clinical setting.

More patients in the cediranib arms, i.e. the cediranib concurrent/maintenance and the cediranib concurrent arm, respectively, had dose reductions (45.6% and 32.7%) and discontinued cediranib/cediranib placebo treatment permanently (39.2% and 32.2%) than in the chemotherapy + placebo arm (discontinuation rate 13.9%).

A very high discontinuation rate was observed in patients aged ≥75 years in the cediranib concurrent/maintenance arm had AEs leading to discontinuation (84.6% vs. 39.2% overall). The lower tolerability in patients ≥75 years is now included in section 4.4 of the SmPC.

The most common reasons for discontinuation were diarrhoea and fatigue. The Applicant argues that this "*likely reflects the extended exposure to cediranib for the cediranib concurrent/maintenance in the maintenance phase of the study*".

Interactions

Pharmacokinetic data demonstrate an interaction between platin/paclitaxel co-administration and cediranib. Paclitaxel exposure was increased by 30% when cediranib was co-administered, however, no increase in peripheral motor neuropathy was observed in ICON6.

Cediranib has shown significant effects on all stages of female reproduction in rats. No interaction studies with oral contraceptives have been conducted. Effectiveness of oral contraceptives when cediranib is co-administered is uncertain because of decreased absorption due to diarrhea and induction of intestinal enzymes involved in metabolism of oral contraceptives by cediranib can not be excluded.

Cediranib should not be combined with anthracyclines in order to avoid potential cardiac toxicity. Cediranib is an anti-angiogenic agent and co-administration of anticoagulants increases the risk of severe bleeding or clotting.

Uncertainty in the knowledge about the unfavourable effects

During the conduct of the study, blood transfusions were not recorded as SAE, but as concomitant medication. However, as there were very few and a similar number of blood transfusions, anaemia, anaemia SAE and Hb < 8g/dL in each arm, the impact on the safety profile is considered low.

It was found that not every Grade 3 or 4 neutropenia were reported as SAEs. However, only few Grade 3 or 4 neutropenia led to hospitalisation. Neutropenia was reported more frequently in the maintenance arm: 51.3% chemo-arm, 69.9% concurrent and 70.3% maintenance arm. Also Grade 3 and 4 were reported more frequently in the maintenance arm than in the concurrent and chemo-alone arm, 12.7% vs. 8.2% and 3.5% respectively. The number of patients being hospitalised due to neutropenia is similar between the chemo-alone and the concurrent arm (4.3% vs. 4.1%), but is relatively higher in maintenance arm (8.2%). Very few cases of neutropenia led to discontinuation. It was pointed out that not all (or the lowest) nadir neutropenia were reported, although the CRF had requests for reporting of unscheduled blood samples. The post-unblinded monitoring activity did not include monitoring of lab results. Despite the higher number of neutropenia in the concurrent and maintenance arm, it seems clinically manageable and only few events led to hospitalisation, however, there seems to be a lack of reporting nadir neutropenia. Thus, nadir neutropenia is most likely underreported.

AE start dates were only collected for SAEs, thus, the study visit on which the AE was reported was used to determine events that were included in summaries. Furthermore, changes in CTCAE grade and AE resolution dates were not recorded for non-serious AEs. This means that it is not possible to assess non-serious AEs duration or outcome. Also, the Applicant claims that there may have been an over-reporting AEs. It seems that when an SAE was reported or an SAE led to treatment discontinuation, all the associated symptoms were also coded as AEs. Last but not least, CTCAE v.3 was used at the study onset but was changed to CTCAE v.4. This could have an impact and led to inconsistency of allocated AE grades throughout the trial. These issues together are considered a weakness of the safety database.

Some SAEs were re-classified by the sponsor, MRC. According to the Applicant, in total 50 SAEs were reclassified by the sponsor, who was blinded to treatment arm. However, the majority of the SAEs (34 events) were related to progression of disease or AEs. If the issues regarding SAE only pertain to these 50 reclassified SAE, and the events were already in the safety database, the reclassification of the AEs would not give rise to any major concern with regard to the robustness of the safety database. However, it has not been made clear by the applicant how was determined

which (S)AEs were not properly classified and as a consequence, how it can be assured that the need for reclassification of SAE only pertains to these 50 events. This raises uncertainty on the completeness of the safety database.

