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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Variation assessment report

Invented name: Caprelsa

International non-proprietary name: vandetanib

Procedure No. EMEA/H/C/002315/II/0016

Marketing authorisation holder (MAH): Genzyme Europe BV



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List of abbreviations

AE(s): Adverse event(s)

ALT: Alanine aminotransferase

AST: Aspartate aminotransferase

AUC(0-24h): Area under the plasma concentration-time curve from zero to 24 hours post dose

AUC(0-t): Area under the plasma concentration-time curve from zero to time t post dose

BSA: Body surface area

CEA: Carcinoembryonic antigen

CL/F: Total body clearance of drug from plasma

C_{max} : Maximum concentration

C_{min}: Minimum concentration

CR: Complete response

CSP: Clinical study protocol

CSR: Clinical study report

CTC: Common toxicity criteria

CTCAE: Common terminology criteria for adverse events

CTN: Calcitonin

CV Coefficient of variation

DBP: Diastolic blood pressure

DLT(s): Dose-limiting toxicity(ies)

EGFR: Endothelial growth factor receptor

FDA: Food and Drug Administration

IND: Investigational new drug

IRB: Institutional review board

LD: Longest diameter

MEN: Multiple endocrine neoplasia

MRI: Magnetic resonance imaging

MTC: Medullary thyroid carcinoma

MTD: Maximum tolerated dose

NCI: National Cancer Institute

NIH: National Institute of Health

NOS: Not otherwise specified

ORR: Objective response rate

OS: Overall survival

P Pre-dose

PBPK: Physiologically based pharmacokinetics

PD: Pharmacodynamic(s)

PFS: Progression-free survival

PI: Principal Investigator

PK: Pharmacokinetic(s)

PR: Partial response

QTc: Corrected QT interval

QTcB: QT interval corrected for heart rate by Bazett's method

RECIST: Response evaluation criteria in solid tumours

RET: Rearranged during transfection

RTK: Receptor tyrosine kinase

SAE(s): Serious adverse event(s)

SD: Standard deviation

SE: Standard error

SGOT: Serum glutamic oxaloacetic transaminase

SGPT: Serum glutamic pyruvic transaminase

Tmax: Time to maximum plasma concentration

ULN: Upper limit of normal

VEGFR: Vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 17 July 2015 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of Indication to include paediatric patients aged 5 to 18 with unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC) for Caprelsa; as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information from studies IRUSZACT0098, ISSZACT0004, IRUSZACT0051 and IRUSZACT0061. The Package Leaflet and Risk Management plan (v.12.1) are updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and Risk Management Plan.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0285/2013 the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0285/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0285/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

Additional marketing exclusivity

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation

(EC) No 726/2004 - One year of market protection for a new indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pierre Demolis Co-Rapporteur: Paula Boudewina van Hennik

Timetable	Actual dates
Application submitted on :	17 July 2015
Rapporteur's preliminary assessment report circulated on:	19 October 2015
CoRapporteur's preliminary assessment report circulated on:	19 October 2015
Joint Rapporteur's updated assessment report circulated on:	13 November 2015
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 November 2015
MAH's responses submitted to the CHMP on:	28 January 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	14 March 2016
2 nd Request for supplementary information and extension of timetable adopted by the CHMP on:	01 April 2016
MAH's responses submitted to the CHMP on:	24 May 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	08 June 2016
Updated Rapporteur's assessment report circulated on:	14 June 2016
3 rd Request for supplementary information and extension of timetable adopted by the CHMP on:	23 June 2016
MAH's responses submitted to the CHMP on:	10 August 2016
The marketing authorisation for Caprelsa was transferred to Genzyme Europe BV on:	08 September 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	13 September 2016
PRAC RMP advice and assessment overview adopted by PRAC on:	29 September 2016
4 th Request for supplementary information and extension of timetable adopted by the CHMP on:	13 October 2016
MAH's responses submitted to the CHMP on:	13 October 2016

Timetable	Actual dates
The MAH submitted a request for consideration of one additional year of market protection in accordance with Article 14(11) of Regulation (EC) No 726/2004. The MAH informed the EMA of their intention to not submit an application for an extension of the supplementary protection certificate <i>as per</i> Article 36 of Regulation (EC) No 1901/2006.	13 October 2016
Joint Rapporteur's updated assessment report on the MAH's responses circulated on:	02 November 2016
CHMP opinion:	10 November 2016
The CHMP adopted a report on similarity of Caprelsa and Cometriq on: (Appendix 1)	10 November 2016
The CHMP adopted a report on the significant clinical benefit for Caprelsa in comparison with existing therapies on: (Appendix 2)	10 November 2016

2. Scientific discussion

2.1. Introduction

Problem statement

About the disease

Aggressive and symptomatic medullary thyroid cancer (MTC) in children and adolescents with unresectable locally advanced or metastatic disease.

Medullary Thyroid Carcinoma (MTC) is a rare, calcitonin (CTN)-producing tumour that arises from the parafollicular cells (C-cells) of the thyroid. According to the American Joint Committee on Cancer (AJCC), locally advanced and metastatic tumours are classified under Stage III-Stage IVA-IVB, and Stage IVC (M1 – distant metastasis present) respectively.

The terms “symptomatic and aggressive” disease correspond to a rapid deterioration of clinical condition (clinical, biological and radiological signs) i.e., patients at urgent need of treatment.

Carcinoma of the thyroid is the most common malignancy of the endocrine system and includes mostly (85%–95%) well-differentiated tumors (papillary or follicular). About 2.5% to 10% of thyroid cancers are medullary carcinoma and other are anaplastic.

The incidence rates of medullary thyroid cancer (MTC) is 0.11 per 100 000 person-years with no noted substantial differences by race/ethnicity and sex, respectively (ESMO Guideline). MTC presents mainly as a sporadic cancer (70-75% of cases) or as part of a hereditary syndrome (25-30%). The age-adjusted death rate was 0.5 per 100 000 men and women per year in the US (Howlader N et al. Surveillance, Epidemiology, and End Results registry of the National Cancer Institute (SEER) Cancer Statistics Review 1975–2008).

Hereditary MTC is divided into 3 distinct clinical subtypes. Multiple endocrine neoplasia (MEN) 2A, or Sipple's syndrome, is the most common subtype, accounting for approximately 70% to 80% of patients with hereditary MTC. MEN 2B is less common than MEN 2A, accounting for approximately 5% of MTC

cases. Familial MTC is the third clinical subtype of inherited MTC. It accounts for 10% to 20% of hereditary MTC cases.

Paediatric thyroid cancer is rare, and among these cases, medullary thyroid cancer is even rarer, making up about 5% of paediatric thyroid cancer cases (Gerber et al 2015, Hogan et al 2009). Based on data from the SEER collected between 1975 and 2012 within the broad age range of zero to 20 years, the incidence of thyroid cancer has been slowly increasing over a number of years for unknown reasons, with a more marked apparent increase within the past decade. If the current incidence of all types of thyroid cancer in this age range is taken as approximately 1.0 per 100 000 persons at risk, and if medullary thyroid cancer makes up 5% of those cases, the incidence of medullary thyroid cancer is currently about 0.05 per 100 000 persons at risk. The sporadic form of MTC generally occurs mainly in adults with a very low incidence in children. Many paediatric cases of MTC arise from new, sporadic germline mutations in the RET gene and children also present in the context of a history of RET-mutation-dependent familial cancers, such as those seen in the Multiple Endocrine Neoplasia (MEN) syndromes (Waguespack, 2011).

All familial forms of MTC and MEN 2 are inherited in an autosomal-dominant fashion. Mutations in the RET proto-oncogene are found in at least 95% of kindreds with MEN 2A and 88% of familial MTC (NCCN Guideline, 2016). RET was also found to be mutated in some tumours of patients with sporadic MTC, and patients with RET mutations (especially the common M918T mutation).

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

Patients with MEN 2A typically present with a thyroid nodule or neck mass by 15 to 20 years of age but MTC can appear as early as 5 years of age (Eng et al 1996, Brandi et al 2001, Kouvaraki et al 2005). MEN 2B is characterised by a clinically more aggressive form of MTC that is manifest at a younger age (second decade) and can be detected in children as young as 1 year of age. Familial MTC is less aggressive and has an older age at onset, usually between 20 and 40 years of age, compared to MEN 2A and 2B (Farndon et al 1986, Eng 1999). The sporadic form of MTC most often presents in middle-aged patients as a solitary nodule in the thyroid.

Hogan et al worked with the SEER database (1973 to 2004) to summarize 1753 cases of paediatric thyroid cancer. The authors report that patients with medullary thyroid cancer had a 96% 5-year survival, and an 86% 15-year as well as 30-year survival (Hogan et al 2009).

The tumour is relatively unresponsive to conventional doses of radiation therapy and standard or novel chemotherapeutic regimens (Wu et al 1994, Di Bartolomeo et al 1995, Marsh et al 1995, Modigliani et al 1998, Kebebew et al 2000, Nocera et al 2000, Brandi et al 2001, Quayle and Moley 2005). Surgery is the only standard treatment and patients with MTC can only be cured by thyroidectomy, but only if the tumour has remained confined to the thyroid gland. Early recognition through genetic screening and detection of one of the characteristic mutations, followed by prophylactic thyroidectomy, has become the standard of care (Wells and Skinner 1998, Peczkowska et al 2005).

The treatment practices for children with MTC are identical to those for adults. Chemotherapy has not been shown to have a benefit in children with MTC, and there is currently no standard treatment for children who have metastatic or unresectable disease.

About the product

Caprelsa (Vandetanib) is a small molecule belonging to the class of receptor tyrosine kinase (RTK) inhibitors that potently inhibits vascular endothelial growth factor receptor (VEGFR)-2 (VEGFR-2 also known as kinase insert domain containing receptor [KDR]), epidermal growth factor receptor (EGFR) and

RET tyrosine kinases. Vandetanib is also a sub-micromolar inhibitor of vascular endothelial receptor-3 tyrosine kinase.

Caprelsa was granted EU approval on the 17th of February 2012 for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in adult patients with unresectable locally advanced or metastatic disease.

The MAH applied for an extension of indication to include the treatment of medullary thyroid cancer (MTC) in paediatric patients with unresectable locally advanced or metastatic disease.

The proposed indication for Caprelsa in the paediatric population is as follows:

“Caprelsa is indicated for the treatment of children ages 5 to 18 years of age with unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC).”

The final agreed indication is as follows:

“Caprelsa is indicated for the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in patients with unresectable locally advanced or metastatic disease.

Caprelsa is indicated in adults, **children and adolescents aged 5 years and older**.

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

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

An Environmental Risk Assessment (ERA) has previously been submitted as part of the initial MA application. Due to the low percentage (1.8%) of new cases of thyroid cancer for patients below 20 years old reported in the US SEER between 2008 and 2012 a significant increase in the environmental exposure is not anticipated. Therefore, a revised ERA for vandetanib was not provided by the MAH.

2.2.2. Conclusion on the non-clinical aspects

The justification provided for the lack of ERA studies is considered acceptable.

Non-clinical study reports for one month and six month oral toxicity studies in rats and one month toxicity study in dogs had previously been provided. These study reports showed that daily dosing of vandetanib for 1 month resulted in a dose-related dysplasia of the epiphyseal growth plates of the femoro-tibial joint in rats and in the femur of dogs, and that these changes were reversible following a 4-week recovery period. The dysplasia is considered to be a consequence of VEGF receptor inhibition (see SmPC section 5.3). Paediatric adverse event reports will be closely monitored and specific adverse drug reaction form will be provided to the health care professional to solicit information specific to growth, bone and teeth development in the patient (see Clinical safety and RMP).

2.3. Clinical aspects

2.3.1. Introduction

To support the use of vandetanib in paediatric patients, the MAH has provided data from an NCI-sponsored study (Study IRUSZACT0098; Study 98; IS-Study 98) and from three investigator-sponsored studies in different indications (see below). Furthermore, PK data from the pivotal study in adults with MTC (Study 58]) were also provided.

IRUSZACT0098 (Study 98): A dose-finding, intra-patient dose-escalation, non-controlled, single-arm, single-agent, open-label, single-institution trial to evaluate pharmacokinetics, safety and activity of vandetanib in children from 5 years to less than 18 years of age with unresectable, recurrent or metastatic hereditary medullary thyroid carcinoma
ISSZACT0004 (Study 04): 'A Phase I Study of the Combination of Vandetanib and Dasatinib Administered During and After Radiation Therapy in Children with Diffuse Intrinsic Pontine Glioma (DIPG)'
IRUSZACT0051 (Study 51): 'A Phase I Clinical Trial of Vandetanib (ZD6474, Zactima) Administered Concurrently with Local Radiation Therapy in the Treatment of Paediatric Patients with Newly Diagnosed Diffuse Brainstem Glioma'
IRUSZACT0061 (Study 61): 'A Phase I Study of ZACTIMA (ZD6474) Alone and in Combination with Retinoic Acid in Patients with Relapsed or Refractory Neuroblastoma and Medulloblastoma'.

GCP

The main study IRUSZACT0098 (Study 98) was performed in accordance with GCP as claimed by the applicant.

2.3.2. Pharmacokinetics

Pharmacokinetics data are available from study 98. Two paediatric studies in glioma-related indications (ISSZACT0004 [Study 04], and IRUSZACT0051 [Study 51]) provide additional pharmacokinetic data in paediatric patients. In all paediatric patients, vandetanib was dosed was on the basis of their Body Surface Area (BSA).

Table 1: Age of patients and dosing range in paediatric patient studies

Study	Mean age years	Standard deviation	Min-Max years	Starting dose mg/m ² /day (N)
98 ^a	14.2	2.6	9-17	100 (15) 150 (1)
04	6.1	3.8	2-17	65 (22) 85 (3)
51	6.9	3.8	2-16	50 (3) 65 (3) 85 (3) 110 (16) 145 (10)

Data from CSRs for Study 98, Study 04, and Study 51.

a. Mean (SD) age of the 10 patients with PK data was 14.1 (2.6) years. All patients with PK data started on the 100 mg/m²/day dose

Study IRUSZACT0098 (study 98)

Method

Details on the Method are presented under 'clinical efficacy'.

The primary PK Objective was to assess the PK of vandetanib at steady state (end of Cycle 2; a cycle was defined to facilitate study assessments as 28 days, although vandetanib was dosed continuously throughout each treatment cycle) in children and adolescents with hereditary MTC.

PK data were collected in Cycle 2 (Day 28) and Cycle 3 (Day 1), and trough concentrations at cycle 1 day 2, predose cycle 4 and 5.

Starting dose of vandetanib in paediatric patients with MTC was 100 mg/m² with the option to increase the dose to 150 mg/m² after 8 weeks.

Results

Sixteen patients were enrolled and received treatment with vandetanib. The initial dose was 100 mg/m²/day for 15 patients and 150 mg/m²/day for 1 patient. Based on a 70 kg /150 cm adult female (BSA equivalent to 1.65 m²), doses of 100 mg/m²/day and 150 mg/m²/day are equivalent to 55% and 82% respectively of the fixed adult daily dose of 300 mg daily. Limited intra-patient dose escalation was allowed in the 100 mg/m²/day group (an option to escalate to 150 mg/m²/day 12 after 2 or 3 months treatment at 100 mg/m²/day). PK data were only collected in Cycle 2 (Day 28) and Cycle 3 (Day 1), and the available PK data could only be analysed for 10 patients, all of whom had received a dose of 100 mg/m²/day; however, 6 of the 15 patients who started at a dose of 100 mg/m²/day had a later dose escalation to 150 mg/m²/day. The one patient who started vandetanib at 150 mg/m²/day remained on this dose during the study.

All 16 patients completed Cycle 1 and 15 patients completed both Cycles 1 and 2; the remaining patient did not complete Cycle 2 due to disease progression. The available PK data could only be analysed for 10 patients, all of whom had received a dose of 100 mg/m²/day.

Although Study 98 was protocolled to recruit patients aged 5 to 18 years, the actual age range of the patients recruited was 9 to 17 years, with a lowest BSA of 0.90 m².

The PK analysis included data from plasma samples drawn during Cycle 2, Day 28 and Cycle 3, Day 1, using the long-term stability window of 3 years. Based on the limited PK data, no trends in the potential effects of age or body weight on vandetanib exposure were observed. The absorption of vandetanib was slow and prolonged with a t_{max} of 6 hours (range: 1 to 24 hours). Steady state levels of vandetanib in

plasma were approached after 2 months of dosing (i.e., Cycle 2, Day 28). There was moderate inter-patient variability in the PK parameters assessed.

This patient population received a median of 750.0 days of treatment during the study, which was equivalent to a median treatment duration of 24.6 months. The majority of patients were able to maintain a dose of 100 mg/m²/day or greater during the study (13 patients [81.3%]). Only 1 patient started vandetanib at 150 mg/m²/day.

There was a moderate inter-patient variability in exposure to vandetanib with a Coefficient of variation (CV) for AUC₀₋₂₄ and C_{max} of 27.4% and 25.6%, respectively (Table below). The total body clearance of drug from plasma (CL/F) was relatively low with moderate inter-patient variability (geometric mean [CV%] value of 8.83 L/h [33.7%]).

Table 2 Summary of PK parameters of 100 mg/m²/day vandetanib at steady-state in paediatric patients with MTC (Study 98)

Parameter	Summary statistic	Vandetanib (N=16)
AUC ₀₋₂₄ (ng h/mL)	n	10
	Geometric mean	15438
	CV (%)	27.4
C _{max} (ng/mL)	n	10
	Geometric mean	739.0
	CV (%)	25.6
C _{min} (ng/mL)	n	12
	Geometric mean	602.0
	CV (%)	33.1
t _{max} (h)	n	10
	Median	6.0
	Range	1 to 24
CL/F (L/h)	n	10
	Geometric mean	8.8
	CV (%)	33.7

Source: Table 11.2.10 Study 98 CSR.

Note: PK analysis included values from Cycle 2, Day 28 and Cycle 3, Day 1.

AUC₀₋₂₄: area under the plasma concentration-time curve from zero to 24 hours post dose; CL/F: total body clearance of drug from plasma; C_{max}: maximum concentration; C_{min}: minimum concentration; CV: coefficient of variation; t_{max}: time to maximum plasma concentration.