The pharmacological mode of action for Cediranib seems very unspecific as the compound binds to multiple targets, besides VEGFs. Potential outcome of this should be discussed in relation to the multitude of toxicological effects seen in non-clinical species.

It is unclear why so many patients discontinued due to diarrhoea and fatigue. The Applicant suggests that these adverse effects were not managed adequately in the ICON6 study. However, it is unclear whether they can be managed better without discontinuation of treatment, if managed according to the instructions in the SmPC. The Applicant provided a number of possible explanations (shortcomings in instructions to patients, reluctance to prescribe loperamide to avoid constipation, suboptimal adherence to guidelines for management of AEs). It is likely that the toxicity profile in ICON6 reflects the situation if cediranib would be used in clinical practice, which is of concern. A relationship was found between the average cediranib plasma concentration and the probability of observing higher grade diarrhoea and hypertension. Pharmacokinetics of cediranib is highly variable, and body weight and age could explain the variability to a small extent. Variability in metabolic pathways of cediranib has not been explored sufficiently. Also, the interaction potential of cediranib and metabolites with other medicines needs further investigation.

No exposure-adjusted analysis for permanent discontinuations is provided. The Applicant is asked to provide this analysis and discuss the results. The Applicant is also asked to clarify how many AEs leading to permanent discontinuation resolved with/without sequelae-, and how many that did not resolve. Also, the Applicant is asked to present data on the time from discontinuation of cediranib concurrent and cediranib concurrent/maintenance to progression of disease or death. Most of the AEs are manageable in the clinical setting, but the impact on QoL is uncertain, due to insufficient collection of QoL-data.

The majority of deaths seems to occur in the Post-treatment follow-up period and the majority seems to be related to the underlying disease, where there is a clear difference in favour of Arm B and C. There is a small difference between Arm B and C, but it is not considered substantial (33.9% vs. 31.1%). However, a considerable number of deaths are classified as “Other”, where there is a considerable higher frequency in the cediranib arms. The Applicant is asked to clarify what is meant by “Other”. Furthermore, the Applicant is asked to present data (incl. reasons) on non-PD deaths <90 days post-treatment, and discuss any difference.

Cediranib was less tolerated in patients with moderate renal impairment resulting in more AE related cediranib discontinuations. There are limited efficacy and safety data in patients with severe renal impairment. Cediranib is mainly eliminated by metabolism. Data suggest that patients with moderate hepatic function are at risk for higher cediranib exposure. Patients with moderate hepatic impairment were not included in ICON6.

Effects Table

Table 29. Effects Table for cediranib for the treatment of patients with epithelial ovarian, fallopian tube or serous primary peritoneal carcinoma that have encountered PD after 1st line platinum-containing chemotherapy (ICON6 study; data cut-off: 19 April, 2013)*.

Effect	Short Description	Unit	Treatment		Control	Uncertainties / Strength of evidence	References
			Conc / maintenance	concurrent			
	Favourable Effects						
invPFS	Investigator assessed PFS	HR	0.57 CI 0.44-0.73	0.70 CI 0.55-0.98		Nonuniform conduct of the trial and potential bias due to post-unblinding data handling question the validity of the PFS results; BRAC status unknown; effect in patients receiving prior VEGF therapy unknown.	
Median PFS	Median Investigator assessed PFS	Months	11.0	9.9	8.7	limited number of planned scans, potential bias, limited retrospective blinded independent central review	
OS	Overall survival	HR	0.84; CI 0.63-1.11	0.95; CI 0.72-1.24		p>0.05	
Median OS	Median overall survival	Months	27.9	26.7	19.9		
	Unfavourable Effects						
SAE	Serious adverse events	%	38.0	36.8	33.9	Incomplete safety profile (neutropenic events incompletely recorded; blood transfusions not recorded.	
AE leading to permanent discontinuation of cediranib		%	39.2	32.2	13.9		
neutropenia		%	70.3	69.9	51.3	neutropenic events incompletely recorded	
diarrhoea		%	93.0	87.1	65.2	Uncertain whether proposed measures to treat diarrhoea and fatigue are effective in	