Due to the low number of patients in Study 98, analyses of PK by intrinsic factors (e.g., race, sex and renal or hepatic impairment) and extrinsic factors (e.g., food, alcohol use, tobacco use and drug:drug interactions) have not been performed. Based on the limited PK data available from Study 98, no effect on the PK of vandetanib was found for patient's age or body weight when vandetanib was dosed as 100 mg/m² (Figure below).

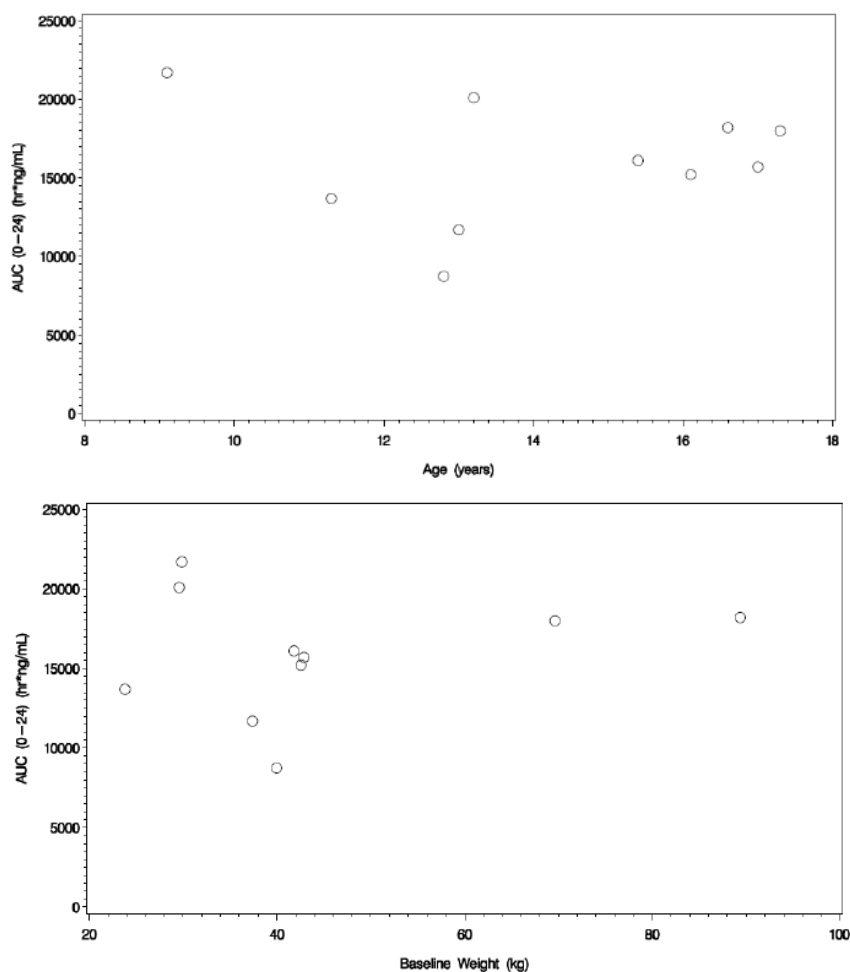
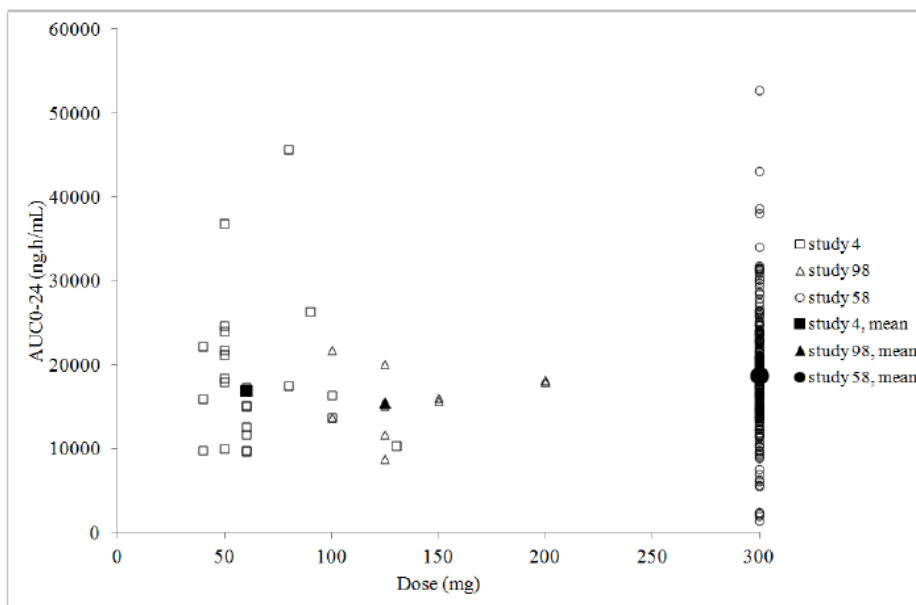


Figure 1: Effect of age (top) and bodyweight (bottom) on the steady-state exposure of vandetanib in paediatric patients with MTC dosed 100 mg/m² vandetanib (study 98)

Comparison vandetanib exposure in paediatric patients and adult patients with MTC

In the paediatric MTC study, Study 98, the initial dose of vandetanib was 100 mg/m²/day. This is approximately equivalent to 60% of the fixed adult daily dose of 300 mg daily. The average vandetanib exposure was 15% lower in paediatric patients dosed 100 mg/m² compared to adults dosed 300 mg, but there is a complete overlap in exposure (Figure 2). Further, no effect on the PK of vandetanib was found for patient's age or body weight in paediatric patients with MTC when vandetanib was dosed as 100 mg/m².



Source: Response to EMA/PDCO Modification Summary Report (EMA-000052-PIP01-07-M03) dated 27

Figure 2 Individual and geometric mean AUC0-24 at steady state for paediatric patients in Studies 04 (65-85 mg/m²/day) and 98 (100 mg/m²/day) and adults patients with MTC (Study 58, 300 mg once daily) versus dose

2.3.3. PK/PD modelling

PopPK analysis

A non-linear mixed-effects modelling approach was used to compare adult PK data (Study 58) to paediatric data collected in MTC patients (Study 98). A total of 130 plasma concentrations were available for the analysis from Study 98 compared with 1624 samples from Study 58.

The aim of the analysis was to assess whether the adults and paediatric patients share the same population PK model with the same covariate structure. A bayesian approach was employed, which made use of the adult Study 58 population parameter estimates and uncertainty in estimate distributions as priors. However back-extrapolation of the adult covariate model resulted in an under-prediction of PK parameters in paediatric patients.

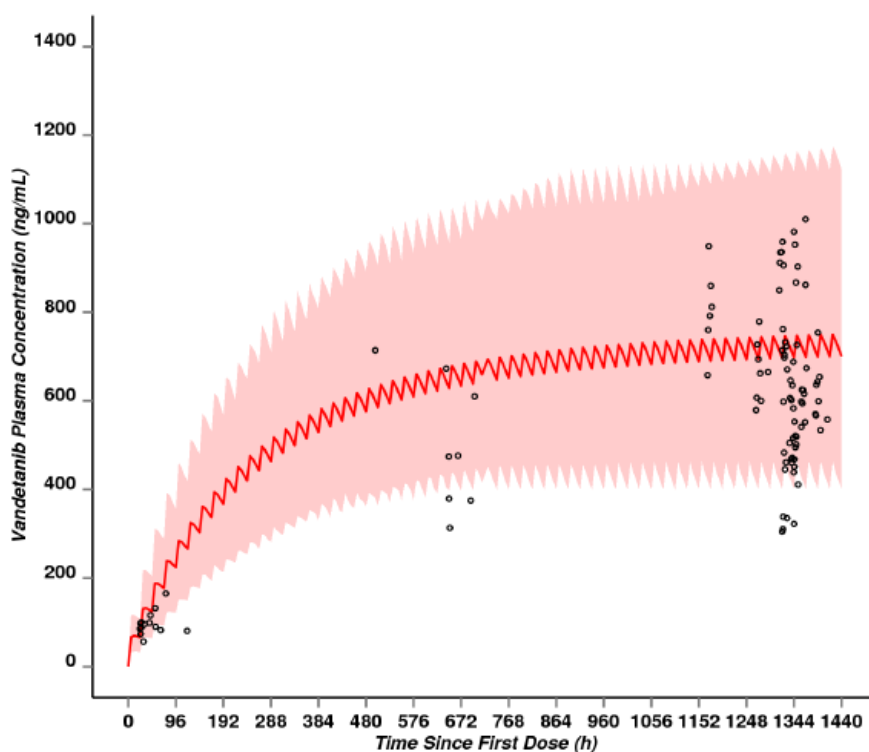
PBPK modelling

In study 98 no patients younger than 9 years were included, therefore, PBPK modeling was used to estimate the difference between paediatric patients 5-9 years and 9-17 years of age using data collected in Studies 04, 51 and 98.

A Simcyp model was previously developed to predict adult PK of vandetanib. Observed plasma concentration data at 100 mg/m² dose level from IS-Study 98 was used to compare and evaluate the physiologically based pharmacokinetics (PBPK) modelling was used to predict exposures in MTC patients aged 5 to 9 years PBPK model simulated plasma concentration. Due to limited individual plasma concentration data being available from IS-Study 4 and IS-Study 51, these studies were not used for comparison in this analysis. Individual plasma clearance values were available from IS-Study 4 and this data was used to compare CL values predicted based on PBPK model.

The PBPK model that described pharmacokinetics in adult population was used to simulate PK in paediatric population consisting of 9 to 18 years old. The paediatric module in Simcyp population based

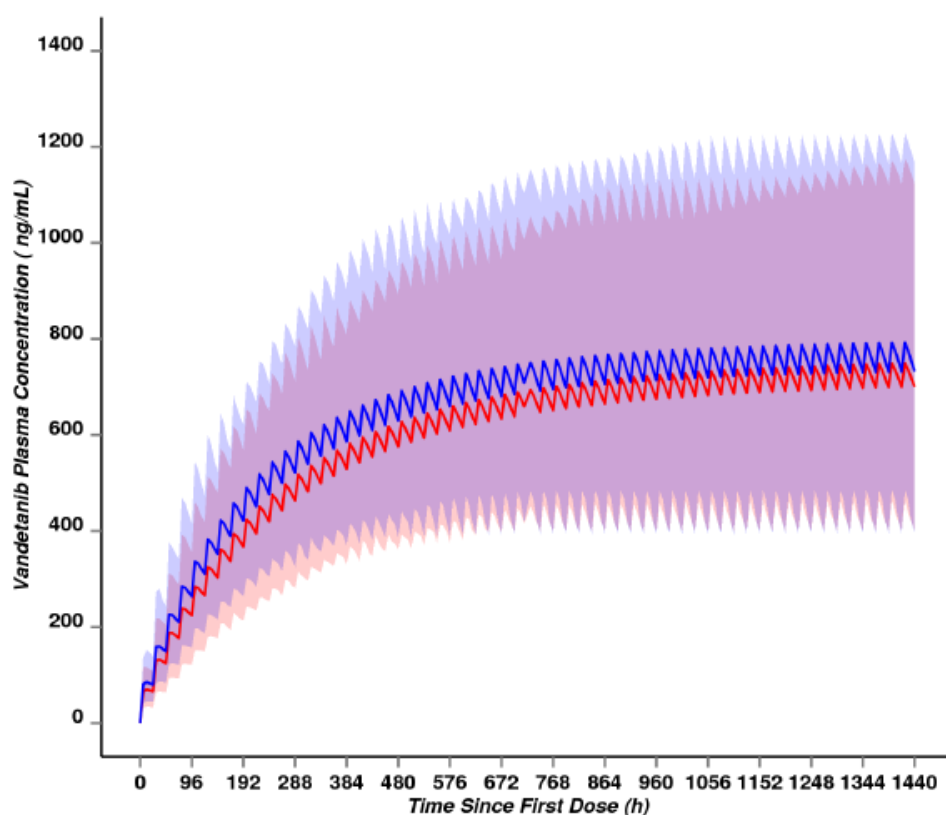
simulator was used to perform these simulations. Plasma concentrations were simulated for 100 mg/m² dose level. An allometric scaling option available in Simcyp was used to scale for differences in PK parameters (Clearance) between adult and paediatric populations. This simulation was performed in a virtual paediatric population in Simcyp consisting of 9 to 18 year olds and the PBPK model structure, physiochemical and PK input parameters were retained as for the adult population.



In figure 2, shaded area represent 90% prediction intervals for simulated vandetanib plasma concentration and black open circles represent observed plasma concentration from IS study 98 at 100 mg/m² dose level. The red solid line represents the median of the simulated plasma concentration.

Figure 3 PK profile for vandetanib at 100 mg/m² once daily in paediatric population from 9 to 18 years of age, with observed concentrations from Study 98.

The Model developed for paediatric population was used to predict the PK in a population consists of 5 to 9 years of age. Simulation of PK for 5 to 9 years of age for 100 mg/m² dose level was performed and the simulated plasma concentrations were compared with that of from the group of 9-18 years of age.

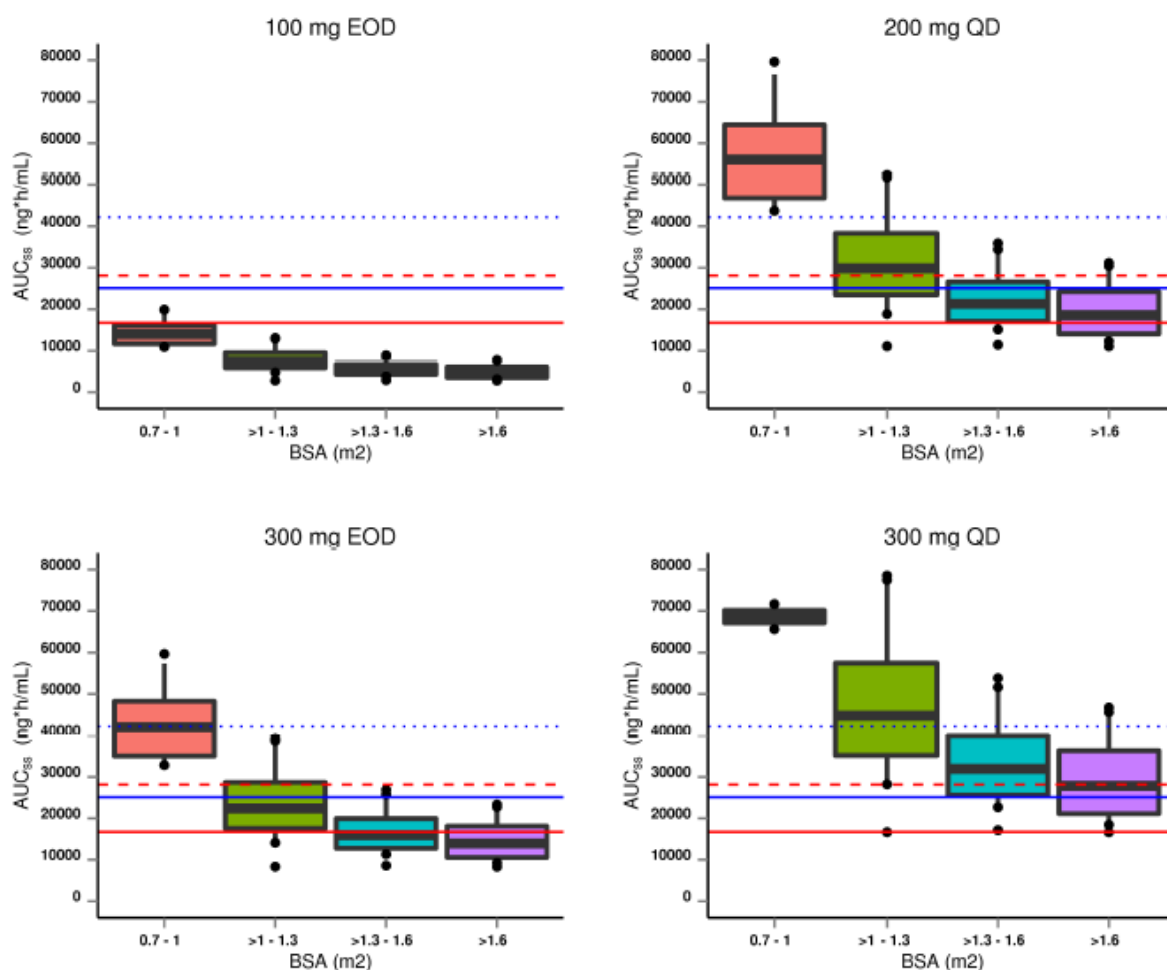


In figure 3, blue and red shaded area represent 90% prediction intervals for simulated vandetanib plasma concentration for paediatric population of 5 to 9 and 9 to 18, years of age, respectively. Blue and red lines represent medians of simulated vandetanib plasma concentration for paediatric population of 5 to 9 and 9 to 18, years of age, respectively.

Figure 4: Simulation representing PK profiles for paediatric age group of 5 to 9 years and 9 to 18 years of age at 100 mg/m²

Table 3: Comparison of predicted and observed CL (L/h/m²) in paediatric population of 5 to 18 years old

Study number	Age Groups	Number of Subjects	CL (L/h/m ²) Median (%CV)
IS-Study 4	5 to 9	12	4.10 (43.0)
IS-Study 4	> 9	3	5.06 (57.1)
Predictions *	5 to 9	100 Simulated subjects	5.76 (34.6)
Predictions *	> 9 to 18	100 Simulated subjects	5.86 (34.5)



The following figure representing simulated AUC_{ss} (ng*h/mL) for vandetanib at different dose levels in paediatric population consisting 5 to 18 years of age and BSA groups are displayed as different colours. Red solid line and red dashed line represent the median and the upper confidence interval (95th) of simulated plasma concentrations for 100 mg/m² respectively. Blue solid line and blue dotted lines represent the median and the upper confidence interval (95th) of simulated plasma concentrations for 150 mg/m², respectively.

Figure 5: Results of different dosing regimen tested for different BSA

Optimised PBPK model

Additional analyses to optimise the PBPK model were performed. The PBPK model was updated to be based on the contribution of respective CYP enzymes to the clearance of vandetanib, whereas the previous model used CL_{oral} as input and scaled pharmacokinetics between adult and paediatric population using an allometric scaling approach. In addition, minimal PBPK model as implemented in Simcyp (version 14) was also optimised by including additional PBPK parameters (V_{sac}, K_{in} and K_{out}). These additional PBPK parameters were estimated using the 'parameter estimation option' and observed plasma concentration data after single dose administration of vandetanib in study 51.

The model predicted plasma concentration at 100 mg/m² dose level (Figure 6) was compared to the observed plasma concentrations from study 98. The predictions based on CYP enzymes appear marginally different and there was less over-prediction compared to the predictions based on allometric scaling approach.

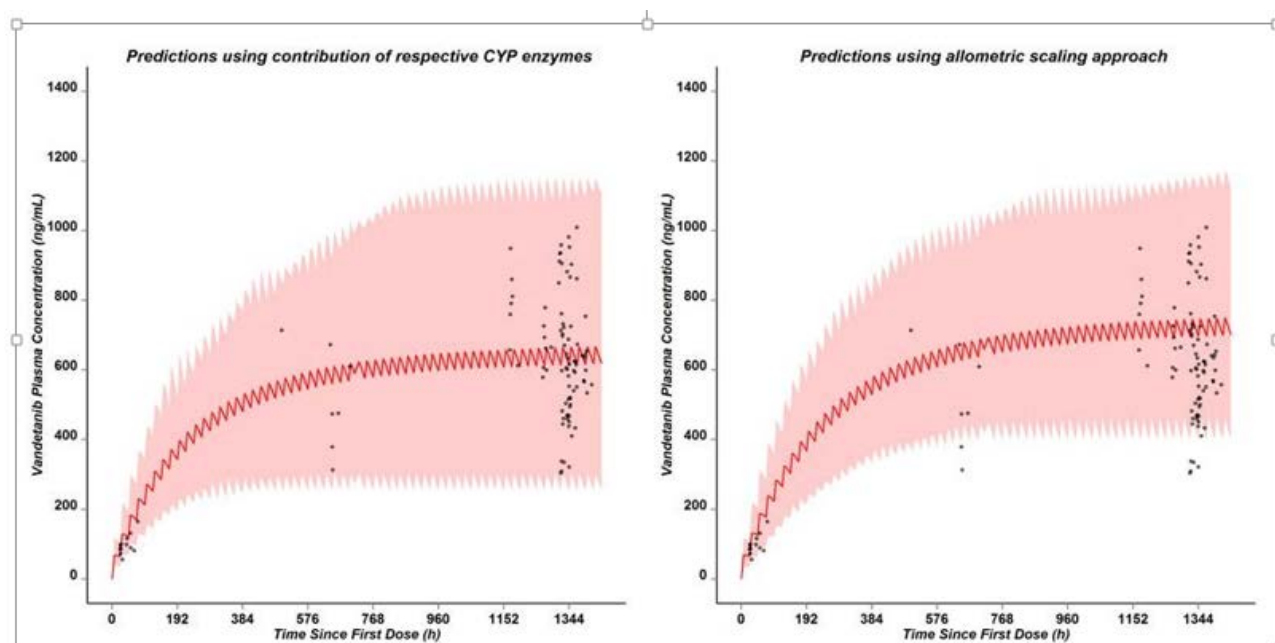


Figure 6 : Comparison of PBPK predictions using CYP contribution approach versus oral clearance and allometric scaling

Note: Black circles represent the observed plasma concentrations from study 98; shaded area represent 95% prediction intervals for simulated plasma concentrations based on the PBPK model.

In addition to comparing study 98 data with predictions, the MAH also used plasma concentration data (dose: 110 mg/m²) from study 51 to assess the refined PBPK model for its adequateness. The model predicted the steady state plasma concentration at 110 mg/m² well however appeared to under-predict the plasma concentrations after the first (single) dose (Figure 7).

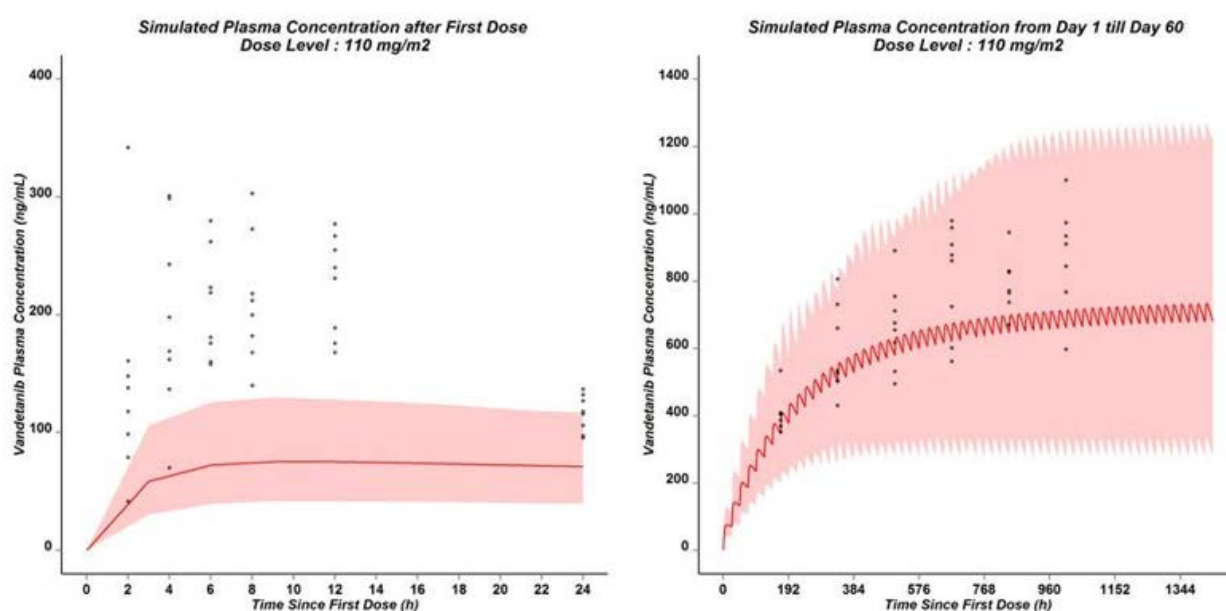


Figure 7: Comparison of updated PBPK model predictions versus single dose and steady state data from study 51

Note: Black open circles represent the observed plasma concentrations from study 51; shared area represent 95% prediction intervals for simulated plasma concentrations based on the PBPK Model.

Exploratory PopPK model

In addition to optimizing PBPK model, an exploratory population PK model was developed using the data from paediatric studies 98 and 51. In total, 447 plasma PK samples from 38 paediatric patients treated with vandetanib were available for inclusion in this analysis. Two samples from one subject were flagged in the analysis dataset by a non-critical error and so these samples were not included in the analysis. Number of samples/subject ranged from 5 to 20, 1 to 12 for Study 51 and Study 98, respectively.

This population PK analysis was exploratory because the data from study 51 were sourced from an investigator sponsored study and the MAH was not able to show traceability of individual plasma concentrations, actual time of dose administration and actual time of sample collection data. Individual plasma concentration data were not available from study 04, though the secondary PK parameters are available from a publication. Despite of these limitations, a two compartment PK model with first order absorption rate constant was developed to explain the time course of plasma concentration after multiple doses of vandetanib administration in this population. Due to the sparse nature of the data, prior information on pharmacokinetic parameters were used from a population PK model developed previously to describe PK in adult population. Similar to the PK model used for the adult population, this PK model used weight as a covariate to explain the variability in CL/F and V₂/F. Age could not be included as a covariate and the effect of age on PK parameters could not be explored. This population PK model was subjected to a limited evaluation process including a visual predictive check. Due to limited number of subjects involved in the analysis, a proper validation of model (bootstrap, other simulation based evaluations) was not feasible.

The PK parameter estimates are presented in the table below.

Table 4 : Population PK model parameter estimates

OFV	-1606.5			
Condition Number	357			
Parameters	Units	Population Mean	RSE (%)	Shrinkage (%)
CL/F	L/h	13.1	< 1	-
Vc/F	L	2152	2.19	-
Q/F	L/h	9.42	5.96	-
Vp/F	L	4664	4.69	-
Ka	h ⁻¹	0.293	13.1	-
BW-CL/F (exponent)		1.27	5.95	-
BW- Vc/F (exponent)		1.49	4.17	-
Between Subject Variability (as %CV)				
CL/F	% CV	33.7	11.2	10.2
Vc/F	% CV	50.3	1.84	28
Q/F	% CV	15.9	1.50	65.2
Vp/F	% CV	103	2.46	23.1
Ka	% CV	15.9	<1	52.1
Residual Variability				
Proportional Error	%	28.7	9.24	8.96

Abbreviations: OFV: Objective Function Value; RSE: Relative standard error; CL/F: apparent clearance; Vc/F: apparent central volume of distribution; Q/F: apparent intercompartmental clearance; Vp/F: apparent peripheral volume of distribution; Ka: first-order absorption rate constant; BSV: Between Subject variability; CV%, percent coefficient of variation;

In Figure 8 and Figure 9, simulated concentrations were compared with observed concentrations. At steady-state conditions (Figure 9), the median of predicted data from the PopPK model was slightly lower than the observed data. Variability in vandetanib exposure was higher in study 51 on dose/sample collection but potential effect of age on pharmacokinetics of vandetanib was not evaluated.

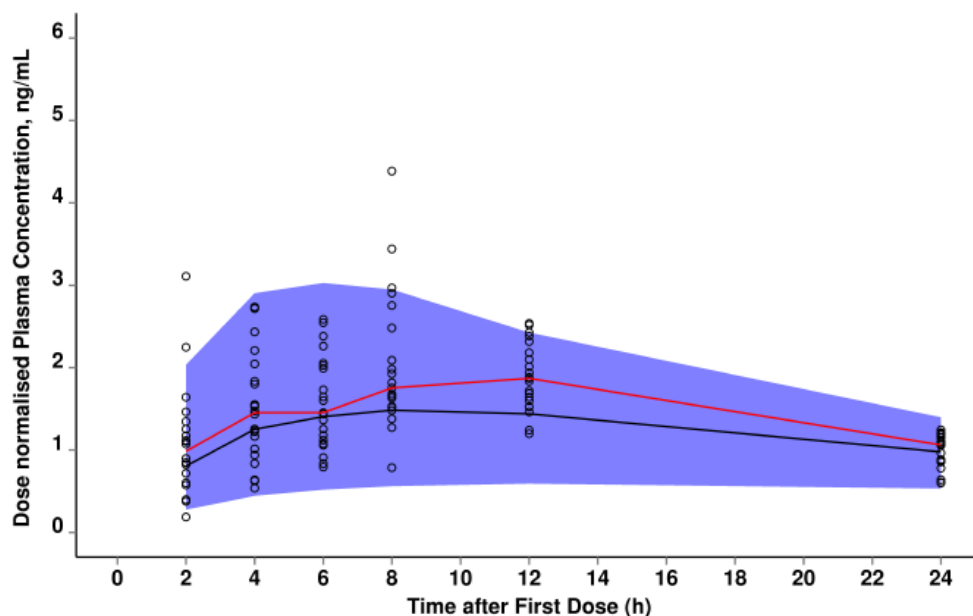


Figure 8 : VPC of the model depicting model adequateness. Simulated plasma concentrations plotted against time after dose

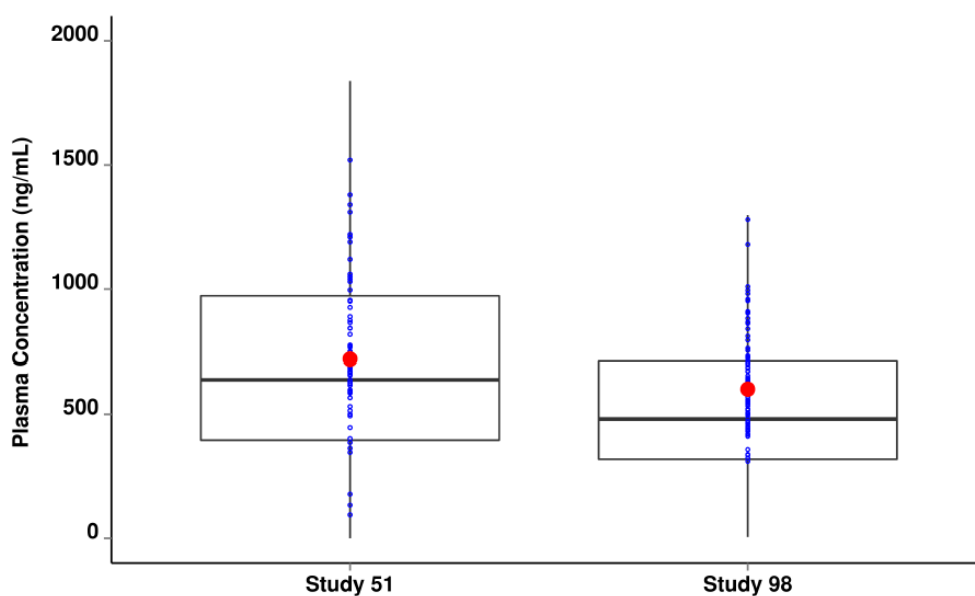


Figure 9 : Comparison of simulated and observed plasma concentration at steady-state (after cycle 2) stratified by study

Note: Blue dots represent observed plasma concentration and box-whiskers plot represent the distribution of simulated vandetanib concentration at steady-state. Red closed circle represent the median of observed concentrations at steady-state.

Effect of body weight and age

The exploratory population PK analysis using data from pediatric studies 51 and 98 evaluated the effect of body weight on pharmacokinetics. In an adult population PK modelling (based on study 58) covariate

effect of age, body weight and BSA on pharmacokinetics of vandetanib was evaluated and only body weight showed a significant effect on pharmacokinetic parameters. Based on this prior information and considering the limited number of paediatric subjects, only body weight was considered as a covariate in this exploratory population PK modelling for paediatric studies.

This exploratory population PK model applied body weight as a covariate on clearance and distribution parameters. Further, this model was used to simulate PK concentrations after multiple dose administration of vandetanib in different regimens for a population consisting of 5 to 18 years of age and calculated secondary PK parameters including Area under the Curve steady state (AUCss) at day 60 and stratified by discrete BSA ranges. The AUCss predictions obtained from simulations based on the population PK analysis were in good agreement with AUCss predictions obtained from the optimised PBPK method, see Figure 10.

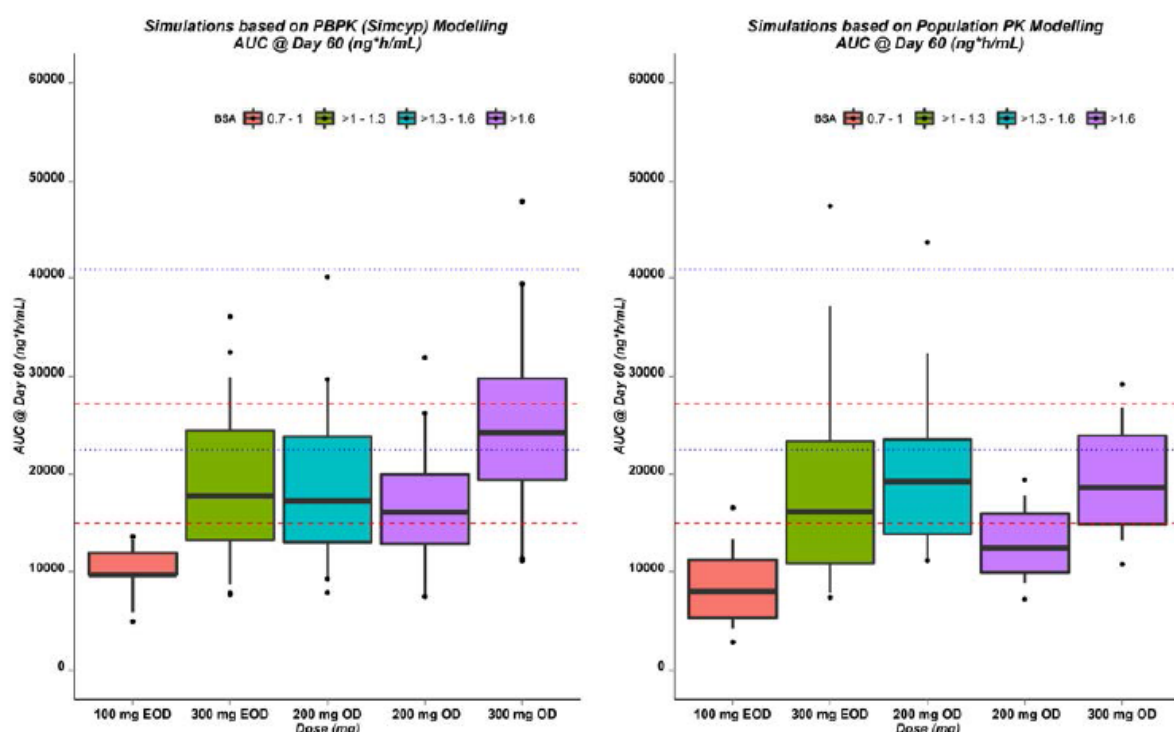


Figure 10 : Comparison of exposure predictions from popPK (left panel) simulation and optimized PBPK model (right panel)

Figure 10 depicts simulated AUCss (ng*h/mL) for vandetanib at different dose levels in paediatric patients 5 to 18 years of age divided in 4 different BSA groups displayed in different colours. Red solid line and red dashed line represent the median and the upper confidence interval (95%) of simulated plasma concentrations for 100 mg/m², respectively. Blue solid line and blue dotted lines represent the median and the upper confidence interval (95%) of simulated plasma concentrations for 150 mg/m², respectively.

The MAH was also requested to present C_{trough,ss} (dose normalised to 100 mg/m²) as function of age and as function of bodyweight for paediatric patients in studies 04, 51, and 98 in order to provide a substantiated dose regimen in children 5-8 years of age. The trough plasma concentrations (dose normalised to 100 mg/m²) as function of age and as function of bodyweight for paediatric patients in studies 04, 51, and 98 are provided in Figure 11 and Figure 12.