Effect	Short Description	Unit	Treatment		Control	Uncertainties / Strength of evidence	References
			Conc / maintenance	concurrent			
						preventing discontinuation	
fatigue		%	97.5	91.2	91.3		
hypertension		%	59.5	62.0	37.4		
Neutrophil count decreased		%	70.3	69.0	49.6	neutropenic events incompletely recorded	
proteinuria		%	28.5	21.1	12.2		
Bleeding/haemorrhage		%	31.6	22.8	13.0		

Abbreviations: conc: concurrent, maint: maintenance. *for OS, results emerged from updated analyses (data cut-off: 1 November 2014).

Balance

Importance of favourable and unfavourable effects

Carboplatin or cisplatin in combination with a taxane is the standard, first-line treatment for ovarian cancer. Despite responding to treatment, approximately 70% of patients subsequently relapse and experience disease progression. When ovarian cancer relapses ≥ 6 months after completion of initial platinum-based chemotherapy, patients are defined as having platinum sensitive relapsed (PSR) disease. For these patients, a second course of treatment with platinum-based combination chemotherapy is the standard of care. Traditionally, this is a poor prognosis population with a short expected OS, usually <12 months. Often platinum-based chemotherapy is repeated, but there is a need for additional therapies. Several choices of treatment exist for these patients, among which bevacizumab. Cediranib is a VEGF signalling inhibitor that targets all 3 VEGF receptors which can be given orally, not only concomitantly with chemotherapy, but also thereafter. However, bevacizumab given as concurrent/maintenance treatment added to platinum-based chemotherapy in the same setting (study AVF4095g: patients with platinum-sensitive, recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer) resulted in a larger median PFS benefit (4.0 months (12.4 vs. 8.4 months.) and similar HRs. The only difference is that in study AVF4095g, patients were not allowed to be pre-treated with bevacizumab or another VEGF targeting agent. In ICON6, 28 patients (6.1%) had received bevacizumab as part of first line chemotherapy with no indications that the treatment effect of cediranib would be different, though this is based on a very small subpopulation.

PFS was the primary outcome in the pivotal ICON6 study with OS as secondary outcome, which is considered acceptable to assess the efficacy of cediranib in this situation provided that the estimated treatment effect on OS ensures that there are no relevant negative effects on this endpoint. PFS results show a benefit for cediranib, both for the cediranib concurrent/maintenance arm (median PFS 11.0 vs. 8.7 months; p<0.001) and for the cediranib concurrent arm (median PFS 9.9 vs. 8.7; p=0.004). Various sensitivity analyses confirmed the benefit observed in the primary analysis. However, the PFS benefit is considered modest specifically in relation to the long duration of treatment (i.e. 18 months in the concurrent/maintenance arm). In addition, concerns remain about the integrity of the database and reliability of the PFS assessment. OS results (updated analysis at 74% maturity) appear to point towards an improvement for patients treated with cediranib compared to placebo, although not statistically significant at this interim stage (a 6.8 and 8.0 months difference in favour of cediranib concurrent and concurrent/maintenance therapy, respectively). This is in line with the HRQOL not deteriorating in both experimental study arms compared to the control arm.

The safety and tolerability profile of Cediranib observed in ICON6 and other studies are more or less consistent with the class effects known for VEGF inhibitors. Typical AEs such as hypertension, proteinuria, diarrhoea and bleeding/haemorrhage were relatively common in the cediranib arms. However, concerns remain about the completeness of the safety database (reporting of SAE; reporting of neutropenia). Furthermore, a high proportion of patients in both cediranib arms (i.e. 32% concurrent and 39% concurrent/maintenance), permanently discontinued cediranib treatment due to an AE with diarrhoea and fatigue being the most frequent reasons to stop treatment. This is considered important, because the in the SmPC proposed or additional measures have not shown to be effective in prevention of discontinuation. For comparison, with bevacizumab a discontinuation rate of 19.8% has been reported in a similar patient population.