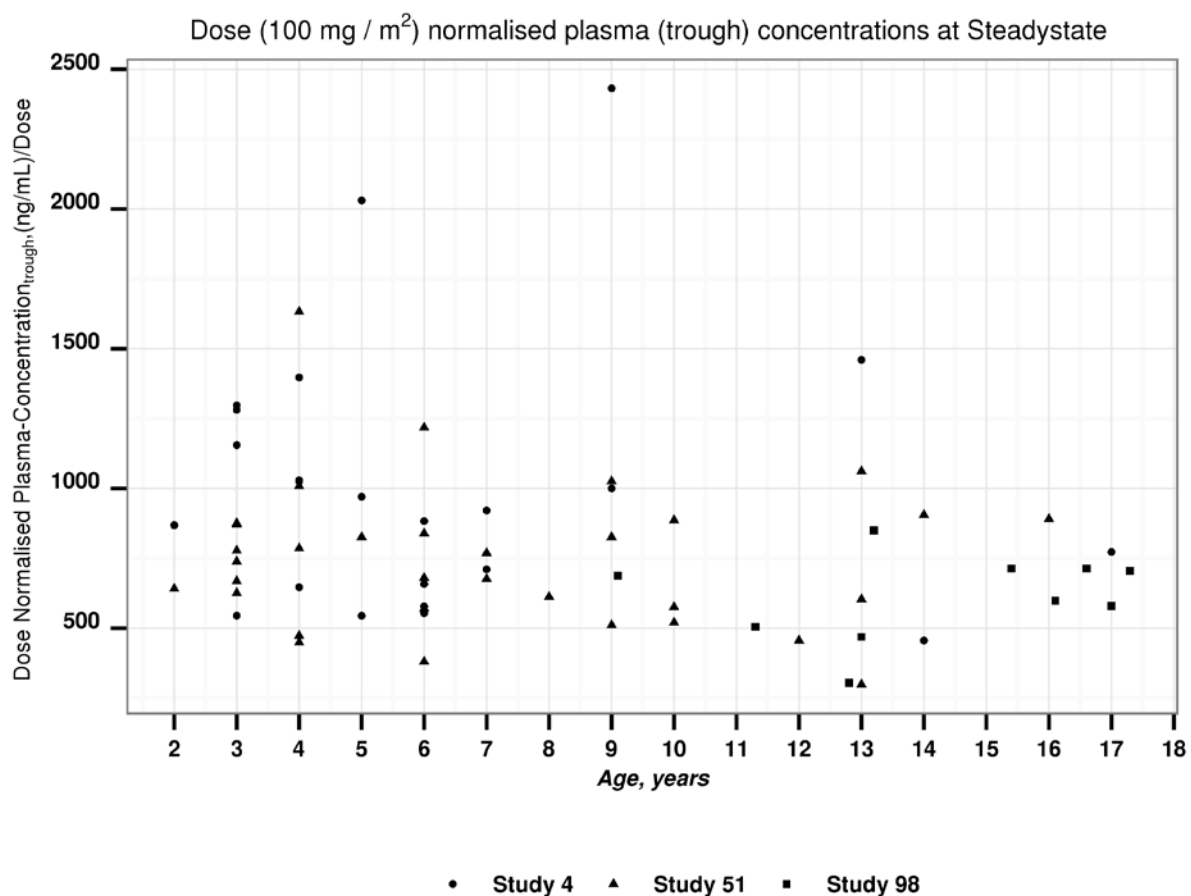


Figure 11 : Dose normalized (100 mg/m²) plasma concentrations (trough) in steady-state conditions for Study 4, Study 51 and Study 98 at different age groups

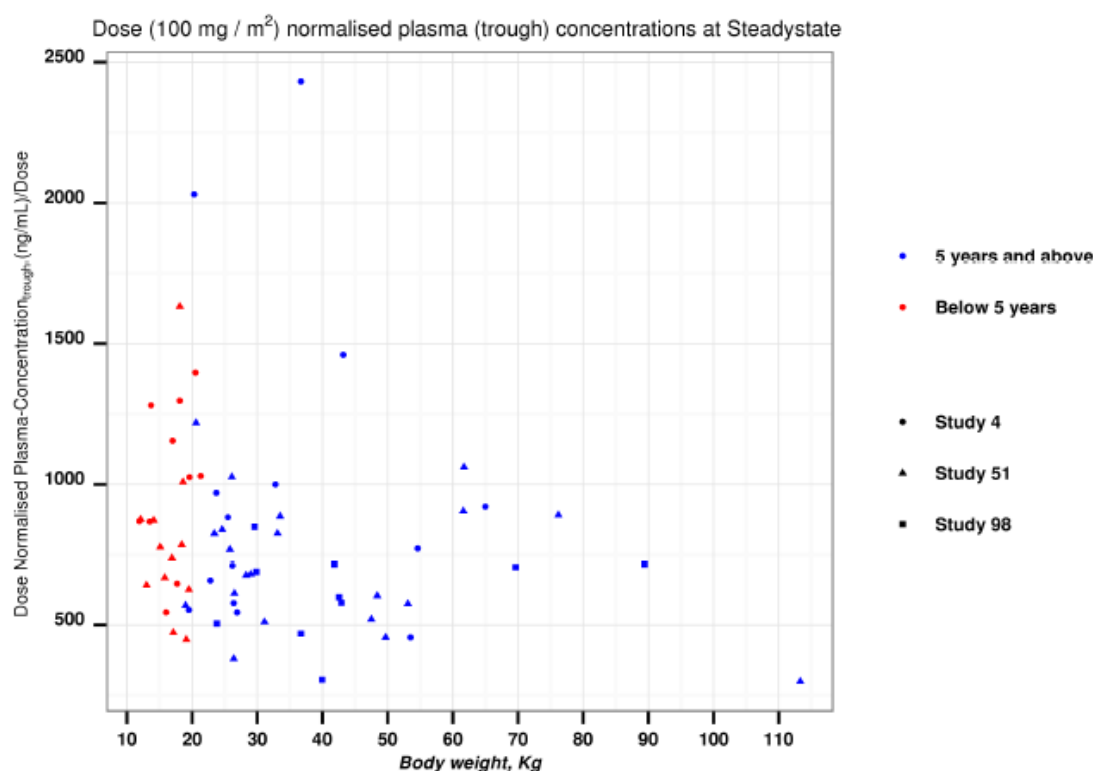


Figure 12 : Dose normalized (100 mg/m^2) plasma concentrations (trough) in steady-state conditions for Study 4, Study 51 and Study 98 across different body weight (kg)

Based on Figure 11 and Figure 12, dose normalised trough plasma concentrations appeared to be similar across different age and body weight groups. For study 98, plasma concentrations were obtained after cycle 2 day 28 and/or cycle 3 day 1. Details of pharmacokinetic sampling and dose are provided in Broniscer, 2010 and Broniscer, 2013 for Study 51 and Study 4, respectively. In study 04, 51 and 98, patients were dosed based on their body surface area and not their age.

2.3.4. Pharmacodynamics

Mechanism of action

Hereditary MTC is often caused by germline activating mutations in the rearranged during transfection (RET) proto-oncogene. Because the mutations to RET in MTC result in constitutively activated RET tyrosine kinase, this RTK is a potential direct therapeutic target in this disease.

Vandetanib is a small molecule that potently inhibits vascular endothelial growth factor receptor (kinase insert domain receptor) tyrosine kinase activity, RET RTK, Fms-related tyrosine kinase 4 and epidermal growth factor receptor, tyrosine kinases (Carlomagno et al 2002, Wedge et al 2002).

Because vandetanib may have particular benefit for those patients with activating mutations in the RET gene, tumour samples were collected to establish the mutational status of the RET gene and to relate this to clinical outcome data derived from this study. In total, 15 of the 16 patients in Study 98 (93.8%) had the M918T mutation.

Exposure-effect relationships

There was no apparent relationship between exposures (steady state C_{min}) and best response (grouped into partial response and stable disease + progressive disease) in paediatric patients with MTC (see Figure 13).

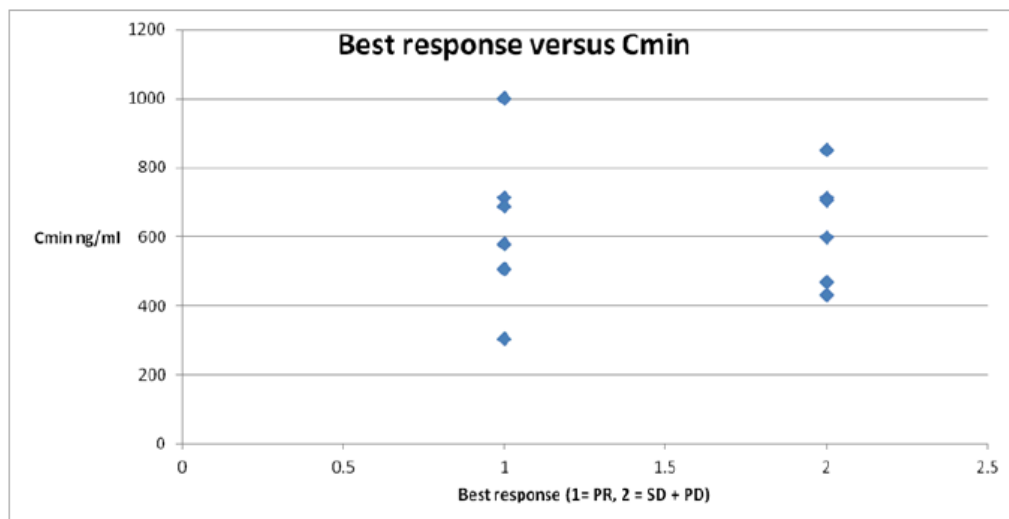


Figure 13 Individual C_{min} versus best response in paediatric patients with MTC (N=12, Study 98, 100 mg/m²/day)

MTC cells secrete Calcitonin CTN and Carcinoembryonic antigen CEA, and several biogenic amines. CTN and CEA levels are associated with tumour burden, and elevated levels are associated with disease progression and metastases. Most patients were responders (75%) based on calcitonin (CTN) data and half of the patients were responders (50%) based on carcinoembryonic antigen (CEA) data. (see also clinical efficacy part).

2.3.5. Discussion on clinical pharmacology

Vandetanib is marketed as 100 mg and 300 mg film-coated tablets. There is no specific paediatric formulation of vandetanib. However, in the clinical paediatric studies, vandetanib was supplied as 10 mg/ml oral solution and 50 mg and 100 mg tablets. In the original MAA submission, it was shown that the relative bioavailability of vandetanib comparing tablets vs. oral solution was 100% (study 30), therefore, the pharmacokinetic results obtained with solution are interchangeable with tablets.

Because of a possible over-estimation, and the use of different formulations, there are some doubts on the quality of the initial modelling regarding the 9 to 18 years old patient population. Furthermore, the initial PBPK model did not seem to predict the exposure in younger children (5-9 years old) accurately enough to allow dose recommendations. The PBPK model was updated based on the contribution of respective CYP enzymes to the clearance of vandetanib and includes additional PBPK parameters (V_{max}, K_{in} and K_{out}). Inclusion of CYP enzymes for clearance of vandetanib in the PBPK model resulted in less over-prediction compared to the predictions based on allometric scaling approach for study 98. However, there still appears some underestimation for paediatric patients in study 51 especially following single dose administration (Figure 6). The difference between single dose and steady-state prediction was unexpected as vandetanib pharmacokinetics was not time dependent in adults. No documentation on the updated factors, covariate distribution and variabilities of the simulation data sets was provided, hampering evaluation of the PBPK model. An additional popPK model was provided and seemed to be reasonably appropriate. However, there were limitations in the data traceability (in study 51) and

assumptions of a similar structural PK model to which described the PK in adult population. Overall the PBPK and popPK model were not considered fully reliable.

Hence, pharmacokinetics data were mainly available from study IRUSZACT0098 (study 98). Although study 98 was initially designed to recruit patients aged 5 to 18 years, the actual age range of the patients recruited was 9 to 17 years, with a lowest BSA of 0.90 m². Therefore, additional data for younger (≥ 2 years old) and smaller children were requested by the CHMP. Based on data from studies 04, 51 and 98, vandetanib trough concentrations at steady state, normalised by dose, were in general between 500-1000 ng/ml vandetanib dose, which is comparable to the mean C_{trough} concentrations of 750 ng/ml in adults with MTC. C_{trough} values seem to be fairly similar in children between 5 to 8 years old compared to older children, and in children with BSA below 1 m². Therefore, CHMP did not consider necessary to exclude children with a BSA of 0.7-1.0 m². These PK data support dosing based on BSA in paediatric patients.

Based on the very limited PK data available, no effect on the PK of vandetanib was found for patient age or body weight.

Vandetanib is commercially available as either 100 or 300 mg tablets. The MAH was highly recommended to develop an adequate formulation (e.g. 50 mg tablet) for use in the paediatric population. Considering the submitted PK data showed a small variability in exposure between the alternate 100-200 mg dosing regimen compared to 150 mg QD, an alternate dosing regimen was considered acceptable (see table below).

Due to the long elimination half-life of vandetanib (8-19 days), vandetanib exposure cannot be quickly reduced when intervention is needed. Therefore, it is proposed to use the same strategy as was used in study 98, start with 100 mg/m² and increase the dose of vandetanib to 150 mg/m² when vandetanib is tolerated well. Based on this, a dosing schedule based on BSA in mg/m² is recommended (see table below). Considering the age range (5 to 18 years old), the paediatric population was grouped by BSA 0.7 m² to <0.9 m², 0.9 m² to <1.2 m², 1.2 m² to <1.6 m² and ≥ 1.6 m².

BSA (m ²)	Start dose (mg) ^a	Dose increase (mg) ^b when tolerated well after 8 weeks at starting dose	Dose reduction (mg) ^c
0.7 - <0.9	100 every other day	100 daily	-
0.9 - <1.2	100 daily	7 day schedule: 100-200-100-200-100-200-100	100 every other day
1.2 - <1.6	7 day schedule: 100-200-100-200-100-200-100	200 daily	100 daily
≥ 1.6	200 daily	300 daily	7 day schedule: 100-200-100-200-100-200-100

^a The starting dose is the dose at which treatment should be initiated

^b Higher vandetanib doses than 150 mg/m² have not been used in clinical studies in paediatric patients

^c Patients with an adverse reaction requiring a dose reduction should stop taking vandetanib for at least a week. Dosing can be resumed at a reduced dose thereafter when fully recovered from adverse reactions

Considering the complex dosing regimen and the risk of dose miscalculation and/or error, the MAH has provided educational material designed to guide parents to manage the dosing regimen. The MAH will also put in place measures to assess the treatment compliance, and measures to minimise medication

errors (see RMP). Pediatric patients treated with Caprelsa and patients' caregivers must be given the dosing guide and be informed on the correct dose to be taken with the initial prescription and each subsequent dose adjustment (see SmPC section 4.2).

Data provided by the MAH about palatability and acceptability of tablets dispersed in water have been assessed in the initial MA and are acceptable. For children not able to swallow, vandetanib tablets may be dispersed in half a glass of non-carbonated drinking water. This is considered acceptable as regard to the expected rarity of such situation and the possibility to administer via nasogastric route.

There is no experience with the use of vandetanib in paediatric patients with renal impairment. Considering the data available in adult patients with renal impairment: No change in starting dose is recommended in paediatric patients with mild renal impairment. The reduced dose as specified in Table above could be used in paediatric patients with moderate renal impairment. Individual patient management will be required by the physician, especially in paediatric patients with low BSA; Vandetanib is not recommended in paediatric patients with severe renal impairment (see SmPC section 4.2).

Vandetanib is not recommended for use in paediatric patients with hepatic impairment (serum bilirubin greater than 1.5 times upper limit of reference range (ULRR), this criterion does not apply to patients with Gilbert's Disease and alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase (ALP) greater than 2.5 times ULRR, or greater than 5.0 times ULRR if judged by the physician to be related to liver metastases (see SmPC section 4.2).

There was no apparent relationship between C_{min} and best response in paediatric patients with MTC. The number of patients was small and some of the patients may have had a dose escalation to 150 mg/m² but no exposure data are available for this higher dose. For adults with MTC, analysis of the best observed response versus predicted steady-state exposure suggested a better response at higher vandetanib plasma concentrations: a steady-state AUC of 21 µg.h/mL or greater was required for the predicted probability of partial response to be 50% or more and a steady-state AUC of at least 7.0 µg.h/mL for the probability of stable disease to be 50% or more as best response. Exposure of vandetanib in all paediatric patients was higher than the level for the probability of stable disease to be 50% or more as best response. Further, response to biomarkers calcitonin and carcinoembryonic antigen was comparable in paediatric patients and in adults with MTC. In adults, CTN and CEA response rate was higher after administration of 300 mg vandetanib compared to the response rates after administration of 100 mg vandetanib. Overall, the starting dose of 100 mg/m² in paediatric patients with MTC is supported by comparable vandetanib exposure and comparable biomarker responses compared to adult MTC patients dosed 300 mg. Exposure to vandetanib and biomarker response was comparable in paediatric patients with MTC (age 9-17) administered vandetanib 100 mg/m²/day and adult patients with MTC administered 300 mg qd.

2.3.6. Conclusions on clinical pharmacology

The pharmacokinetic parameters of vandetanib in paediatrics MTC patients aged 9-18 years were similar to those in adults. There is no experience in pediatric patients with hereditary MTC below 9 years of age (see SmPC section 4.2, 4.8 and 5.1). Vandetanib exposure in children between 5 to 8 years old with glioma-related indications was comparable to MTC patients aged 9-18 years. Dosing at 100 mg/m²/day of the indicated posology (function of BSA) in paediatrics delivers similar exposure to that achieved in adults at 300 mg daily (see SmPC section 5.2). Educational material and measures to assess compliance and minimise medication errors will be put in place by the MAH (see RMP).

2.4. Clinical efficacy

2.4.1. Dose response study

No dose response study was provided. A dose-finding component was included in pivotal study 98. This component used an intra-patient dose escalation design to ensure all patients received doses equivalent to those used in the adult Phase II studies (see Main study below).

2.4.2. Main study

IRUSZACT0098 (study 98)

Methods

Study participants

The patient population was planned to include male and non-pregnant female patients aged 5 to 18 years, inclusive, with histologically-confirmed hereditary MTC (multiple endocrine neoplasia [MEN] 2A or MEN 2B) that was unresectable, recurrent or metastatic.

Patients must have previously had a characteristic germline mutation in the rearranged during transfection (RET) proto-oncogene documented.

Patients were to have had measurable disease and a Lansky (for patients 10 years of age or younger) or Karnofsky (for patients older than 10 years) performance score >50. Patients must have been able to take one of the oral formulations of vandetanib (administration of the liquid formulation via a nasogastric tube or gastrostomy was allowed). Patients who had previously had a thyroidectomy must have been receiving thyroid hormone replacement therapy.

Treatments

Study 98 used a 10 mg/mL oral solution formulation of vandetanib, and either 50 mg or 100 mg film-coated tablets. Patients received vandetanib continuously for cycles of 28 consecutive days starting with the first day of treatment (Day 1); there was to be no limit to the duration of therapy.

Vandetanib was administered orally, once daily, either as a tablet (50 mg and 100 mg tablets), which was to be swallowed whole, or an oral solution (10 mg/mL solution); patients could receive the oral solution through a nasogastric tube or gastrostomy, if required. Tablets and the oral solution could be combined, as needed, to give more accurate dosing. The dose of vandetanib was determined from the patient's BSA using a dosing nomogram (see Table below). The BSA was recalculated prior to each treatment cycle and the dose was adjusted, if necessary, based on the nomogram. Treatment was administered in an outpatient setting.

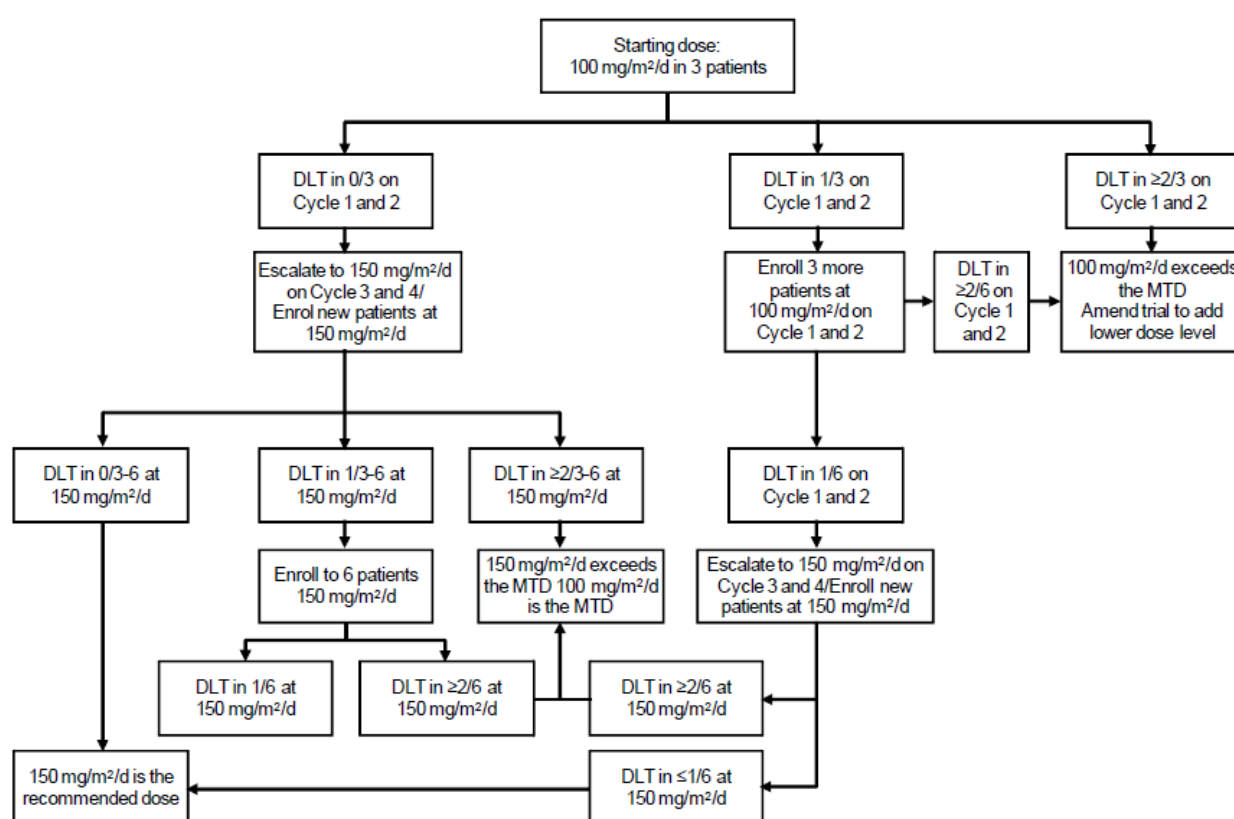
Table 5 *Vandetanib dosing nomogram*

Dose Level (mg/m ²)							
100	BSA (m ²)	0.50-0.62	0.63-0.87	0.88-1.12	1.13-1.37	1.38-1.75	>1.75
	Dose (mg)	50	75	100	125	150	200
150	BSA (m ²)	0.50-0.75	0.76-0.91	0.92-1.16	1.17-1.50	1.51-1.83	>1.83
	Dose (mg)	100	125	150	200	250	300

Note: Vandetanib was supplied as 10 mg/mL oral solution and 50 and 100 mg tablets. A combination of tablets and oral solution could be used. For example, a dose of 75 mg could be one 50 mg tablet plus 2.5 mL of oral solution.

BSA: body surface area.

Dose escalation was based on toxicity information.



DLT: dose-limiting toxicity; MTD: maximum tolerated dose.

Figure 14: Flow chart of dose escalation procedure

There was only 1 treatment group in this study. However, there were cohorts of patients involved in the intra-patient dose escalation part of the study. Initially, 3 adolescent patients, aged 13 to 18 years, were enrolled and started on the lower dose of vandetanib (100 mg/m²/day) before undergoing dose escalation (Cohort 1). Once it was established that the 100 mg/m²/day dose was tolerated, a second cohort of 3 child patients, aged 5 to 12 years was enrolled at the lower dose and underwent dose escalation (Cohort 2). From this dose-escalation part of the study, an MTD or recommended dose was defined; the remaining patients (15 planned) were to receive this dose from enrolment (Cohort 3).

Objectives

The primary objectives of the study were:

1. To assess the activity of daily oral vandetanib in children and adolescents with hereditary MTC by measuring:
 - Change in tumour size compared to baseline using RECIST (primary endpoint),
 - Change in tumour biomarkers (CTN and CEA) compared to baseline,
 - Change in tumour-related diarrhoea (frequency and consistency), compared to baseline;
2. To assess the safety and tolerance of vandetanib in children and adolescents at a dose that was equivalent to the recommended dose in adults using a limited intra-patient dose escalation;
3. To assess the PK of vandetanib at steady state (end of Cycle 2) in children and adolescents with hereditary MTC.

The secondary objectives of the study were:

1. To determine the progression-free survival (PFS) and overall survival (OS) in children and adolescents with hereditary MTC treated with vandetanib;
2. To assess the expression of RET, EGFR, VEGFR and somatostatin receptor by immunohistochemistry in archival tissue blocks from children and adolescents enrolled on this protocol;
3. To assess gene expression by microarray prior to and during treatment with vandetanib;
4. To screen for gains or losses of DNA sequences in tumour tissue using comparative genomic hybridisation;
5. To perform RET gene mutational analysis in tumour and peripheral blood mononuclear cells prior to treatment and in tumour at the time of disease progression on treatment with vandetanib to discover tumour-specific somatic mutations that may be responsible for drug resistance;

Outcomes/endpoints

Primary endpoint

The primary efficacy endpoint variable was the Overall Response Rate according to RECIST 1.0 using the evaluable for response analysis set. The ORR was defined as the proportion of responders (patients with a complete response [CR] or partial response [PR]) over the course of the study.

Evaluation of Target Lesions:

- CR: Disappearance of all target lesions
- PR: At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.
- Progressive disease: At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of 1 or more new lesions.
- Stable disease: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum LD since the treatment started.

Evaluation of Non-Target Lesions:

- CR: Disappearance of all non-target lesions and normalisation of tumour marker levels. If tumour markers are initially above the upper normal limit, they must normalise for a patient to be considered in complete clinical response.
- Stable disease (or incomplete response): Persistence of 1 or more non-target lesion(s) or maintenance of tumour marker level above the normal limits.
- Progressive disease: Appearance of 1 or more new lesions or unequivocal progression of existing non-target lesions. Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or PI).

Response criteria for CEA and CTN were:

- CR: Normalisation ($\leq$ ULN) of CEA or CTN level following treatment, confirmed with a repeated CEA/CTN level at least 4 weeks apart.
- PR: A $\geq 50\%$ decrease in the CEA or CTN level relative to the baseline level, confirmed with a repeated CEA/CTN level at least 4 weeks apart.
- Progression: A $\geq 50\%$ increase in the CEA or CTN relative to the prior value on 2 consecutive measurements at least 4 weeks apart. The patient must have been taking vandetanib for 4 weeks prior to the first measurements and must have continued to take the drug during the time that the second measurement was drawn.
- Stable: $< 50\%$ increase or decrease in CTN or CEA level relative to the baseline level.

Secondary endpoints

The secondary outcomes variables were PFS and OS according to RECIST 1.0.

Sample size

The preliminary response rate in adults, at the time of CSP finalisation, was 5/18 patients (28%; lower 1-sided 95% [confidence interval] bound = 10%). This study was designed to determine whether the response rate in children and adolescents with hereditary MTC exceeded 10% and was consistent with a response rate as high as 30%. With a planned sample size of 21 evaluable patients, using a 1-sided 0.1 alpha level exact binomial test, the study had 80% power to rule out a 10% response rate in favour of a 30% response rate. In practice, 5 responses in 21 patients would have marginally ruled out 10% as a response rate, and also could be consistent with a response rate of approximately 40%.

Randomisation

Not applicable.

Blinding (masking)

This study was open-label.

Statistical methods

No statistical analysis plan was prepared for this study. Summary statistics of the main primary and secondary endpoints were presented by cohort. Listings of the data, by patient, indicating dose and cohort were produced. The tumour biopsy data were not available at the data cut-off date for this study.

No formal statistical analyses were carried out in support of this report. Data were summarised descriptively.

The 'All Patients analysis set' was defined as all patients who were enrolled in the study. This analysis set was used across all safety, efficacy and PK outputs.

Results

Participant flow

All 16 patients enrolled into the study, received treatment. All 16 patients completed Cycle 1 and 15 patients completed both Cycles 1 and 2; one patient did not complete Cycle 2 due to disease progression. At the time of data cut-off, 4 patients had discontinued treatment due to disease progression, 2 of whom were terminated from the study.

Table 5: Patient Disposition

	Number (%) of patients		
	Starting at Dose Level 1 100 mg/m ² /day	Starting at Dose Level 2 150 mg/m ² /day	Total
Patients enrolled	15 (100.0)	1 (100.0)	16 (100.0)
Patients who received treatment	15 (100.0)	1 (100.0)	16 (100.0)
Patients who discontinued treatment	4 (26.7)	0	4 (25.0)
Due to disease progression	4 (26.7)	0	4 (25.0)
Patients who are ongoing treatment	11 (73.3)	1 (100.0)	12 (75.0)
Patients who terminated study	2 (13.3)	0	2 (12.5)
Withdrew consent	1 (6.7)	0	1 (6.3)
Other ^a	1 (6.7)	0	1 (6.3)
Patients who are ongoing study	13 (86.7)	1 (100.0)	14 (87.5)
Patients who completed Cycle 1	15 (100.0)	1 (100.0)	16 (100.0)
Patients who completed Cycle 1 and 2 ^a	14 (93.3)	1 (100.0)	15 (93.8)

Data from Table 11.1.1 and Appendices 12.2.1 and 12.2.5.

^a Patient 3 did not complete Cycle 2 due to progression during Cycle 2.

Recruitment

This study was conducted by the National Cancer Institute (NCI) and was a single-centre study in the US.

The first subject was enrolled on 20 July 2007 and data cut-off was 17 July 2011; the study was ongoing at the time of data cut-off.

Conduct of the study

The original clinical study protocol (CSP) was dated 31 January 2007. There have been 8 CSP amendments. In particular, amendment D and E involved personnel changes. With amendment F to the consent documentation proteinuria was added as side effect of Caprelsa. Amendment H involved personnel and small textual and administrative changes in the protocol and consent documentation. With amendment G the eligibility assessment and enrolment was changed.

There were 5 patients identified as having protocol deviations.

Table 6 : Important protocol violations

	Number (%) of patients (N=16)
Number of patients with at least 1 important deviation	5 (31.3)
Incorrect assessment of response during the study (calculated versus baseline rather than versus best response) resulting in an incorrect categorisation of response (stable disease rather than progressive disease) and continuation in the study.	1 (6.3)
Blood samples for laboratory assessments collected more than 72 hours prior to starting treatment with vandetanib.	1 (6.3)
No site PI in place for patients enrolled between 19 June and 25 September 2009 (CI: 19 June 2009 to 25 September 2009)	3 (18.8)

Data provided by NCI.
PI: Principal investigator.

Baseline data

Table 7: Demography and baseline characteristics

		Number (%) of patients (N=16)
Demographic characteristics		
Sex (n and % of patients)	Male	8 (50.0)
	Female	8 (50.0)
Age (years)	Mean (SD)	14.2 (2.6)
	Range	9 to 17
Race (n and % of patients)	White ^a	15 (93.8)
	Black or African American	1 (6.3)
Baseline characteristics		
Height (cm)	Mean (SD)	157.7 (15.3)
	Range	131 to 190
Weight (kg)	Mean (SD)	42.1 (17.8)
	Range	20 to 89
Body mass index (kg/m ²)	Mean (SD)	16.3 (4.1)
	Range	11 to 25

Data from Table 11.1.2 and Appendix 12.2.4.1.

^a Four of the 15 White patients (26.7%) were Hispanic.

SD: standard deviation.

The mean disease duration (number of years between diagnosis and start of treatment in Cycle 1) was 3.1 years (range: 0 to 12 years). Most patients (13 patients [81.3%]) had previously undergone a partial or total thyroidectomy (prior surgery to the thyroid gland) before entering the study.

In total, 15 of the 16 patients in this study (93.8%) had the M918T mutation, which is a characteristic of the MEN 2B subtype of hereditary MTC (Waguespack et al 2011).

Numbers analysed

Patients who were evaluable for ORR were those with measurable disease defined by RECIST at baseline; therefore, all patients (N=16) were evaluable.

Outcomes and estimation

Objective response

The majority of patients achieved PR (7 patients [43.8%]) or had stable disease for at least 8 weeks (5 patients [31.3%]); no patients showed CR (Table 10). The ORR was 43.8%. The remaining 4 patients either had disease progression (1 patient [6.3%]) or were categorised as not evaluable (3 patients [18.8%]); those not evaluable either had stable disease for less than 8 weeks or no evaluable follow-up assessment was available.

Table 8 : Summary of best objective response

Response status	Best objective response	Number (%) of patients (N=16)
Response	Total	7 (43.8)
	CR ^a	0
	PR ^a	7 (43.8)
Non-response	Total	9 (56.3)
	Stable disease $\geq$ 8 weeks	5 (31.3)
	Unconfirmed CR or PR ^b	1 (6.3)
	Stable disease	4 (25.0)
	Progression	1 (6.3)
	Not evaluable	3 (18.8)
	Stable disease <8 weeks	1 (6.3)
	No evaluable follow-up assessment	2 (12.5)

Data from Table 11.2.3.

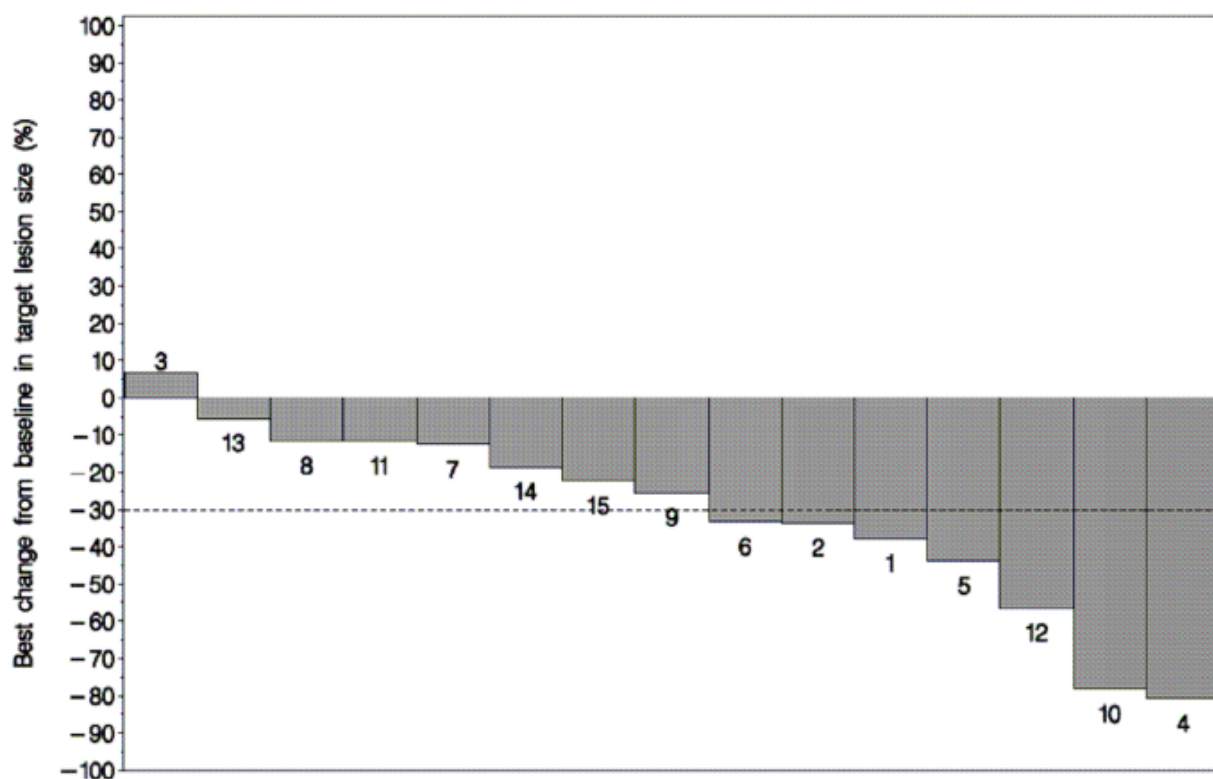
^a Response requires confirmation.