Benefit-risk balance

The estimated benefit in terms of median PFS of 2.3 months for patients receiving cediranib as concurrent and maintenance treatment may be clinically relevant since it is accompanied by no detrimental effect on OS and (in principle) manageable toxicity. The unfavourable effects of treatment were consistent with the class effects known for VEGF inhibitors and manageable, as was reflected by the observation that HRQOL did not deteriorate in the cediranib concurrent/maintenance arm, but the number of drop-outs was relatively high. The benefit already occurs when given concomitantly with chemotherapy, although the observed PFS benefit (1.1 months increase in median PFS) is considered too modest to justify the associated toxicity. Additional benefit may be obtained by maintenance therapy although further discontinuation due to side effects may occur. Therefore, the benefit/risk of maintenance therapy may be questioned as no statistically significant add-on effect is demonstrated vs. concurrent therapy. This is important, since the median duration of exposure to cediranib was 18 months in ICON6. However, since the added benefit seems to be partly derived from the maintenance phase (see sensitivity analyses), the appropriate comparison with the chemo + placebo arm could be justified.

The overall B/R of cediranib is not considered positive at this stage due to issues pertaining to the reliability of the data and the integrity of the database and the modest PFS benefit in relation to the substantial toxicity and the duration of treatment.

Discussion on the benefit-risk assessment

The modest benefit in terms of median PFS of 2.3 months for patients receiving cediranib as concurrent and maintenance treatment may be clinically relevant since it is accompanied by no detrimental effect on OS and HRqOL and (in principle) manageable toxicity. In this respect, the unfavourable effects of treatment were consistent with the class effects known for VEGF inhibitors. However, treatment duration is long and the number of discontinuations relatively high. The difference in PFS already occurs when given concomitantly with chemotherapy, although the observed PFS benefit (1.1 months increase in median PFS) in this arm is too limited to be considered of clinical relevance in relation to the toxicity profile.

The Applicant has undertaken several activities to validate the ICON6 database. All sites including at least one patient were subjected to a post-Source Data Verification (SDV) by an independent third-party, which were able to verify data from 97% of the patients. All sensitivity analyses performed (including planned analyses by the Applicant as well as post-hoc analyses, some of which requested by the CHMP) were all consistent with the primary analysis of PFS. However, after unblinding, the SDV process was initiated to verify data collected in the CRF and transferred to the database against real source data. Importantly, the post-unblinding monitoring activity did not include laboratory results or scans (CT or MRI). The Applicant is asked to comment on this.

The high discordance rate of (41%) observed in three study sites based on an initial concordance analysis introduce uncertainty about the adjudication of PFS. The impact of the GCP issues on the primary and secondary efficacy and safety analyses should also be discussed. In the supportive study, NCI 8348, cediranib added to olaparib only showed a difference in PFS in patients with wild type or unknown BRCA status. No data on BRCA status were provided for the ICON6 study.

With the proposed indication, cediranib could be used in PSR OC patients that are previously treated with anti-VEGF treatments while very few patients with prior exposure to anti-VEGF treatment were included in the pivotal study. Therefore, the indication wording should be revised as proposed below:

Zemfirza in combination ***with carboplatin and paclitaxel*** *followed by maintenance monotherapy is indicated for the treatment of adult patients with platinum sensitive relapsed (PSR) ovarian cancer (including fallopian tube or primary peritoneal),* ***who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.***

According to EMA guideline for a single pivotal study, in this case the ICON6 study (CHMP/EWP/2330/99), the minimum requirement for one pivotal study (ICON6) is that it should provide exceptionally compelling evidence with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency. This requirement is not considered met for the time being, because of uncertainties about the completeness and integrity of the database used for the analyses as presented. Specifically, concerns remain about the assessment of the primary outcome PFS and of the safety database (reporting of SAE; reporting of nadir neutropenia). This needs to be discussed further.

5.1. Conclusions

Cediranib have a different mechanism of action than bevacizumab, and alternative treatment options are highly welcomed in a patient population with relapsed disease.

However, the application is currently not approvable, as the overall B/R of cediranib is not considered positive at this stage due to remaining issues pertaining to the reliability of the data and the integrity of the database and the modest PFS benefit in relation to the substantial toxicity leading to discontinuation of treatment.