^b CR or PR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.

CR: complete response; PR: partial response.

Best percentage change in tumour size

Of the 15 patients for whom data were available, 14 patients (93.3%) had a best percentage change in tumour size that represented a decrease from baseline (see figure below). No data were available for 1 patient (Patient 16) as he had not received follow-up scans at the time of data cut-off and was, therefore, ineligible for tumour response evaluation.



Data from [Figure 11.2.6](#).

Note: Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. The numbers on the bars represent subject numbers.

RECIST: Response evaluation criteria in solid tumours.

Figure 15 : Waterfall plot showing summary of best percentage change from baseline in target lesion size (RECIST investigator assessment)

Change in tumour biomarkers

Only patients with average pre-treatment CTN and CEA levels that were greater than 2 times the ULN were evaluable for response; all 16 patients met this criterion.

Calcitonin (CTN)

Overall, 12 patients (75.0%) achieved PR and no patients had CR based on CTN data (Table 10). The remaining 4 patients (25.0%) either had stable disease for 12 or more weeks (1 patient [6.3%] with an unconfirmed PR) or were not evaluable (3 patients [18.8%]).

In total, 13 patients (81.3%) had a best percentage change in CTN levels that represented a decrease from baseline of at least 50.0% during the study (Figure 3). No data were available for 1 patient (Patient 16) as he did not have any biomarker values recorded at the baseline assessment and was, therefore, ineligible for biomarker response evaluation.

Table 9 : Summary of best objective response for calcitonin

Response status	Best objective response	Number (%) of patients (N=16)
Response	Total	12 (75.0)
	CR ^a	0
	PR ^a	12 (75.0)
Non-response	Total	4 (25.0)
	Stable disease ≥ 12 weeks	1 (6.3)
	Unconfirmed CR or PR ^b	1 (6.3)
	Stable disease	0
	Progression	0
	Not evaluable	3 (18.8)
	Stable disease <12 weeks	3 (18.8)

Data from Table 11.2.4.

^a Response requires confirmation.

^b CR or PR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.

Note: Complete response: Normalisation ($\leq$ ULN) following treatment, confirmed with a repeat assessment at least 4 weeks apart. Partial response: A $\geq 50\%$ decrease relative to baseline, confirmed with a repeat assessment at least 4 weeks apart. Progression: A $\geq 50\%$ increase relative to the prior value on 2 consecutive measurements at least 4 weeks apart. Stable disease: A $< 50\%$ increase or decrease relative to baseline. Only patients with average pre-treatment CTN levels that were > 2 times the ULN were evaluable for response.

CR: complete response; CTN: calcitonin; PR: partial response; ULN: upper limit of normal.

Carcinoembryonic antigen (CEA)

Overall, 7 patients (43.8%) achieved PR and 1 patient (6.3%) achieved CR based on CEA data (Table 11). Of the remaining 8 patients (50.0%), 4 patients (25.0%) had stable disease for 12 or more weeks, 2 patients (12.5%) had disease progression and 2 patients (12.5%) were not evaluable.

In total, 9 patients (56.3%) had a best percentage change in CEA levels that represented a decrease from baseline of at least 50.0% during the study. No data were available for 1 patient (Patient 16) as he did not have any biomarker values recorded at the baseline assessment and was, therefore, ineligible for biomarker response evaluation.

Table 10 : Summary of best objective response for carcinoembryonic antigen

Response status	Best objective response	Number (%) of patients (N=16)
Response	Total	8 (50.0)
	CR ^a	1 (6.3)
	PR ^a	7 (43.8)
Non-response	Total	8 (50.0)
	Stable disease ≥ 12 weeks	4 (25.0)
	Unconfirmed CR or PR ^b	0
	Stable disease	4 (25.0)
	Progression	2 (12.5)
	Not evaluable	2 (12.5)
	Stable disease <12 weeks	1 (6.3)
	Unconfirmed CR or PR ^b	1 (6.3)

Data from Table 11.2.5.

^a Response requires confirmation.

^b CR or PR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.

Note: Complete response: Normalisation ($\leq$ ULN) following treatment, confirmed with a repeat assessment at least 4 weeks apart. Partial response: A $\geq 50\%$ decrease relative to baseline, confirmed with a repeat assessment at least 4 weeks apart. Progression: A $\geq 50\%$ increase relative to the prior value on 2 consecutive measurements at least 4 weeks apart. Stable disease: A <50% increase or decrease relative to baseline. Only patients with average pre-treatment CEA levels that were >2 times the ULN were evaluable for response.

CEA: carcinoembryonic antigen; CR: complete response; PR: partial response; ULN: upper limit of normal.

Change in tumour-related diarrhoea

Two patients (12.5%) had CTN-mediated diarrhoea (≥ 5 watery stools per day) at enrolment; and were evaluable for response based on their diarrhoea data. no patient achieved a CR.

Table 11: Summary of response for CTN-mediated diarrhoea

	%
ORR	43.8 (19.8, 70.1)
SD	31.3 (11.0, 58.7)
ORR for CTN	75 (47.6, 92.7)
ORR for CEA	50 (24.7, 75.4)
>50% reduction in CTN	81.3 (59.5, 98.3)
>50% reduction in CEA	60.0 (32.3, 83.7)

Progression-free survival

In total, investigator assessed progression events were reported for 4 patients (25.0%) at the time of PFS analysis (Table 12). All 16 patients were alive at the time of data cut-off.

Table 12 : Summary of progression status at the time of data cut-off

	Number (%) of patients (N=16)
Progression ^a	4 (25.0)
No progression	12 (75.0)
Censored RECIST progression or death ^b	0
Alive at the time of analysis	12 (75.0)
Discontinued study	0
Withdrawn consent	0

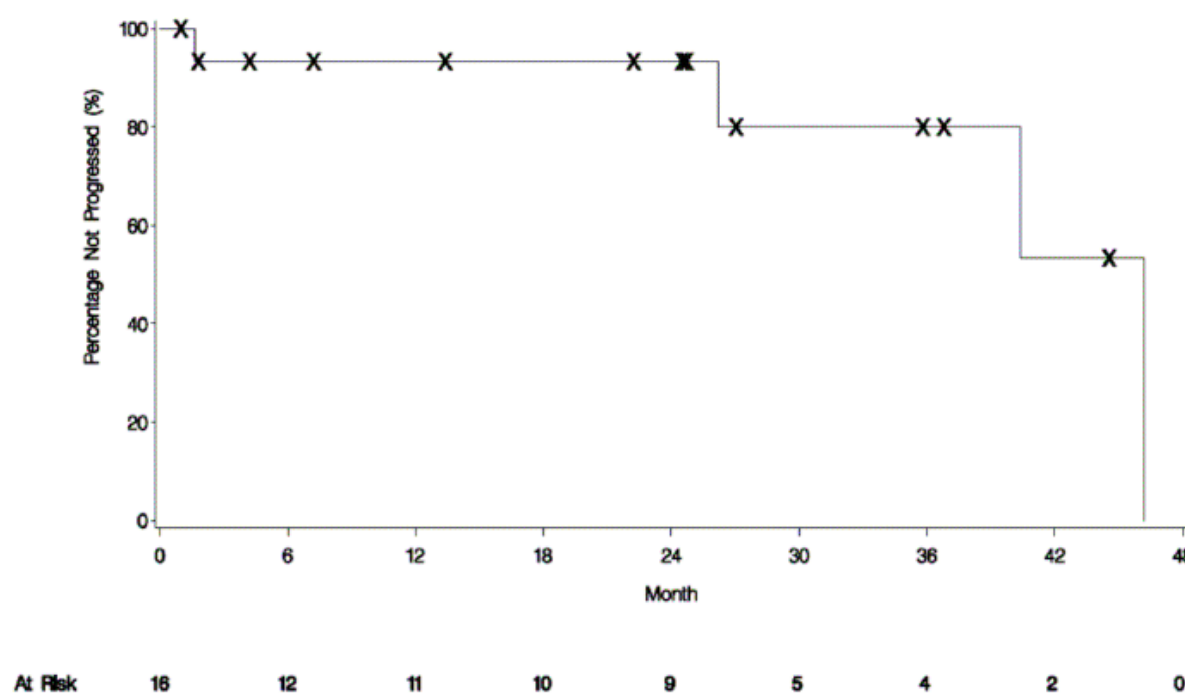
Data from [Table 11.2.1](#).

^a Progression events that do not immediately follow 2 or more non-evaluable tumour assessments; all patients who progressed were alive at the time of analysis.

^b Progression events that occur immediately following 2 or more non-evaluable tumour assessments.

RECIST: Response evaluation criteria in solid tumours.

The median PFS time was approximately 46 months



Data from [Figure 11.2.2](#).

Note: Date last known to be progression-free for patients with no progression event.

Figure 16 : A Kaplan-Meier plot showing progression-free survival by month

Overall survival

No patients had died at the time of data cut-off; consequently, OS could not be calculated for this patient population at this time. The minimum time from first dose to data cut-off or study discontinuation was 30 days, while the maximum time was 1405 days.

Summary of main study

The following table summarises 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 IRUSZACT0098

Title: Phase I /II Trial of Vandetanib (ZD6474, ZACTIMA) in Children and Adolescents with Hereditary Medullary Thyroid Carcinoma – Study 98			
Study identifier	IRUSZACT0098		
Design	Open-label, single-centre, non-comparative Phase I/II study in children and adolescents with hereditary medullary thyroid carcinoma (MEN2A or 2B)		
	Study Initiation Date:		20 July 2007
	Data cut-off:		17 July 2011
Hypothesis	Exploratory: to assess maximum tolerated dose (Phase1) and efficacy, safety and PK (Phase2) of vandetanib in children and adolescents.		
Treatment groups	Vandetanib (n=16)		100 or 150 mg/m ² once daily as tablet or oral solution. Dose calculated based on body surface area.
Endpoints and definitions	Primary endpoint	ORR	Complete remission or partial remission in patients with measurable disease at baseline defined by RECIST
	Secondary endpoints	PFS	Investigator assessed
		OS	Overall survival
Results and analysis			
Analysis description	Primary analysis		
Analysis population and time point description	All treated patients, n=16.		
Descriptive statistics and estimate variability	Treatment group	Vandetanib	
	Number of subjects	n=16	
	ORR	43.8% (n=7)	
	Median PFS	46 months	
	OS	NE (all patients alive at time of primary analysis)	

Effect estimate per comparison	N/A
--------------------------------	-----

2.4.3. Supportive studies

Some comparison to the adult MTC data (Studies 08, 58 and 68) was made.

In Study 08, 30 patients received vandetanib 300 mg. There were more females than males, and the majority of patients were Caucasian. The mean age for this study population was 48.7 years. All but 1 patient had metastatic disease at the time of study entry. The majority of patients had MEN2a, which is representative of the hereditary MTC population. All 30 patients (100%) had previously undergone disease-related surgery; 36.7% had received radiotherapy, and 26.7% had received other cancer therapy. The World Health Organization performance status (WHO PS) score at study entry was 0 (normal activity) for 50.0% of the patients, 1 (restricted activity) for 46.7%, and 2 (in bed $\leq$ 50% of the time) for 3.3% (1 patient). Thirteen patients were discontinued from vandetanib therapy because of patient not willing to continue treatment (n=2), adverse events (AEs; n=7), and disease progression (n=4).

In Study 68, 19 patients with locally advanced or metastatic hereditary MTC received vandetanib 100 mg. The majority of patients were male, and all but 1 patient was Caucasian; the mean age was 44.7 years. All patients except 1 had distant metastases at study entry; the most common metastatic sites were the liver, bone and locomotor, lymph nodes, and respiratory. RET mutation status was positive for 17 patients and unknown for 2 patients. A total of 8 patients treated with vandetanib 100 mg discontinued from vandetanib therapy, because of patient not willing to continue treatment (n=1), AEs (n=3), or condition under investigation worsened (n=4).

In Study 58, a total of 231 patients were randomised to the vandetanib arm and 100 patients to the placebo arm. All patients randomised to vandetanib received vandetanib and all patients except 1 who were randomised received study drug. One patient was randomised to placebo but died of progressive MTC before receiving treatment. A total of 111 (48.1%) patients in the vandetanib arm continued to receive randomised treatment at the date of data cut-off (31 July 2009), compared with 28 patients (28.0%) in the placebo arm. Mean age was 51.5 years and there were more males than females (57.4% vs 42.6%). A total of 95.2% of patients were Caucasian (White).

Overall, 90.3% of patients had undergone thyroidectomy before entering the study. A total of 45.0% of patients had a medical history of diarrhoea and 15.4% of patients had a history of fatigue, while 94.6% of patients in the 2 treatment groups had Stage IVC disease at entry. Among patients with hereditary MTC, 48.5% of patients in the 2 treatment arms had a family history of MTC. MEN2a was the most common associated syndrome in the 2 treatment arms.

Table 14 : Summary of results for common efficacy outcome variables in study 98, study 08, study 68 and study 58

Variable	Paediatric MTC patients	Adult MTC patients			
	Study 98 Vandetanib 100 or 150 mg/m ² (N=16) ^a	Study 08 Vandetanib 300 mg (N=30) ^a	Study 68 Vandetanib 100 mg (N=19) ^a	Study 58	
PFS	46	27.9	16.2 ^c	30.5 ^c	19.3
Median, months					
ORR	7 (43.8%)	6 (20.0%)	3 (15.8%)	104 (45.0%)	13 (13.0%) ^d
Number of responses, (%)					
DCR	12 (75.0%) ^e	22 (73.3%)	13 (68.4%)	200 (86.6%)	71 (71.0%) ^d
Number with best response of CR, PR, or SD ≥ 24 weeks, (%)					
DOR ^b	Not available	10.2	5.5	22.2 ^c	16.3 ^{c,d}
Median, months					
CTN response rate	12 (75.0%)	24 (80.0%)	3 (15.8%)	160 (69.3%)	3 (3.0%)
Number of responses, (%)					
CEA response rate	8 (50.0%)	16 (53.3%)	1 (5.3%)	119 (51.5%)	2 (2.0%)
Number of responses, (%)					

Data derived from Section 7 of [Study 08](#), [Study 68](#), [Study 58](#) and [Study 98](#) CSRs. Note: The predicted median PFS for Study 68 was derived after completion of the CSR; therefore, this result is not cited in the text of the CSR nor in the supporting tables in Section 11.2 of the CSR.

Note: Results for progression and response for Study 58 are based on a central imaging review ("central read"), independent of AstraZeneca. Results for Study 08 and Study 68 are based on a site imaging review.

^a Refers to treated patients in Study 98, Study 08 and Study 68 and randomised patients in Study 58.

^b From onset of response.

^c Represents predicted median based on a Weibull model.

^d The intention to treat analysis included patients who received open-label vandetanib before disease progression was documented according to the central read. A total of 12 of the 13 objective responses in the placebo arm in Study 58 occurred during open label treatment with vandetanib.

^e DCR based on an SD of ≥ 8 weeks in Study 98

CEA: Carcinoembryonic antigen; CTN: Calcitonin; CR: Complete response; CSR: Clinical study report; DCR: Disease control rate; DOR: Duration of response; ORR: Objective response rate; PFS: Progression-free survival; PR: Partial response; SD: Stable disease.

2.4.4. Discussion on clinical efficacy

This application is supported by one pivotal study in children and adolescents with MTC (study 98) and 3 supportive studies in paediatric patients with glioma-related tumours (study 04, 51 and 61). Study 98 is an open-label single-centre, non-comparative Phase I/II study. The primary efficacy endpoint is ORR, assessed by the investigator. Secondary endpoints included change in calcitonin (CTN) and carcinoembryonic antigen (CEA) levels, PFS and OS.

The planned single arm design of the paediatric study 98 in 21 patients was discussed in the PDCO. It was considered that a single non controlled study in a small number of patients using other than time-related endpoints would not be sufficient to establish efficacy. Nevertheless, it was acknowledged that it was under debate whether a comparative study is feasible, given the very low incidence of MTC in the paediatric population and the lack of standard treatment for these patients. Originally it was planned to include 21 patients, but due to recruitment difficulties only 16 patients of the age between 9 and 17 were

enrolled. Thus, the PDCO considered that existing paediatric data from study 98 should be provided together with additional analyses synthesising the data from study 98 and further paediatric studies (studies 04, 51 and 61). A modelling report was also requested for assessment in order to predict pharmacokinetic variability and to substantiate dosing proposals (see clinical pharmacology).

Paediatric clinical trial data with vandetanib in MTC is limited to 16 patients aged 9 years to 17 years with hereditary MTC. There is no experience with Caprelsa in patients 5-8 years of age in this study (see SmPC section 5.1). Although hereditary MTC is rare in children aged 5 to 9 years of age, it is anticipated that the effects of vandetanib are similar to those in children from 9 years of age and older because of disease similarities.

The clinical study did not include paediatric patient with sporadic MTC, which is acceptable as this occurs much less frequently in the paediatric population than hereditary MTC.

The use of ORR according to RECIST 1.0 as primary endpoint is not considered the most recommendable variable for a confirmatory trial. Nevertheless, given the design of the study and the unmet medical need, this could be acceptable. Other secondary variables are supported. With regards to protocol amendments, no impact on the B/R assessment of Caprelsa is expected for the use in paediatric metastatic MTC.

Although the number of patients was limited, results based on the primary endpoint are considered clinically meaningful. ORR in the evaluable population was 43.8%. All the responses were partials (43.8%) or stable disease for at least 8 weeks (31.3%). Disease Control Rate including best response or Stable Disease >24 weeks was 75.0% (see table 14). The radiologic response results were supported by responses on the tumours markers CTN and CEA. In this respect, in total 13 of the 15 evaluable patients (81.3%) had a best percentage decrease in CTN levels from baseline of at least 50% and 9 of the 15 evaluable patients (56.3%) had a best percentage decrease in CEA levels from baseline of at least 50%. These response rates (ORR and on tumour markers) were comparable with the response rates that were reported for adult MTC in the pivotal registration study 98 and indicate an anti-tumour activity of Caprelsa against MTC in children with a RET mutation.

The median progression-free survival (PFS) time was approximately 46 months. The accuracy of this median PFS data is doubtful given the open label design of the study with PFS assessed by the investigator, the low number of patients included in the study and the low frequency of tumour assessment i.e. after the first 5 treatment cycles only once every 4 cycles (of each 28 days). No patients died during the study and follow-up for overall survival (OS) ranged from 30 to 1405 days. Although it is not clear whether the children included in the study had symptomatic disease, and the provided information on the aggressiveness of the tumours in the study population was limited, aggressive disease is anticipated for most of study population because almost all of the patients included in study 98 had MEN2B tumours which are generally highly proliferative tumours with a relative high mortality rate. In one large study, death from MTC occurred in 50 percent of patients with MEN2B versus 9.7 percent of those with MEN2A (Eng C, et al., 1996). Therefore, the same restrictions of the indication is recommended for paediatric population i.e. patients with aggressive and symptomatic, unresectable locally advanced or metastatic, medullary thyroid cancer.

Furthermore, in total 15 of the 16 patients in Study 98 (93.8%) had the M918T mutation, which is a characteristic of the MEN 2B subtype of hereditary MTC. No data regarding the effect of Caprelsa in paediatric MTC without RET mutation is available. Thus, in line with the adult indication, a statement regarding the lack of efficacy data for RET negative patients is included in section 4.1 of the SmPC.

In all cases (adult patients, paediatric patients and at every moment during treatment) continuation of treatment should be evaluated by the physician. Adult patients were treated with Caprelsa until objective disease progression, provided they did not meet any other withdrawal criteria. It seems that there is no or only very limited experience with treatment continuation after progression and the benefit of treatment

beyond progression is questioned. Therefore, vandetanib may be administered until disease progression or until the benefits of treatment continuation do no longer outweigh its risk, thereby considering the severity of adverse events (see sections 4.8) in relation to the degree of clinical stabilization of the tumour status (see section 4.2).

2.4.5. Conclusions on the clinical efficacy

Whilst the pivotal study size is small owing to the rarity of MTC in children, it is considered representative of the target population (see SmPC sections 4.1, 4.8 and 5.1). The totality of the data supports the efficacy of vandetanib in children and adolescents aged 5 years and older.

2.5. Clinical safety

Introduction

The existing safety profile of vandetanib in adults was mainly based on one pivotal Phase 3 trial (study 58) investigating the efficacy and safety of vandetanib 300mg versus placebo in 331 patients with unresectable locally advanced or metastatic MTC. Supportive safety data was obtained in two Phase II studies (08 and 68) in adult patients with MTC.

The most commonly reported adverse drug reactions have been diarrhoea, rash, nausea, hypertension, phototoxicity and headache. Vandetanib at a dose of 300 mg is associated with a substantial and concentration dependent prolongation in QTc (mean 28 msec, median 35 msec). Serious toxicities, such as Torsades de pointes, Stevens-Johnson syndrome, erythema multiforme, interstitial lung disease (sometimes fatal) and posterior reversible encephalopathy syndrome (PRES, Reversible posterior leukoencephalopathy syndrome -RPLS) have infrequently occurred in patients treated with vandetanib monotherapy.

Patient exposure

The safety data for vandetanib use in paediatric patients is provided from the NCI-sponsored study in MTC (Study 98) and 3 investigator-sponsored paediatric studies in different indications (Glioma, or neuroblastoma and medulloblastoma). This includes 16 patients in Study 98, 9 patients in Study 04, 35 patients in Study 51 and 10 patients in Study 61 (total of 70 paediatric patients).

The MAH was not the sponsor for these studies; however, the MAH sought additional data and information from the NCI for Study 98 and a CSR has been completed. Information on the 3 investigator-sponsored paediatric studies in indications other than MTC is based on published manuscripts.

These data show that the median duration of exposure to vandetanib in the paediatric MTC study (Study 98; 750 days) was similar to that in the pivotal adults MTC study (Study 58; 630.7 days).

Table 15: Comparative table of exposure; paediatric and adult studies

	Studies in MTC				Paediatric studies in other indications		
	Study 98 paediatric MTC N = 16	Study 08 adult MTC N = 30	Study 68 adult MTC N = 19	Study 58 adult MTC N = 231	Study 04 paediatric DIPG N = 25	Study 51 paediatric glioma N = 35	Study 61 paediatric neuroblastoma/ medulloblastoma N = 10
Doses studied	100 mg/m ² /day (15 patients) 150 mg/m ² /day (1 patient plus 6 patients who started on 100 mg/m ² /day and had a dose increase)	300 mg/day fixed dose	100 mg/day fixed dose	300 mg/day fixed dose	65 or 85 mg/m ² /day vandetanib with 130 or 170 mg/m ² /day dasatinib.	50, 65, 85, 110 and 145 mg/m ²	50 mg/m ² /day
Mean (SD) duration of exposure (days)	681.3 (482.7)	525.9 (371.4)	261.7 (132.3)	525.0 (252.0) ^a	NA	NA	NA
Median (range) duration of exposure (days)	750 (31 – 1406)	NA (19 – 1167.0)	NA (1 – 501)	630.7 (14 – 931) ^a	184 (8 – 819)	212 (3 – ≥674)	NA
Number (%) patients with dose reductions	3 (18.8)	21 (70.0)	2 (10.5)	83 (35.9)	4 (16.0)	0	NA

Data from CSRs for [Study 98](#), [Study 08](#), [Study 68](#), [Study 58](#), [Study 04](#), [Study 51](#) and [Study 61](#)

^a Exposure data in CSR are quoted in weeks and converted to days by multiplying by 7.

DIPG Diffuse Intrinsic Pontine Glioma; MTC medullary thyroid cancer; NA Not available; SD: standard deviation

Adverse events

The most common AEs in Study 98 were diarrhoea (93.8%), prolonged QTc interval (93.8%), elevation of alanine aminotransferase (ALT; (81.3%), proteinuria (81.3%) and rash: acne/acneiform (81.3%).

Diarrhoea, prolonged QTc interval and rash were also reported commonly in adults in Study 58, although the incidences were lower than in paediatric patients. Although increases in ALT and proteinuria were not reported as frequent AEs in adults in Study 58, laboratory data in adults showed that these also occurred in adult patients treated with vandetanib.

Table 16 : Number (%) of patients who had at least 1 adverse event in any category - Study 98

AE category	Number (%) of patients (N=16)
Any AE	16 (100.0)
Any causally ^a related AE	16 (100.0)
Any CTCAE of Grade 3 or above	13 (81.3)
Any SAE (including events with outcome = death)	1 (6.3)
Any SAE with outcome other than death	1 (6.3)
Any AE with outcome = death	0
Any AE leading to discontinuation of treatment	0
Any causally ^a related AE leading to discontinuation of treatment	0

Data from Table 15 Study 98 CSR.

^a As assessed by the investigator.

Note: Patients with multiple events in the same category were counted only once in that category. Patients with events in more than 1 category were counted once in each of those categories. All AE terms were coded using Common Toxicity Criteria Version 3.0.

AE: adverse event; CTCAE: Common terminology criteria for adverse events; SAE: serious adverse event.

The most common CTCAEs $\geq$ Grade 3 in Study 98 included diarrhoea and increases in transaminases (ALT and aspartate aminotransferase; AST). A higher proportion of patients in Study 98 had adverse events of common terminology criteria for adverse events (CTCAE) Grade 3 or above (81.3% [13 patients]) compared with Study 58 (55.4% [128 patients]).

Table 17: Study 98: Summary of most frequent adverse events (CTCAE Grade $\geq$ 3; reported by more than 1 patient) by CTC category and term

CTC category CTC term	Number (%) of patients (N=16)
Any AE	13 (81.3)
Gastrointestinal	9 (56.3)
Diarrhoea	7 (43.8)
Dehydration	2 (12.5)
Vomiting	2 (12.5)
Metabolic/laboratory	5 (31.3)
Elevations of ALT (SGPT)	4 (25.0)
Elevations of AST (SGOT)	3 (18.8)
Calcium, serum-low (hypocalcaemia)	2 (12.5)
Pain	5 (31.3)
Pain: Abdomen NOS	2 (12.5)
Pain: Head/Headache	2 (12.5)
Cardiac arrhythmia	2 (12.5)
Prolonged QTc interval	2 (12.5)

Data from Table 18 Study 98 CSR

Note: Patients with multiple AEs for CTCAE Grade 3 or higher were counted once for each CTC category and CTC term. Number (%) of patients with AEs, sorted by descending frequency for CTC category and CTC term. All AE terms were coded using CTC Version 3.0.

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CTC: common toxicology criteria; NOS: not otherwise specified; QTc: Corrected QT interval; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase.

Review of the growth curves and considering the vandetanib use prior to data cut-off showed maintenance of each patient's growth velocity during drug treatment. Some of the patients actually had an improvement in their growth velocity during vandetanib treatment.

Thyroid status was also monitored and some of the patients were periodically hypothyroid requiring dose adjustments of thyroxine (LT4) during the study. Dose increases, on average, of LT4 equal to 36.6% from baseline doses were required to normalize the patients' thyroid status. In this population, there were no clinical sequelae as a result of periods of hypothyroidism including no impact on growth velocity.

Serious adverse event/deaths/other significant events

No deaths were reported in the paediatric MTC study, Study 98, and a discussion of deaths in the other paediatric studies is not considered relevant for the MTC indication, since glioma and neuroblastoma are associated with a much worse prognosis than MTC (24 of the 25 patients in Study 04, 24 of the 35 patients in Study 51 and 2 of the 10 patients in Study 61, died due to disease progression during the study period).

Laboratory findings

In the paediatric MTC study, Study 98, there were no clinically significant findings in haematology, clinical chemistry or urinalysis for any of the patients. AEs relating to clinical chemistry changes were consistent with findings in the adult population.

Safety in special populations

In the paediatric MTC study, Study 98, the impact of vandetanib on the growth plate and therefore linear growth of the patient was evaluated. The results of the magnetic resonance imaging scans were difficult to interpret as the mean growth plate volumes measured across all patients fluctuated over the course of the study; however, all children and adolescents demonstrated linear growth while receiving vandetanib. A similar lack of effect on the growth plate was also reported in the glioma studies.

A search has been performed of the MAH patient safety database (the SAPPHIRE database) for suspected, unexpected serious adverse reactions (SUSARs); no cases were reported in this database from Study 98 during the period from the data cut-off date for the Study 98 (17 July 2011) to 15 June 2015.

Discontinuation due to adverse events

No patients in Study 98 were discontinued from treatment because of AEs. In contrast, 28 (12.1%) of adult patients in the vandetanib group of Study 58 discontinued due to an AE; asthenia and rash were the most common events leading to discontinuation in the adult population. Dose reduction was used to manage toxicity and the most common dose limiting toxicity (DLT) was diarrhoea (required for 3 patients; Summary of Clinical Safety).

Post marketing experience

At the last data lock point for the assessment of post-marketing safety data (6 April 2015), vandetanib had been approved in over 40 countries worldwide. The cumulative worldwide patient exposure (excluding clinical trial exposure) was estimated to be approximately 5325 patients and 2626 patient-years.

Post-marketing pharmacovigilance data show that the safety profile for vandetanib has not changed significantly since first marketing authorisation. The safety profile remains under surveillance for new findings or trends, as per standard safety reporting obligations.

2.5.1. Discussion on clinical safety

The most common adverse events in Study 98 were diarrhoea (93.8%), prolonged QTc interval (93.8%), elevation of alanine aminotransferase (ALT); (81.3%), proteinuria (81.3%) and rash: acne/acneiform (81.3%). Diarrhoea, prolonged QTc interval and rash were also reported commonly in adults in Study 58, although the incidences were lower than in paediatric patients. Although increases in ALT and proteinuria were not reported as frequent AEs in adults in Study 58, laboratory data in adults showed that these also occurred in adult patients treated with vandetanib. The most common CTCAEs $\geq$ Grade 3 in Study 98 included diarrhoea and increases in transaminases (ALT and aspartate aminotransferase; AST). Diarrhoea was also one of the most common CTCAEs $\geq$ Grade 3 in Study 58 and increases in transaminases to Grade 3 were observed in laboratory data.

Overall, the provided data show that vandetanib in children with hereditary MTC, at doses of 100 or 150 mg/m²/day, has a global safety profile consistent with that of adult patients with MTC receiving vandetanib 300 mg daily. Although the frequency of most adverse events was higher in the paediatric population than in the adult population, the comparison is limited without direct comparison.

Based on provided PK data and disease similarity, the safety and toxicity of vandetanib in adult patients is considered relevant for the paediatric population. Nevertheless, for the paediatric population specific safety and toxicity issues, including dental and physeal dysplasia were identified which do not occur in the adult population. The MAH has presented data showing that use of vandetanib had no adverse effect on growth in children and adolescents. Based on height measurements at all visits, all children and adolescents in a paediatric study demonstrated linear growth while receiving vandetanib. Accelerated growth due to puberty was taken into account when concluding that growth was linear. However, data

are limited and long term safety data in paediatric patients are not available. Teeth and bone development in the paediatric population have been included as new important potential risks in the RMP. Paediatric AE reports related to/associated with abnormalities in the linear growth, bone and teeth development will be closely monitored, and a specific targeted/guided questionnaire will be provided to the health care professional to solicit information specific to growth, bone and teeth development in the patient. The data will be periodically reviewed, and also presented as an annual review and analysis in PSUR.

To overcome the lack of suitable formulation, complex dosing regimens have been proposed and could lead to dose miscalculation/error or poor compliance (see clinical pharmacology). Medication error related to paediatric population has been included in the RMP as new important potential risk and an educational material designed to guide parents and healthcare professionals to manage the dosing regimen have been developed (see RMP).

Dose adjustments in paediatric patients with MTC also apply. In the event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval, dosing with vandetanib should be at least temporarily stopped and resumed at a reduced dose when toxicity has resolved or improved to CTCAE grade 1. Patients who are on the starting dose (a in Table 1 of SmPC section 4.2), should be recommenced at the reduced dose (c in Table 1). Patients who are on the increased dose (b in Table 1), should be recommenced at the starting dose (a in Table 1). If another event of common terminology criteria for adverse events (CTCAE) grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with Caprelsa should be at least temporarily stopped and resumed at a reduced dose (c in Table 1) when toxicity has resolved or improved to CTCAE grade 1. If a further event of CTCAE grade 3 or higher toxicity or prolongation of the ECG QTc interval occurs, dosing with vandetanib should be permanently stopped (see SmPC section 4.2).

The patient must be monitored appropriately. Due to the 19 day half-life, adverse reactions including a prolonged QTc interval may not resolve quickly (see sections 4.2 and 4.4).

Effects on reproduction in paediatric patients treated with vandetanib are not known (see SmPC section 4.6).

2.5.2. Conclusions on clinical safety

The safety profile of vandetanib is well characterised in the adult population and has been shown to be comparable in children aged 9 to 18 years old. There is no experience in pediatric patients with hereditary MTC below 9 years of age (see SmPC section 4.2, 4.8 and 5.1). A similar exposure to vandetanib is expected in 5-8 years old patients compared to patients aged 9-18 years based on data obtained in glioma-related indications (see clinical pharmacology). A similar safety profile is expected in paediatric patients aged 5-8 years old and ≥ 9 years old. Warnings in the SmPC and measures included in the RMP are considered adequate to minimise the risk in the paediatric population. Paediatric adverse events reports related to/associated with abnormalities in the linear growth, bone and teeth development as well as long term use will be closely monitored. Furthermore, educational material to mitigate the new important potential risk of medication error will be implemented (see RMP).

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

The PRAC considered that the RMP version 12.0 (dated 29 July 2016) is not acceptable; therefore the applicant should implement the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur updated assessment report (AR) dated 23 September 2016.

The CHMP endorsed this advice.

The applicant implemented all changes to the RMP, as requested by the PRAC and the CHMP.

The CHMP approved the RMP version 12.1 (dated 04 October 2016) with the following contents.

Safety concerns

Table 18 : Summary of the safety concerns

Important identified risks	Cerebrovascular events Cholelithiasis Diarrhoea Heart failure Hypertension Infections Interstitial lung disease Intestinal perforation and/or obstruction Pancreatitis Phototoxicity Pneumonia Posterior reversible encephalopathy syndrome (PRES) (also known as Reversible posterior leukoencephalopathy syndrome [RPLS]) QTc prolongation and Torsades de pointes Renal toxicity Toxic epidermal necrolysis, toxic skin eruption, exfoliative dermatitis, and other skin reactions
Important potential risks	Hepatic failure Reproductive toxicity Teeth and bone abnormalities in the paediatric population Medication errors related to paediatric population
Missing information	Long-term use Use during pregnancy Use in elderly patient population Use in non-Caucasian patient population Use in patients with cardiac impairment Use in patients with hepatic impairment Use in patients with moderate to severe renal impairment

Pharmacovigilance plan

Table 19 : Ongoing and planned additional pharmacovigilance activities / studies in the PV 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)
Yearly survey to CAPRELSA prescribers and potential prescribers to assess effectiveness of educational materials; Survey respondents, who agree to participate, will also take part in a chart review in order to validate the survey responses. (Category 3)	To evaluate the effectiveness of educational materials to minimise the risk of posterior reversible encephalopathy syndrome (PRES) and QTc prolongation and Torsades de pointes	Posterior reversible encephalopathy syndrome (PRES) and QTc prolongation and Torsades de pointes	Started	Starting one year (12 months) after Caprelsa is approved / marketed and continuing for 3 consecutive years
Study D4200C00104 European, Observational, Prospective Study to Evaluate the Benefit/Risk of Vandetanib (CAPRELSA) 300 mg in RET Mutation Negative and RET Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Thyroid Cancer (MTC) (Category 2)	To determine the Objective Response Rate (ORR), Disease Control Rate (DCR), Duration of Response, & Time to Response of for patients treated with vandetanib who are RET mutation positive and patients treated with vandetanib who are RET mutation negative To explore the clinical outcomes (including but not limited to PFS and ORR) amongst RET mutation negative patients not treated with vandetanib To compare Progression-Free Survival (PFS) for patients treated with vandetanib who are RET mutation positive to patients treated with vandetanib who are RET mutation negative	Evaluation of the incidence of QTc prolongation and associated risks for QTc prolongation in patients receiving vandetanib who are RET mutation positive and RET mutation negative. Assessment of the incidence of SAEs and AEs leading to discontinuation of vandetanib.	Started	3Q 2020

Risk minimisation measures

Table 20 : Summary of the risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risks		
Cerebrovascular events	Wording in SmPC section 4.8	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cholelithiasis	Wording in SmPC section 4.8	
Diarrhoea	Wording in SmPC section 4.4, 4.8	None
Heart failure	Wording in SmPC section 4.4, 4.8	None
Hypertension	Wording in SmPC section 4.4, 4.8	None
Infections	Wording in SmPC section 4.8	None
Interstitial lung disease	Wording in SmPC section 4.8	None
Intestinal perforation and/or obstruction	Wording in SmPC section 4.8	None
Pancreatitis	Wording in SmPC section 4.8	None
Phototoxicity	Wording in SmPC section 4.4, 4.8	None
Pneumonia	Wording in SmPC section 4.8	None
Posterior reversible encephalopathy syndrome (PRES)	Wording in SmPC section 4.4	Objective and rationale: To reduce the risk, mitigate the clinical impact, and enable appropriate diagnosis and treatment of PRES by educating HCPs about the safe and effective use of vandetanib via the SmPC and additional educational materials. To reduce the risk, mitigate the clinical impact, and enable appropriate diagnosis and treatment of PRES by providing materials to educate patients to recognise symptoms associated with PRES. Proposed actions: Provide risk minimisation tool (educational materials) to reinforce the prescriber's awareness about the risk of PRES and awareness about performing an MRI for symptoms suggestive of PRES. All potential prescribers will be provided, before launch and thereafter, with enough patient alert cards to distribute to their patients with each prescription. Implementation of a yearly survey to CAPRELSA prescribers and potential prescribers to assess effectiveness of education materials; starting one year (12 months) after Caprelsa is approved / marketed and continuing for 3 consecutive years. Survey respondents, who agree to participate, will also take part in a chart review in order to validate the survey responses.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
QTc prolongation and Torsades de pointes	Wording in SmPC section 4.4	Objective and rationale: To reduce the risk, mitigate clinical impact, and enable appropriate treatment of torsades de pointes by educating HCPs about appropriate monitoring of QTc prolongation, and how to appropriately interrupt or reduce the dose of vandetanib, via the SmPC and additional educational materials. To reduce the risk, mitigate clinical impact, and enable appropriate treatment of torsades de pointes by providing educational materials for patients. Proposed actions: Provide risk minimisation tool (educational materials) to reinforce prescriber's awareness about the risk of QTc prolongation and torsades de pointes. All potential prescribers will be provided with enough patient alert cards to distribute to their patients with each prescription. Implementation of a yearly survey to Caprelsa prescribers and potential prescribers to assess effectiveness of education materials; starting one year (12 months) after Caprelsa is approved / marketed and continuing for 3 consecutive years. Survey respondents, who agree to participate, will also take part in a chart review in order to validate the survey responses
Renal toxicity	Wording in SmPC section 4.8	None
Toxic epidermal necrolysis, toxic skin eruption, exfoliative dermatitis, and other skin reactions	Wording in SmPC section 4.4, 4.8	None
Important Potential Risk		
Hepatic failure	No specific risk minimisation activities identified	None
Reproductive toxicity	Wording in SmPC section 4.6	None
Teeth and bone development	SmPC wording in Section 5.3	Educational materials to HCPs
Medication errors related to paediatric population	SmPC wording in Section 4.2	Educational materials to HCPs (physicians dosing guide) and patients/caregivers (dosing guide)
Long term use	No specific risk minimisation activities identified	None
Use during pregnancy	SmPC wording in section 4.2, 4.6	None
Use in elderly patient population	SmPC wording in section 4.2	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in non-Caucasian patient population	No specific risk minimisation activities identified	None
Use in patients with cardiac impairment	No specific risk minimisation activities identified	None
Use in patients with hepatic impairment	Wording in SmPC section 4.2	None
Use in patients with moderate to severe renal impairment	Wording in SmPC section 4.2	None

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Annex II was also updated to reflect the changes to the information about additional risk minimisation measures in line with the revised RMP. Furthermore, the description of the specific obligation was also shortened for readability. Details of the design of the study are included in the risk management plan.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable due to the limited proposed changes to the PI that do not significantly alter the readability of the approved document.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study IRUSZACT0098 recruited 16 patients aged between 9 and 17 years who all but one received an initial dose of 100 mg/m²/day. One patient received 150 mg/m²/day. The primary efficacy endpoint of the pivotal study (Study IRUSZACT0098) was ORR assessed by the investigator. Of the 16 patients included in the study 7 patients had a PR, which is 43.8% of the patients. No CRs were reported. Stable disease for at least 8 weeks was reported in 5 patients (31.3%). The median PFS for the patients treated with vandetanib was 46 months.

The radiologic response results were supported by responses on the tumours markers CTN and CEA. In this respect, in total 13 of the 15 evaluable patients (81.3%) had a best percentage decrease in CTN levels from baseline of at least 50% and 9 of the 15 evaluable patients (56.3%) had a best percentage decrease in CEA levels from baseline of at least 50%.

Supportive evidence of efficacy in patients with MTC is available from relevant data obtained in the adult population (study 58).

Uncertainty in the knowledge about the beneficial effects

The study size is small owing to the rarity of MTC in children. Nevertheless the study is considered representative of the target population.

There is no experience in paediatric patients with hereditary MTC below 9 years of age. However similar exposure to vandetanib is expected in patients aged 5-9 years old based on PK data in paediatric patients with glioma. Hence, vandetanib is indicated in paediatric patients above 5 years of age. Vandetanib is not indicated in children below 5 years of age (see SmPC 4.1). Given the rarity of unresectable or metastatic hereditary MTC in paediatric patient, studies had been waived for patients <5 years of age, as the disease is extremely uncommon in this age group.

The median PFS for the patients treated with vandetanib was 46 months. The accuracy of this median PFS data is uncertain given the open label design of the study with PFS assessed by the investigator, the low number of patients included in the study and the low frequency of tumour assessment i.e. after the first 5 treatment cycles only once every 4 cycles (of each 28 days). Moreover, due to the lack of comparative data, interpretation of the PFS data is hampered. However, it does give support to efficacy taking into account the type of patients that were included in the clinical trial.

Risks

Unfavourable effects

The most common AEs in Study 98 were diarrhoea (93.8%), prolonged QTc interval (93.8%), elevation of alanine aminotransferase (ALT) (81.3%), proteinuria (81.3%) and rash: acne/acneiform (81.3%).

In this respect, Grade 3 or higher grade AEs were reported in 13 (81.3%) of the paediatric patients. The most frequently reported events were diarrhoea (43.8%), ALT and AST elevations (25% and 18.8%) respectively. One patient had SAEs which included liver dysfunction/failure, obstruction gastrointestinal, and pain. None of the patients discontinued study treatment due to AEs.

Despite the high incidence of Grade ≥ 3 AEs, the toxicity of vandetanib in children seems to be manageable as none of the patients discontinued treatment due to AEs. Moreover, the long treatment period (median of more than 24) suggests that the anti-cancer therapy was reasonably tolerated.

Overall, the provided data show that vandetanib in children with hereditary MTC, at doses of 100 or 150 mg/m²/day, has a global safety profile consistent with that of adult patients with MTC receiving vandetanib 300 mg daily. The frequency of most adverse events was higher in the paediatric population than in the adult population although no formal conclusion can be made without direct comparison.

Uncertainty in the knowledge about the unfavourable effects

The follow up time of patients was limited and the long term safety of vandetanib including the effect of vandetanib on developmental and maturation processes in children is not known. While the available data are limited, these showed that use of vandetanib had no adverse effect on growth in children and adolescents treated in study 98. Paediatric adverse events reports related to/associated with abnormalities in the linear growth, bone and teeth development as well as long term use will be closely monitored (see RMP).

There is no experience in paediatric patients with hereditary MTC below 9 years of age. However similar exposure to vandetanib is expected in this patient subgroup based on PK data in paediatric patients with glioma aged 2-17 years. Although hereditary MTC is rare in children aged 5 to 9 years of age, it is anticipated that the safety of vandetanib are similar to those in children from 9 years of age and older because of disease similarities.

Considering the complex dosing regimen there is a potential risk of dose miscalculation and/or error. The MAH has provided educational material designed to guide parents to manage the dosing regimen and will

put in place measures to assess the treatment compliance, and measures to minimise medication errors (see RMP).

Effects Table

Table 21 : Effects Table for vandetanib in paediatric patients with medullary thyroid cancer

Effect	Short Description	Unit	Treatment	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR	Proportion of complete or partial responders (≥30% decrease in the sum of the longest diameter of target lesions) (investigator based assessment)	%	43.8	NA	Results supported by responses on the tumours markers CTN and CEA. Limited number of patients (N=16). Aged 9 years to 17 years. No CR reported.	Study 98 (paediatric)
			45	13	Supportive efficacy data in MTC from adult study 58 (N=331)	Study 58 (adults), See Caprelsa EPAR
PFS	Median time from randomisation to objective disease progression or death (investigator based assessment)	Months	46	NA	Uncertainties because of study design (open label, no independent review) and low frequency of tumour assessment	Study 98 (paediatric)
			30.5 (not reached, predicted)	19.3	Supportive efficacy data in MTC from adult study (N=331)	Study 58 (adults), See Caprelsa EPAR
Unfavourable Effects						
Diarrhoea	Grade ≥ 3	%	43.8	NA	Duration of follow up in the pivotal study is short vs. the need for long duration of treatment. Long term use will be closely monitored (RMP) Teeth and bone abnormalities included in RMP as potential risk based on non-clinical data. Risk of medication errors addressed by educational material	Study 98 (paediatric)
ALT elevations	Grade ≥ 3	%	25			
AST elevations	Grade ≥ 3	%	18.8			
Prolonged QTc interval	Grade ≥ 3	%	12.5			

Abbreviations: CR= Complete response; ORR= Overall response rate; NA = not applicable; CTN= Calcitonin; CEA= Carcinoembryonic antigen; ALT= Alanine aminotransferase; AST= Aspartate aminotransferase; CTCAE= Cancer Therapy Evaluation Program common terminology criteria for adverse events

Note: Study 98 cut-off date: 17 July 2011; Study 58 cut-off date: 31 July 2009. CTCAE version 3.0 used.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Clinically relevant efficacy in the treatment of paediatric patients with unresectable locally advanced or metastatic MTC has been shown. Furthermore, the results of Study 98 showed that vandetanib in children with MTC, at a starting dose of 100 mg/m²/day, has a similar tolerability profile to the adult MTC population (from Studies 58, 08 and 68). Supportive evidence of efficacy and safety of vandetanib in patients with MTC is available from relevant data obtained in the adult population.

Benefit-risk balance

Taking into account the relatively high response rate of vandetanib in paediatric MTC, the general manageable toxicity and the lack of effective alternatives, the benefit of treating children with metastatic or unresectable MTC is considered to outweigh the risks.

Discussion on the Benefit-Risk Balance

Hereditary MTC is characterised by germline mutations in the RET proto-oncogene. The underlying genetic cause of the disease is identical in paediatric and adult patients, therefore the activity of vandetanib in paediatric patients with this disease is expected to be similar to that in adults. Similarity between the adult and paediatric patient population included in the main studies is not completely assured as in the pivotal study in adults (study 58) the patient population was rather heterogeneous with regard to pre-treatment, the type of tumour comprised of hereditary and presumably predominantly sporadic MTC, and consisted mainly of MEN 2A in adults versus almost all MEN 2B in children. However, it is noted that there was a dose-dependent response observed in adults and that the PK results showed comparable exposure between children above the age of 9 years dosed 100 mg/m² and adults dosed at 300 mg. Moreover, there were comparable ORR and biomarker results between the paediatric as adult MTC patients, while in the adult study it was shown that positive ORR translated in prolongation of the PFS. Therefore, available data in adult are considered relevant in support of the paediatric indication.

Considering the disease similarity and the similar exposure to vandetanib obtained in patients aged 5 to 8 years compared to older children aged 9 to 18 years old, it is considered acceptable to extend the indication to the 5-8 years old population, also taken into account the rarity of the pathology.

When evaluating the data in the adult population at the time of the initial application, it was questioned which patient is most likely to derive the most benefit in particular in a disease setting with a relatively long survival i.e. when the disease is relatively stable (see Caprelsa EPAR). In this perspective, the optimal moment of treatment initiation was also discussed and it was recommended that Caprelsa is used in patients with highly progressive and symptomatic disease who have a pronounced need for immediate therapy. The adult indication was therefore restricted to patients with aggressive and symptomatic, unresectable locally advanced or metastatic medullary thyroid cancer. Given the low number of paediatric patients included it is not possible to identify a specific paediatric subgroup for which Caprelsa treatment would be especially beneficial. However, aggressive disease is anticipated for most of study population because almost all of the patients included in study 98 had MEN2B tumours which are generally highly

proliferative tumours with a relative high mortality rate. Therefore, Caprelsa is also recommended in paediatric patients with aggressive and symptomatic, unresectable locally advanced or metastatic, medullary thyroid cancer.

Based on the totality of the evidence including supportive efficacy and safety data from the adult population, a positive benefit-risk balance is concluded for Caprelsa in the treatment of aggressive and symptomatic medullary thyroid cancer (MTC) in children and adolescents aged 5 years and older with unresectable locally advanced or metastatic disease.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II, IIIA and IIIB

Extension of Indication to include paediatric patients aged 5 to 18 with unresectable locally advanced or metastatic medullary thyroid carcinoma (MTC) for Caprelsa; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated with efficacy and safety information from studies IRUSZACT0098, ISSZACT0004, IRUSZACT0051 and IRUSZACT0061 . The Package Leaflet and Risk Management plan (v.12.1) are updated in accordance.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Risk Management Plan.

Conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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

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

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed

RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

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

An updated RMP shall be submitted annually until renewal.

- **Additional risk minimisation measures**

Prior to launch of CAPRELSA in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The MAH shall ensure that in each Member State where CAPRELSA is marketed, all healthcare professionals (HCPs) and patients / caregivers who are expected to prescribe, dispense and use CAPRELSA have access to/are provided with an **educational package** containing:

HCPs

- The summary of Product Characteristics (SmPC);
- The educational material, including:
 - o Information about the risks associated with CAPRELSA:
 - QTc prolongation and Torsades de pointes
 - Posterior reversible encephalopathy syndrome (PRES);
 - Teeth and bone development abnormalities in pediatric patients
 - Medication errors in the pediatric population
 - o The Physicians' dosing and monitoring guide for paediatric patients;
- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

Patients / caregivers

- The dosing and monitoring guide for paediatric patients and patient's caregivers;
- The Patient Leaflet;
- The Patient Alert Card.

The **HCPs educational materials** should include the following key elements:

QTc prolongation and Torsades de pointes

- CAPRELSA prolongs the QTc interval and can cause Torsades de pointes and sudden death
- CAPRELSA treatment must not be started in patients:
 - o Whose ECG QTc interval is greater than 480 msec;
 - o Who have congenital long QTc syndrome;
 - o Who have a history of Torsades de pointes unless all risk factors that contributed to Torsades de pointes have been corrected;
- The need for an ECG, and serum levels of potassium, calcium and magnesium and thyroid stimulating hormone (TSH) and the times and situations when it should be performed;

- Patients who develop a single value of corrected ECG QTc interval of at least 500 msec should stop taking CAPRELSA. Dosing can be resumed at a reduced dose after return of the ECG QTc interval to pre-treatment status has been confirmed and correction of possible electrolyte imbalance has been made;
- If QTc increases markedly but stays below 500 msec, the advice of a cardiologist should be sought;
- Details of medicinal products where the co-administration of CAPRELSA is either contraindicated or not recommended;
- The role and use of the Patient Alert Card.

Posterior reversible encephalopathy syndrome (PRES) also known as reversible posterior leukoencephalopathy syndrome (RPLS)

- PRES should be considered in any patient presenting with seizures, headache, visual disturbances, confusion or altered mental function. A brain MRI should be performed in any patient presenting with seizures, confusion or altered mental status;
- The need to counsel patients about the risk of prolonged QTc and PRES and inform them of what symptoms and signs to be aware of and the actions to take;
- The role and use of the Patient Alert Card.

Teeth and bone development abnormalities in pediatric patients

- Vandetanib was found not to impair linear growth in clinical trials conducted in children and adolescents
- Vandetanib has demonstrated adverse effect on growing tissue that relies on vascularization such as teeth and growth plates in non-clinical studies
- The need to closely monitor teeth and bone abnormalities in the paediatric population

Medication errors in the paediatric population

The **Physicians' dosing and monitoring guide for paediatric patients** should contain the following key elements:

- How CAPRELSA dose for infants and adolescents is calculated;
- The posology regimens according to patient's body surface area (BSA), including a visual representation of the two-week posology regimen per BSA;
- How CAPRELSA is used / administered;
- Instructions on how to use the dosing and monitoring guide and the daily tracker for paediatric patients and caregivers.

The **dosing and monitoring guide for patients and patient's caregivers** should contain the following key elements:

- What CAPRELSA is, what it treats, how it is administered;
- How CAPRELSA dose is calculated;
- What are the side effects associated with CAPRELSA and which monitoring is requested;
- How to use the daily tracker table (including examples of a completed daily tracker);
- The general daily tracker for 14 days and blank copies of the daily tracker.

The **Patient Alert Card** should include the following key elements:

- Information about the risks of QTc prolongation and Torsades de pointes, and Posterior reversible encephalopathy syndrome (PRES);
- Signs or symptoms of the safety concerns and when to seek attention from a HCP;
- Not to stop taking CAPRELSA, or change the dose, without consulting the prescriber;
- Contact details of the CAPRELSA prescriber.

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

None.

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

Description	Due date
In order to confirm the efficacy and safety of Caprelsa, the MAH should submit the clinical study report of study D4200C00104, an observational study to evaluate the Benefit/Risk of Vandetanib (CAPRELSA) 300 mg in RET Mutation Negative and RET Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Thyroid Cancer (MTC).	3Q 2020

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0285/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Additional data exclusivity / market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers, by consensus, that the new therapeutic indication brings significant clinical benefit in the absence of existing therapies (see Appendix 2).